

Patient-derived xenograft mouse models: A high fidelity tool for individualized medicine (Review)

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Abstract. Patient-derived xenograft (PDX) mouse models involve the direct transfer of fresh human tumor samples into immunodeficient mice following surgical resection or other medical operations. Gene expression in tumors may be maintained by serial passages of tumors from mouse to mouse. These models aid research into tumor biology and pharmacology without manual manipulation of cell cultures *in vitro*, and are widely used in individualized cancer therapy/translational medicine, drug development and coclinical trials. PDX models exhibit higher predictive values for clinical outcomes than cell line-derived xenograft models and genetically engineered mouse models. However, PDX models are associated with certain challenges in clinical application. The present study reviewed current collections of PDX models and assessed the challenges and future directions of this field.

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1. Introduction

Anticancer drugs may be tested *in vitro* or *in vivo* using multiple preclinical models. Though >2/3 of agents are tested safely in phase I of clinical trials, the predictive accuracy of drug effectiveness is unsatisfactory in phase II due to the loss of heterogeneity and the specific cell microenvironment and alterations to the mechanism of tumorigenesis (1-3). Therefore, a model to guide individualized medicine is required.

In traditional cell lines, established cells are cultured in artificial conditions that may not accurately simulate complex biological conditions, including tumor progression in low oxygen conditions (4), excessive hypoxia-induced transcription factor activation (5), immune escape mechanism deficiency (6) and angiogenesis (7). In addition, autocrine, paracrine and endocrine mechanisms also serve key functions in tumor development, particularly in breast, ovarian and prostate cancer (8-10). Therefore, *in vitro*-based culture experiments may be inappropriate for individualized medicine.

Patient-derived xenograft (PDX) mouse models were initially proposed 40 years ago. With the development of host animals, numerous academic organizations have renewed their interest in PDX models. PDXs involve the direct transfer of fresh tumor samples into immunodeficient mice following surgical resection or other medical operations. Gene expression in tumors may be maintained by serial passages of tumors from mouse to mouse (11). PDXs aid research into tumor biology and pharmacology without manual manipulation of cell cultures *in vitro*. Multiple PDX studies have reported that, compared with their corresponding parental tumors, PDXs retain sufficient fidelity regarding histology, the transcriptome and genome (12-16). The present study reviewed current collections of PDXs and evaluated the key issues facing their future application.

2. Introduction of animal models

Current animal models. Numerous academic institutions have begun renewing their interest in genetically engineered mouse models (GEMMs), cell line-derived xenografts, and PDX models.

GEMMs. GEMMs are classified into two categories: Transgenic and targeted. In transgenic GEMMs, exogenous oncogenes are

expressed through pronuclear injection of embryonic stem cells. Targeted GEMMs involve homologous recombination in mouse embryonic stem cells, in which targeting vectors modify the homologous arms of a genomic locus to the accuracy of a single base. GEMMs have been used to elucidate multiple aspects of cancer development. Khaled *et al.* (17) summarized data from multiple studies. For example, GEMMs are particularly suitable for deleting or overexpressing targeted genes in a tissue-specific manner, are easy to produce and use endogenous regulatory elements. However, establishing the model takes ~1 year. Another major disadvantage of GEMMs is the low success rate between two targeted sites. In addition, GEMMs may not be able to mimic the individualized therapy associated with a tumor-specific gene. Therefore, GEMMs may not represent the optimal preclinical trial model.

Cell line-derived xenograft models. Cell lines are transplanted into immunodeficient mice to establish tumor models by numerous means, including subcutaneous implantation and orthotopic, venial or peritoneal injection. In 2007, Hajitou *et al.* (18) established the first soft tissue sarcoma cell line-derived tumor in the hind limb of rats. Subsequently, the development of cell line-derived xenograft models has decreased the influence of irrelevant cells when studying a single factor (16), improved the use of experimental cellular operations in researching tumor-associated signaling pathways and molecular mechanisms (19,20), established acute myeloid leukemia animal models to mimic the progression of liquid tumors (21), and aided research into metastatic mechanisms via intravenous or intraperitoneal injection (22). In addition, cell line-derived xenograft mouse models are easily established, and generating tumors takes only 2-8 weeks (23).

However, since generating cancer cell lines may irreversibly alter the biological properties of the derived cells, cell line-derived xenografts have limited predictive value for cancer therapy. The major disadvantages of this model are as follows: Following the dissociation of tumor tissues into a single cell suspension *in vitro*, selection pressure tends to result in a decrease in the heterogeneous characteristics of the tumors; not all cell lines are suitable for patients with certain types of cancer (17) and cell lines may not accurately reflect the complexity of tumor heterogeneity (24), which impacts patient-specific responses to clinical therapy. Therefore, cell line-derived xenograft models may not satisfy the requirements of individualized medicine.

PDX models. Compared with GEMMs and cell line-derived xenograft models, PDX models have more predictive value for clinical outcomes (25,26). Multiple studies have reported the high fidelity of PDXs regarding histology, the transcriptome and genome (12-16). Previous studies have obtained more detailed data on tumor cell population dynamics using deep-genome and single-cell sequencing techniques in PDXs for breast cancer (27,28). Therefore, the present study suggests that PDXs may be optimal models for studying tumor heterogeneity and currently represent the most powerful tool for assessing cancer-associated mechanisms. However, PDXs remain to be popularized in clinical application. Thus, the present study reviewed the progression of PDXs, particularly

the challenges faced by these models, and future directions for individualized medicine (Table I).

Existing PDX mouse models. PDXs may have originally failed to enter mainstream cancer research due to the limitations of using host animals that are not sufficiently immunodeficient and initiate xenograft rejection. However, using animal models is now common, since the number of immunodeficient host animal models has increased and the cost of immunodeficient mice has decreased (29). At present, nude, nonobese diabetic (NOD)/severe combined immunodeficiency (SCID) and NOD SCID γ (NSG) mice represent the three most commonly used types of immunodeficient mice. Nude mice are athymic, which results in a congenital deficiency of T and normal B lymphocytes and enhanced activity of natural killer (NK) cells (30). NOD/SCID mice are generated by crossing C.B.-17-SCID mice with NOD mice. SCID and NOD/SCID mice exhibit a congenital deficiency of T and B lymphocytes; the latter also exhibits decreased NK cell activity, which aids the use of the model since residual NK cells serve a key function in rejecting human tissues. NSG mice exhibit a deficiency of the interleukin 2 receptor γ -chain via the genetic engineering of NOD/SCID mice. NSG mice are the most severely immunodeficient since they exhibit T, B and NK cell deficiency. Therefore, the engrafting success rate in NSG mice is typically increased compared with that in nude or NOD/SCID mice (31). Therefore, NSG mice may be the most suitable of the three to generate tumors (32). NSG mice have been successfully utilized in multiple types of cancer and the present study has summarized the current state of PDXs (Table I).

Additional PDX models. Circulating tumor cells (CTCs) are released from primary tumors into peripheral blood vessels. Conditions permitting, CTCs may infiltrate distant tissues and thereby induce metastasis by providing 'seeds' to distant organs, in accordance with the 'seed and soil' theory (33). CTCs represent a readily accessible method for liquid biopsy. Numerous researchers over the past decades have focused on identifying and improving technically challenging methods of isolating CTCs (34). Currently, the CellSearch System is the only Food and Drug Administration-approved technique for CTC enumeration (35). However, the CellSearch System depends on epithelial cell adhesion molecules (EpCAMs) and therefore may only identify a small number of CTCs, potentially resulting in false negative or positive readings (36). Therefore, researchers have previously used the brain metastasis-selected markers (BMSMs) erb-b2 receptor tyrosine kinase 2 (ERBB2)⁺/epidermal growth factor receptor (EGFR)⁺/heparanase⁺/notch 1⁺ to identify EpCAM⁻ CTCs (37). The infiltration and metastasis of these CTCs were analyzed using BMSMs and these cells were then demonstrated to be invasive and capable of generating brain or lung metastasis in nude mice. Researching EpCAM⁻ CTCs may also serve to improve the understanding of metastasis. Enrichment steps are crucial to increase the isolation success rate. Although enriching CTCs may reach 98% of total CTCs by using the CTC-Chip, this chip has not become available on the market yet (38). Previously, the drug sensitivity of cultured CTCs was tested among multiple CTC lines (39). Furthermore,

Table I. Current progress of patient-derived xenograft models.

Author, year	Type of cancer	Processing method	Mouse strain	Implantation method	Implantation rate (%)	Stable take rate (%)	Time of tumor appearance	Stage of cancer	(Refs.)
Cottu <i>et al.</i> , 2012	Breast	FTP	Nude	Fat pad	36.1 (22/61) 4.2 (13/308)	16 (30/186)	<1 year	Primary (basal-like) Primary (non-basal-like)	(62)
DeRose <i>et al.</i> , 2011; Zhang <i>et al.</i> , 2013			NOD/SCID or SCID	Fat pad	41 (77/186)		73-228 days	Primary	(63,64)
Kabos <i>et al.</i> , 2012						41.6 (10/24)	<6 months		(65)
Petrillo <i>et al.</i> , 2012					25 (5/20)		1-3 months		(66)
Zhang <i>et al.</i> , 2013			NSG	Subcu	31.3 (10/32)	18.8 (6/32)	30 weeks		(64)
Moro <i>et al.</i> , 2012	NSCLC	FTP	Nude NOD/SCID	Subcu RC	30-40 90			Primary	(67)
Nakajima <i>et al.</i> , 2015		Cells	NSG	Subcu		42.1 (8/19)	13-144 days		(68)
Julien <i>et al.</i> , 2012	Colorectal	FTP	Nude	Subcu	54/85-20/26		59.4 days	Primary	(60)
Dangles-Marie <i>et al.</i> , 2007		Cells	NOD/SCID	Subcu-injection	84.4 (27/32)			Primary	(69)
Puig <i>et al.</i> , 2013					100 (8/8)			Metastasis (liver)	(70)
Peng <i>et al.</i> , 2013	Head-neck	FTP	Nude	Subcu		17 (5/30)		Primary	(71)
Priolo <i>et al.</i> , 2010	Prostate	FTP	Nude	RC		39 (9/23)	<3 months	Primary	(72)
			NOD/SCID			48 (11/23)			
Wetterauer <i>et al.</i> , 2015			NSG	Fat pad	37 (10/27)				(73)
Boone <i>et al.</i> , 2015	Ovarian	FTP	SCID	Subcu	65-100			Primary	(74)
Bankert <i>et al.</i> , 2011		Cells	NSG	Intra-injection	85 (34/40) 85 (17/20)		80-140 days 116-177 days	Primary (PSC) Primary	(75)
Han <i>et al.</i> , 2012	Stomach	FTP	Nude	Subcu	94 (107/114)			(Adenocarcinoma) Primary	(76)
Xue <i>et al.</i> , 2012	Pancreatic		NOD/SCID	RC	90				(77)
Pavia-Jiménez <i>et al.</i> , 2014	Kidney	FTP	NOD/SCID	RC	10-15			Primary	(78)
Mohseni <i>et al.</i> , 2014			Nude		67		13-63 days	Primary	(79)

NSCLC, non small cell lung cancer; FTP, fresh tumor pieces; cells, tumor cell suspensions; subcu, subcutaneous implantation; fat pad, mammary fat pad; RC, implanted in renal capsule; subcu-injection, subcutaneous injection of cecum; intra-injection, intraperitoneal injection; PSC, papillary serous carcinoma; NOD, nonobese diabetic; SCID, severe combined immunodeficiency; NSG, NOD SCID γ .

another study demonstrated that testing the drug sensitivity of CTC lines for clinical regimes is in accordance with the clinical treatment response (40). Drug sensitivity testing of CTCs may predict the donor patient's response and direct appropriate therapy for individualized medicine. In addition, CTC-derived xenografts have been used in the laboratory for studying certain types of cancer. One institution reported that the PDXs for small cell lung cancer (SCLC) may reflect the responses of patients to clinical regimes (34). Therefore, CTC-derived xenograft models (CDXs) may be used to detect drug resistance mechanisms.

3. Broad utility of PDXs

Individualized cancer therapy/translational medicine. PDXs are maintained by passaging tumor tissues directly from mouse to mouse. Heterotopic or orthotopic PDXs involve implanting tissues into the subcutaneous flank or the organs of mice. PDXs are considered to be superior to traditional cell line xenografts since the former may be more similar to parental tumors compared with the latter, particularly in terms of tumor, intratumor and intrametastasis heterogeneity (26). Traditional tumor models exhibit poor predictive values due to the associated heterogeneity. The development of PDXs satisfies the requirements of an effective preclinical tool, and PDXs are a predictive model of carcinogenesis physiology and clinical therapy. As genomic research develops, further subtypes of cancer are predicted. For example, five molecular subtypes of breast cancer have been characterized, studied and categorized using the Prosigna Breast Cancer Prognostic Gene Signature assay test: Luminal A, luminal B, ERBB2+, basal-like and normal-like (41). Subtypes are further divided into more detailed types for each individual in clinical practice (42,43).

In addition, studies on targeted drug treatments confirm the accurate predictive value, fidelity and stability of PDXs and PDX-associated clinical prognosis (Fig. 1A, B and C).

In 2014, Stebbing *et al* (44) established PDXs using puncture tissues derived from 29 patients with advanced sarcoma, and tissues derived from 16 of the 29 patients successfully established PDXs. According to the results of the study, 6 of the patients benefited from PDX-guided therapy. The remaining patients exhibited an association between clinical outcomes and their PDXs as demonstrated by retrospective analysis. In 2014, Elena Garralda *et al* (45) combined next-generation sequencing with PDXs to guide individualized treatments for 25 patients with advanced solid tumors. The most effective individualized drugs were selected according to the sequencing results of the PDXs. Subsequently, 14 of the 25 patients received personalized treatments, and 11 achieved durable partial remission. Subsequently, PDX models have increased in popularity.

The use of PDXs is advantageous in drug-screening and resistance mechanism research. PDXs possess an effective predictive value in targeted drug-screening for clinical treatments. The development of optimal regimes, based on drug-screening in PDXs, may improve the survival rate of patients with cancer. Furthermore, gene mutations cause tumorigenesis, particularly those in p53 and phosphatase and tensin homolog (24,46). Although gene mutations may

be identified using whole-genome sequencing, identifying the significant mutations with which specific diseases are associated remains a challenge. Therefore, Berg *et al* (47) aimed to construct a comprehensive dataset, including driver mutations, tumorigenicity variants and clinical responses, but this was discovered to be time-consuming. In addition, drug resistance mechanisms may consist of primary or acquired resistance (48). PDXs may represent intratumor and intrametastasis heterogeneity, and more accurately predict resistance mechanisms to clinical treatments. Therefore, PDXs may potentially represent a platform for evaluating personalized resistance mechanisms. Personalized medicinal strategy may become a future direction for personalized treatment and translational medicine.

Drug development. The poor predictive value of the preclinical models used to select novel drugs is partly responsible for the low success rate of novel agents in clinical application. PDXs are more predictive of clinical outcomes and possess a vast development foreground in the preclinical screening of novel anticancer drugs. Chiron *et al* (49) compared the anticancer effect of aflibercept with that of bevacizumab by using PDXs in multiple genetic backgrounds, demonstrating that aflibercept had increased anticancer functions compared with bevacizumab. Monsma *et al* (50) revealed that vemurafenib was effective in PDXs of melanoma with B-Raf proto-oncogene, serine/threonine kinase (BRAF)^{V600E} or BRAF^{V600V}. Furthermore, the combination of mitogen-activated protein kinase inhibitors and vemurafenib improved the effectiveness of anticancer therapies. Consequently, screening of the susceptibility of drugs may be effectively integrated into clinical translational medicine (Fig. 1C and D).

Coclinical trials. Coclinical trials are characterized by parallel studies between mouse models and patients, which may help determine treatment strategies for patients and to identify underlying cancer-associated mechanisms with the aid of PDXs (51,52). As cancer progresses, the drug becomes less effective and novel resistance mechanisms appear. When and how such mechanisms develop is unpredictable during clinical treatment. Drug resistance may be observed earlier with the aid of PDXs, which may assist in determining subsequent treatment regimes. GEMMs have been used in coclinical trials and exhibited positive results in parallel clinical trials (53), including those involving leukemia, melanoma, prostate cancer and non (N)SCLC (53-56). Furthermore, coclinical trials may also verify relevant hypotheses in a clinical setting and thereby affect the design of future clinical studies (57). However, this may be associated with increased costs (51). PDXs have not been used in large scale coclinical trials (38). Bertotti *et al* (38) reported that 8 patients with metastatic colorectal cancer were successfully treated using targeted PDX-based therapies combining anti-ERBB2 with anti-EGFR to predict resistance to anti-EGFR targeted therapy. Coclinical trials monitor the responses of individuals and parallel mouse models simultaneously and provide an *in vivo* model to research suspicious resistance mechanisms and test combination strategies for overcoming novel spontaneous resistance mechanisms (Fig. 1E).

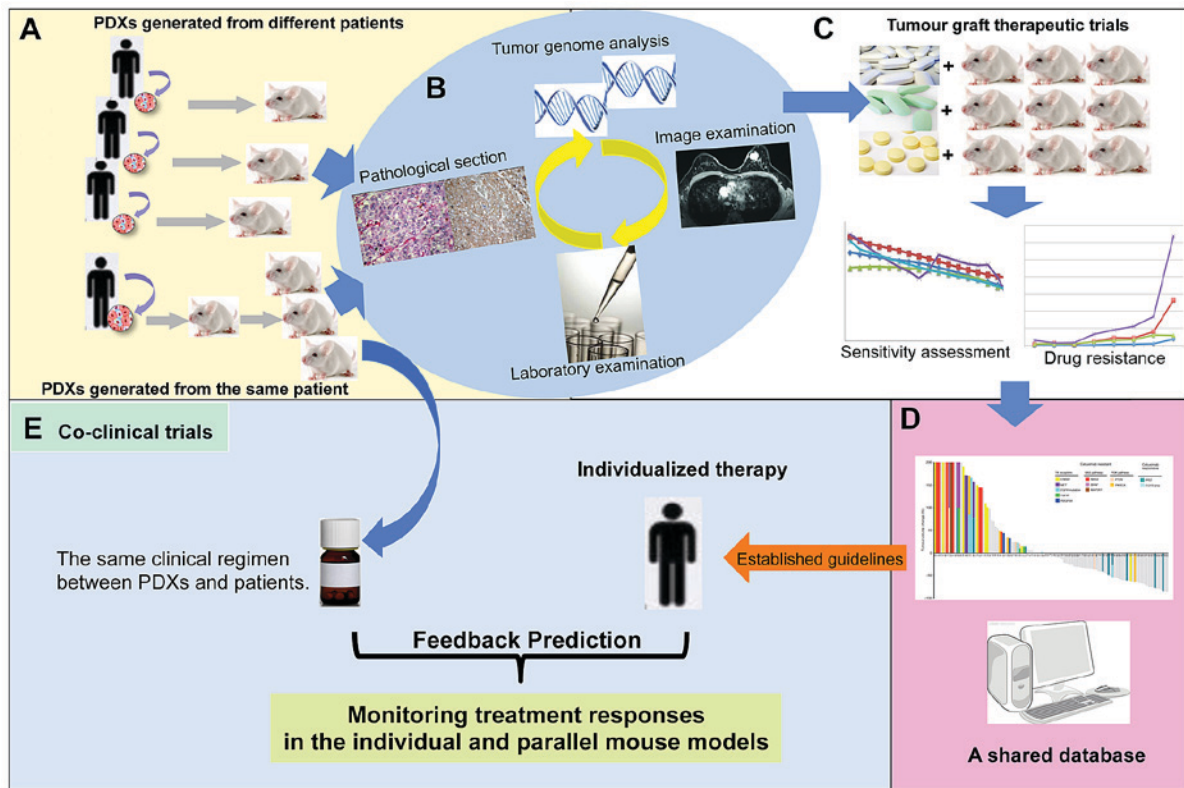


Figure 1. Concept of individualized therapy, drug development and coclinical trials. (A) Tumor graft expansion: PDXs generated from multiple patients or a single patient. (B) Overall preclinical analysis. (C) Preclinical testing of anticancer agents. (D) Establishment of a database to integrate genomic and therapeutic analyses. (E) In coclinical trials, an *in vivo* model to research suspicious resistance mechanisms in cancer cells may be developed. PDX, patient-derived xenograft.

4. Disadvantages of PDX

Though the application of PDXs in tumor research is associated with the aforementioned advantages, certain problems with PDXs remain. PDXs depend on murine immunodeficiency models, which lack functional elements of immune systems. Therefore, due to the lack of stromal cells and degradation of tissue architecture, the tumor microenvironment was virtually non-existent (58). In addition, murine fibroblasts differ from those in humans (45). Morton *et al* (59) successfully isolated CD34⁺ cells from the blood of patients and subsequently intravenously injected them into a mouse to reconstruct a functional immune system in murine models that would mimic that of patients. PDXs with patient-matched immune systems may be valuable for study, particularly when screening immune system-mediating agents.

Furthermore, less aggressive tumors exhibit decreased implantation rates and more aggressive tumors exhibit increased formation rates. For example, estrogen receptor-negative types of breast cancer exhibit increased the rate of successful tumor establishment compared with hormone-positive types of breast cancer (60). Patients with initial tumors may experience improved treatment outcomes compared with those with more advanced tumors. However, constructing a PDX model with initial tumor remains a challenge and tumor formation rate remains low. Therefore, improvement of the implantation rate is urgently required.

Developing PDXs delays treatment schedule and increases costs. Typically, at least 3 months are required to develop

PDXs that may be used for preclinical study. This is a major limiting factor for individualized medicine. Discovering the most suitable conditions for certain subtypes of cancer may decrease the duration of PDX generation. Another critical factor is cost, comprising cloned animal and whole-genome analysis cost and experimental preclinical expenses. Not all patients may be able to afford these costs. Therefore, PDXs remain technically challenging, time-consuming and costly.

5. Perspective

The Human Genome Project was launched in 1990 and has improved the understanding of the genome. However, gene function remains to be fully understood, including regulatory mechanisms and gene interactions. Under the complex background of individual differences, achieving accurate clinical use of the results of genomic analysis is challenging. Therefore, predictive models are crucial. PDXs may provide evidence to personalize clinical treatments for patients.

As aforementioned, the process of generating PDXs differs among researchers. Low engrafting rates are a major factor that restricts the personalized medicine development of PDXs. The aim of the next phase of PDX development is to identify the most appropriate conditions and methods to maximize tumor formation rates. There is an increasing trend in industry and academia to help develop PDXs. Hidalgo *et al* (61) have proposed the concept of the 'EurOPDX Consortium', which aims to establish a network of clinically relevant models of human tumors,

particularly PDXs, and share the characteristics of currently available models. Successfully establishing this shared database globally may help to acquire analogical PDXs quickly by comparing data pertaining to certain patients, thereby altering traditional concepts of clinical treatment. Individualized therapy may be converted into programmatic therapy. By comparing clinical samples with samples in the database, the optimal treatment plan may be identified from the shared database in cases where genomic characteristics are similar or consistent between patients. Thus, treatment schedule delays and high costs may cease to be limiting factors in the clinical application of PDXs. The present study suggests that PDXs may be commonly used in treating patients with cancer in the future.

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Authors' contributions

PL, ML and FL designed the review and revised the manuscript. XL and CX were responsible for manuscript drafting. All authors have reviewed the final version of the manuscript and approved it for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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