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Review Article

Animal Models in Cancer Studies: A Review of Translational Gaps to Clinical Settings

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ABSTRACT

Animal models have been the primary factor in preclinical cancer studies for decades. Despite advances in molecular biology and cell culture, translating animal findings into human trials remains challenging. The present study aimed to comprehensively assess the role of animal models in cancer studies, their contribution to the discovery of new therapies, and their success in predicting human responses. A search was conducted in the PubMed, Web of Science, and Scopus databases for English-language articles published between 2018 and 2025. Inclusion criteria were studies employing animal models (mice, rats, pigs, dogs) and xenograft models that investigated cancer development, metastasis, or treatment, with findings relevant to humans. Of the 3,247 articles found, 94 studies met the inclusion criteria and were ultimately assessed and studies. Genetically engineered mice and human tumor-derived xenograft models were the most common models. In most studies, animal models successfully predicted responses to chemotherapy and immunotherapy. The most important limiting factors included species differences in medication metabolism, differences in tumor microenvironment, and a lack of complete representation of human tumor heterogeneity. Animal models remain indispensable tools for discovering cancer therapies and understanding tumor biology, especially for assessing drug toxicity and pharmacokinetics.

1. Introduction

Cancer remains a leading cause of death worldwide, despite significant advances in diagnostic and therapeutic approaches over the past two decades[1]. Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020, and the economic and social burden of the disease on health systems is increasing[2]. There is a need to discover more effective medicines with fewer side effects, as well as to gain a deeper understanding of tumor biology, the mechanisms of metastasis, and treatment resistance[3,4]. However, basic studies on cancer cell lines (*in vitro*), although rapid and inexpensive, were unable to represent the complexities of a living organism, including the immune system, tumor microenvironment, blood vessels, and systemic metabolism[5,6]. Hence, these limitations have led to the use of *in vivo* animal models as an essential bridge between basic discovery and human clinical trials. Over the past decades, a wide range of animal models has been developed to study cancer[7,8]. These cancer studies include the most basic heterotopic xenografts, where human cancer cells were implanted under the mouse skin, to more sophisticated models such as patient-derived xenografts (PDX), which involve transplanting human tumor tissue directly into mice, and genetically engineered mouse models (GEMM), where oncogenes or tumor suppressor genes are modified[9-11]. In recent years, humanized mice have taken an important step toward greater simulating responses to immunotherapies[12,13]. The history of cancer studies is replete with both successful examples and failures in animal-to-human translation. Regarding successful

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developments, landmark pharmaceuticals such as cisplatin, doxorubicin, and trastuzumab (Herceptin) initially demonstrated efficacy in animal models before progressing to standard clinical applications therapy[14]. However, the examples of failure in *in vivo* investigations are also notable. For instance, the anticancer drug TGN1412 (an immune-stimulating antibody) was completely safe in mouse and even monkey studies, but in a phase I human trial, it caused a life-threatening cytokine storm in all volunteers[15]. Hundreds of other medicines that dramatically reduced tumor growth in mouse models have also failed to demonstrate meaningful efficacy in human trials[16]. The translational gap leads to significant time and financial costs in drug development and, most crucially, postpones access to effective treatments for patients[17]. There is a major knowledge gap due to the lack of a systematic, comprehensive, and quality-based analysis of preclinical cancer trials that can identify the true rate of translatability by model type, cancer type, and treatment class. Hence, the present study aimed to comprehensively assess the role of animal models in cancer studies, therapeutic discovery, and translation of preclinical findings into human clinical trials.

2. Search criteria

A search was conducted in the PubMed, Web of Science, and Scopus databases for English-language articles published between 2018 and 2025. The search strategy was a combination of keywords including animal model or xenograft or PDX OR GEMM AND cancer or neoplasm or tumor and translational or clinical trial or drug therapy. Inclusion criteria included *in vivo* animal studies on cancer models (mice, rats, pigs, dogs, and xenograft models), evaluation of at least one therapeutic intervention (chemotherapy, immunotherapy, or targeted drug), and availability of data comparable to human clinical trials. Exclusion criteria included *ex vivo*, *in silico* studies, narrative reviews, and studies without a control group. Titles, abstracts, and full texts and extracted data, including the type of animal model, cancer type, treatment, and main outcomes (tumor size, survival, metastasis, toxicity), were screened accurately. Of the 3,247 articles found, 94 studies met the inclusion criteria and were studied for the present study.

3. Types of animal models

3.1. Traditional xenograft and patient-derived xenograft models

The most common and oldest animal models in cancer studies are xenograft models, in which cancer cells or human tumor tissue are transplanted into immunodeficient mice, such as BALB/c, NOD, or NSG mice[18-20]. Cell line-derived xenografts (CDX) involve subcutaneous implantation of cancer cells cultured in the laboratory[21]. The CDX models are widely used for initial screening of anticancer compounds and mechanistic studies due to their high speed, relatively low cost, and good reproducibility[22]. However, a major limitation of CDX is that cancer cells lose many of the key features of the original tumor, including genetic heterogeneity, tissue structure, and microenvironment, after prolonged culture on the plate[23,24]. In contrast, PDX offered a significant advancement by directly transplanting small pieces of freshly obtained patient tumor tissue into mice, followed by serial transplants into additional mice[25,26]. The primary benefit of PDX is its ability to maintain intra- and intratumoral heterogeneity, histopathological structure, and some features of the tumor microenvironment[27]. Several studies indicated that treatment response in PDX models more closely reflects clinical response in the same patient, especially with standard chemotherapy drugs[28-30]. Recently, PDXs have been regarded as the new effective method in preclinical cancer studies, particularly for studies related to targeted drugs and treatment resistance[31,32]. The limitations of PDXs are also considerable, as PDXs are labor-intensive and costly, often requiring several months for a tumor to develop in a mouse. Furthermore, the absence of a host immune system, due to the use of immunodeficient mice, makes it infeasible to assess immunotherapies. Additionally, there is a risk that tumor clones may progressively change during serial transplantations[25,26,33]. Figure 1 illustrated evolution of preclinical mouse animal models for cancer therapy.

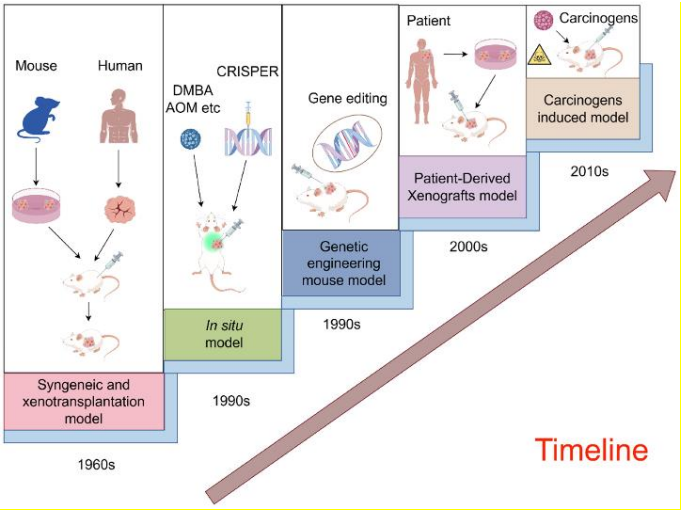

Figure 1. Evolution of preclinical mouse animal models for cancer therapy. The timeline demonstrated a distinct progression from basic subcutaneous tumor models to more advanced genetically engineered and patient-derived xenograft models, which more accurately replicate the tumor microenvironment, metastatic progression, and heterogeneous drug responses observed in human cancers. (Source: MDPI Copyright, 2024; Hildebrandt et al.[34])

3.2. Genetically engineered mouse models and humanized mice

In contrast to xenograft models, which involve implanting a human tumor into a mouse host, genetically engineered mouse models (GEMMs) adopt a fundamentally different approach[35]. In GEMM models, the mouse's own genome is altered to induce oncogenic mutations such as *KRAS*, *MYC*, *HER2*, or deletions of tumor suppressor genes, including *TP53*, *PTEN*, and *RB1*, in specific tissues or systemically[36,37]. Furthermore, GEMM models possess the distinctive advantage of accurately representing

spontaneous tumors within the original (orthotopic) tissue, alongside a complete immune response system[38]. Hence, GEMMs are appropriate models for studying the early stages of tumorigenesis, the progression from hyperplasia to invasive carcinoma, and natural metastasis (without direct injection of cells into the bloodstream), as well as for evaluating immunotherapies such as checkpoint inhibitors, including anti-PD-1 and anti-CTLA-4[39,40]. Classic examples of GEMMs include mice with a *KRASG12D* mutation in the lung, serving as a model for lung adenocarcinoma, and mice with a deletion of antigen-presenting cells (APCs) in the intestine, representing a colon adenomatous polyposis model.[41]. However, GEMMs have limitations; they are costly and time-intensive to develop and maintain often 1-2 years, possess less genetic diversity than human tumors, and often result in tumors with long latency periods and incomplete genetic profiles penetrance[42]. On the other hand, humanized mice are a newer generation designed to overcome the lack of a human immune system in PDX models and the absence of human genes in GEMMs[43,44]. In GEMMs, specific genes within the mouse genome are either activated or knocked out to induce tumorigenesis, without the need for transplantation of human cells[45,46]. Figure 2 illustrates five distinct preclinical tumor models used in cancer studies.

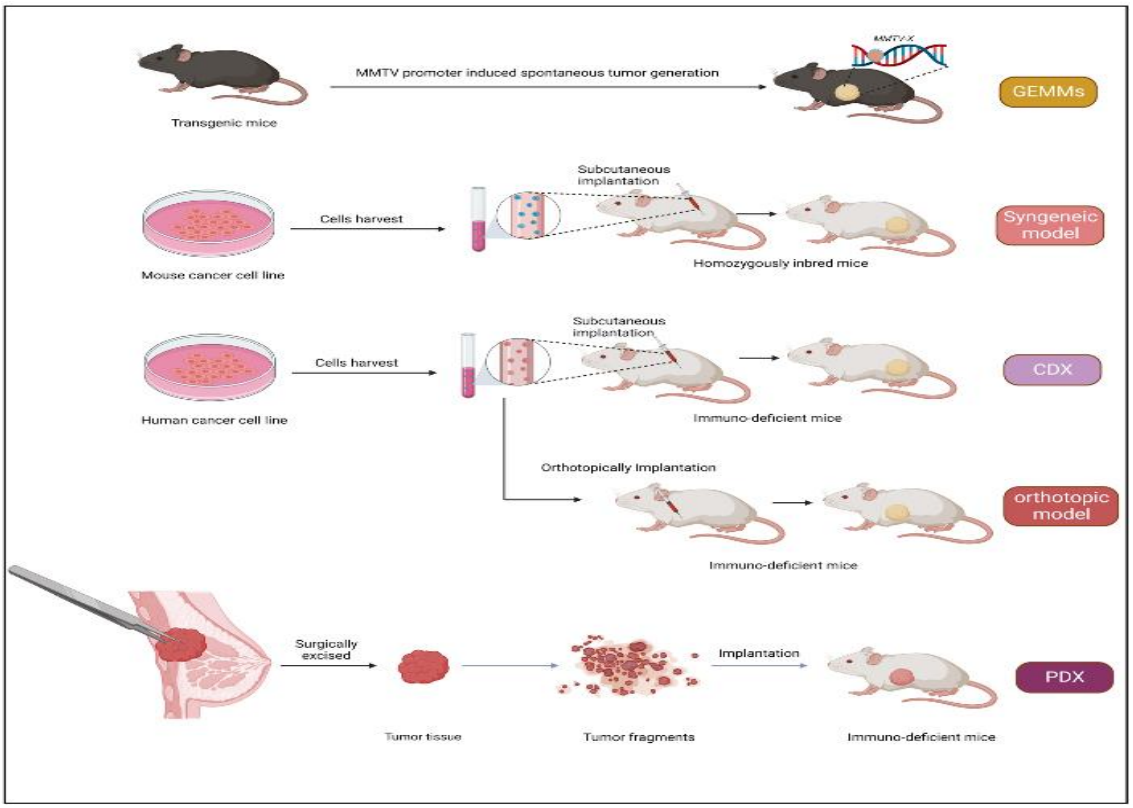

Figure 2. Generation of different mouse tumor models for cancer therapeutics (Source: MDPI Copyright, 2023; Lauber et al.[47])

3.3. Large animal models, metastasis models, and chemical models

Although mice and rats account for more than 90% of animal models of cancer, large-animal models such as dogs, pigs, and, in some cases, monkeys have a special place in certain parts of the translational chain[34,48]. Dogs naturally develop tumors such as lymphoma, osteosarcoma, and melanoma without genetic manipulation. These tumors are more similar to human cancers in their biology and response to treatment than induced tumors in rodents[49,50]. The primary advantage of canine models is their sufficient blood volume, which facilitates pharmacokinetic and toxicity studies on a scale comparable to humans. Additionally, the presence of an intact immune system in a large organism with a comparatively short lifespan enables the investigation of relapse and resistance within a practical time frame[51,52]. On the other hand, metastasis models are perhaps the most challenging type of animal model[53]. While most subcutaneous xenograft models generate localized tumors that rarely metastasize, advanced metastasis models utilize direct injection of cells into the bloodstream (injection into the left ventricle of the heart or the tail vein), the peritoneal space, or the use of highly invasive cell lines such as 4T1 in mouse breast cancer or B16-F10 in melanoma[54]. Orthotopic models, defined as tumor transplantation into the original tissue, such as breast cancer cells into mouse mammary glands, also exhibit a higher rate of spontaneous metastasis and are valuable for studying the tumor microenvironment in the original tissue [55,56]. Finally, chemical models of cancer induction, such as DMBA/TPA for skin cancer and azoxymethane for colon cancer, although less commonly used today, remain useful for studying cancer function[57]. Table 1 compares different animal models used in cancer studies.

Table 1. Comparison of animal models used in cancer studies

Model type	Description	Key advantages	Major limitations	Typical applications	Estimated translational success
Cell line-derived xenograft (CDX)	Subcutaneous implantation of cultured human cancer cells into immunodeficient mice	Rapid, inexpensive, high reproducibility, and easy to handle	Loss of tumor heterogeneity, no human stroma or immune system, subcutaneous site not orthotopic	Initial drug screening, mechanistic studies	Low to moderate
Patient-derived xenograft (PDX)	Direct transplantation of fresh human tumor tissue into immunodeficient mice	Preserves intra- and intertumoral heterogeneity, better predicts clinical response	Time-consuming (months), expensive, no immune system, gradual clonal drift	Targeted therapy testing, resistance studies, personalized medicine	Moderate to high (for chemotherapy)
Genetically engineered mouse model (GEMM)	Mouse genome modified with oncogenes or tumor suppressor gene deletions	Spontaneous tumors, intact immune system, orthotopic tissue, natural metastasis	Very expensive, time-consuming (1–2 years), limited genetic diversity, incomplete penetrance	Early tumorigenesis, immunotherapies, and metastasis studies	Moderate
Humanized mice	Immunodeficient mice transplanted with human immune cells or liver tissue	The human immune system enables immunotherapy testing, better mimicking the human response	Technically complex, expensive, variable humanization efficiency, and still imperfect immune reconstitution	Immunotherapy (checkpoint inhibitors, CAR-T), virus-related cancers	Emerging (promising)
Chemical-induced models	Carcinogens such as DMBA/TPA, AOM are used to induce tumors	Simple, reproducible, useful for prevention studies	Long latency, not all tumor types induced, less relevant for human genetics	Chemoprevention, early carcinogenesis	Low
Large animal models (dogs, pigs)	Naturally occurring tumors in dogs or genetically modified pigs	Intact immune system, sufficient blood volume for PK/PD, similar biology to humans	Expensive, ethical concerns, limited availability, and genetic outbred variability	PK/PD studies, toxicity testing, FDA-required validation	Moderate to high
Metastasis models (orthotopic, injection)	Tumor cells are injected into the orthotopic site or the bloodstream	Allows study of metastatic cascade, more clinically relevant	Technically challenging, may not recapitulate natural metastasis, high variability	Metastasis mechanisms, anti-metastatic drugs	Moderate

CAR-T: Chimeric antigen receptor T-cell, PK/PD: Pharmacokinetics/Pharmacodynamics, FDA: Food and Drug Administration, DMBA: 7,12-Dimethylbenz[a]anthracene, TPA: 12-O-Tetradecanoylphorbol-13-acetate, AOM: Azoxymethane

4. Roles of animal models in cancer treatments

4.1. Classical chemotherapy, targeted drugs, and toxicity screening

Animal models have played a pivotal and undeniable role in the discovery and development of almost all anticancer drugs for several decades[34,58]. In the field of classical chemotherapy, cyclophosphamide, doxorubicin, cisplatin, and paclitaxel (Taxol) first demonstrated significant antitumor effects in mouse models, typically leukemia xenografts or solid tumors, and were then used in established human treatment protocols[59,60]. Animal models primarily served two key functions; first, screening the efficacy of hundreds of new chemical compounds to identify those with potential; second, assessing toxicity and establishing the initial safe dose for progressing to human phase 1 trials[34,61]. Moreover, GEMM models have been used not only for efficacy assessment but also for target identification and validation[62]. For instance, mice with *BCR-ABL* mutations or *HER2* overexpression were the first platforms to demonstrate that inhibition of this molecular pathway leads to tumor regression[63]. However, the translational gap for targeted drugs has been observed more frequently than in chemotherapy; many kinase inhibitors that significantly reduced tumors in mice subsequently failed in humans due to primary or acquired resistance[64,65]. Hence, animal models are inadequate for predicting intrinsic and microenvironmental resistance in humans, and more advanced models, such as PDX and humanized mice, are needed[20,66].

4.2. Immunotherapy and pharmacokinetic/pharmacodynamic studies

In current oncology investigations, immunotherapy, particularly checkpoint inhibitors such as pembrolizumab (anti-PD-1) and ipilimumab (anti-CTLA-4), has significantly transformed cancer treatment[67]. Animal models have played a dual role in immunotherapy; on the one hand, synthetic mouse models (GEMM and homograft) with complete immune systems enabled the initial study of these antibodies and demonstrated that blocking PD-1 could restore antitumor immune responses[68,69]. Additionally, due to significant differences between the mouse and human immune systems, including antibody affinity for receptor binding and immune cell composition, it became necessary to test these medicines in humanized mice or PDX models with co-transplantation of human lymphocytes[12,20,46,70]. Humanized mice or PDX models have demonstrated the ability to predict immune-related adverse effects, including cytokine storm, pneumonitis, and colitis, to a greater extent than in conventional mice[71].

Animal models remain one of the oldest and most crucial tools, with no current alternatives, for pharmacokinetic (PK) and pharmacodynamic (PD) studies[72,73]. Rodent and then large-animal models (dogs

and monkeys) are considered the most suitable for determining drug half-life, volume of distribution, hepatic metabolism (cytochrome P450S are the major species-specific determinants), renal excretion, and the therapeutic index[74]. Regulatory agencies such as the Food and Drug Administration (FDA) indicated that any new anticancer medicines should provide PK/PD data in at least two mammalian species, particularly mice and dogs or mice and monkeys, before they are approved for human use[75].

5. Translational gap

The translational gap between animal studies and human clinical trials is one of the greatest challenges in cancer medicine development, and many anticancer medicines that succeed in mouse models ultimately fail or prove insufficiently effective in humans[76,77]. The first and most important factor in the translational gap is species differences in medicine metabolism[78,79]. Cytochrome P450 family enzymes, which are responsible for phase I metabolism of medicines, differ significantly between mice and humans in their isoforms, expression levels, and patterns of induction and inhibition[80,81]. For instance, mice generally metabolize drugs more rapidly and have shorter half-lives, requiring higher doses and more frequent administration, whereas the same metabolic pathways may produce toxic or inactive metabolites in humans that are not observed in mice[82,83]. The second factor is the difference in the tumor microenvironment between humans and animal models[84]. Human tumors grow in a complex stroma consisting of cancer-associated fibroblasts, endothelial cells, tumor-associated macrophages, and extracellular matrix that is fundamentally different, both cellularly and biochemically, from the microenvironment of subcutaneous mouse tumors[85]. In subcutaneous xenograft models, the tumor grows in a foreign tissue (subcutaneously), and murine stroma replaces human stroma, leading to major changes in signaling, angiogenesis, and therapeutic response[11,43,86]. A third critical consideration is the inadequate representation of the heterogeneity inherent in human tumors within conventional animal models[87]. A human tumor contains diverse cell populations with different mutations and phenotypic characteristics (inter- and intratumoral heterogeneity), while CDX models originate from a single clonal cell line, and even PDX models retain some of the original subclones (especially those with a growth advantage in mice) and lose others after several generations of serial transplantation[88-90].

6. Conclusion

The present study indicated that animal models remain vital and indispensable resources in cancer drug development, particularly for toxicity assessment, pharmacokinetics, and preliminary efficacy evaluation. Their capacity to predict human responses remains reasonably reliable. However, for more complex therapies such as targeted drugs and immunotherapy, conventional rodent models have low translation success rates. The persistent translational gap, attributable to species differences in metabolism, tumor microenvironment, and heterogeneity, remains a significant challenge, further compounded by methodological limitations, including the lack of randomization and blinding. The final suggestion is that, instead of relying solely on a specific model, researchers should use hybrid approaches (PDX with humanized mice, orthotopic models, and complementary non-animal systems such as organoids and organs-on-a-chip). Only by fundamentally improving the design of animal studies and intelligently combining them with new technologies can the translational bridge between mice and humans be strengthened, avoiding the waste of huge amounts of time and resources on fruitless research paths.

Declarations

Authors' contributions

Parichehr Ebrahimi Shahabadi, Sima Saravani, and Mohammad Ali Nazmabadi Nezhad drafted the manuscript and worked on the methodology. All authors read and approved the final edition of the manuscript before submission. All authors checked and approved the final edition of the manuscript for publication in the present journal.

Availability of data and materials

All datasets are available upon request from the corresponding author.

Competing interests

The authors declared that they have no competing interests.

Ethical considerations

All the authors checked and confirmed that ethical concerns, such as plagiarism, permission to publish, research misconduct, data fabrication or falsification, duplicate submissions, and redundant publication, have been thoroughly reviewed. No AI-assisted technologies were used in the generation of this manuscript.

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