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Present-Day Difficulties in Treating Cancer

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Abstract:

Cancer is a complex disease, characterized by genetic heterogeneity, rapid mutations, and the ability to develop resistance to drugs, which compromises the effectiveness of therapeutic development. The limitations of animal models, particularly murine systems, are discussed in this paper. Although these models are the backbone of cancer research, they fail to replicate the complexities of human cancers, including genetic diversity, interactions between the immune system, and tumour microenvironments. These differences contribute to the high rate of failed preclinical findings being translated into successful clinical outcomes. Key issues are explored in detail, showing how they impact the reliability and relevance of study findings. These are tumour heterogeneity, chemoresistance, drug metabolism variation, and inadequacies of animal tumour microenvironments. Innovative techniques providing a more realistic picture of human diseases, such as organoids, genetically edited mice models (GEMs), and patient-derived tumour xenografts (PDTXs), are highlighted as promising alternatives. The review also encourages ethical progress and regulatory facilitation of non-animal approaches while emphasizing the importance of the integration of computational tools, artificial intelligence, and personalized preclinical models to enhance the predictability of research. By overcoming these challenges and using innovative approaches, this review demonstrates the potential to bridge the translational gap in cancer research, which would further increase the precision of preclinical models and accelerate the development of novel cancer treatments.

Keywords: Cancer, Genetic Heterogeneity, Rapid Mutations, Animal Models, Genetic Diversity, Immune System Interactions, Tumor Microenvironments, Heterogeneity, Chemoresistance, Drug Metabolism, Microenvironments, Patient-Derived Tumor Xenografts (PDTXS), Genetically Engineered Mouse Models (GEMS).

1. INTRODUCTION

Cancer is one of the most challenging and diverse diseases despite intensive development in the approach of treatments. It is difficult to tackle because of its unpredictable course and tendency to offer resistance to the treatments. Animal-based models have been crucial for long in cancer research since they form the main platform

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used to investigate resistance mechanisms, research into tumour biology, and testing of new drugs. Although animal models, especially murine systems, have significantly advanced our knowledge of cancer, they have not been able to accurately capture the complexities of human diseases. The species variations between people and animals are one of the main obstacles, leading to disparities in the behavior, progression, and response to therapy of malignancies [1]. This shows that the complexity of human tumours, with its immense variety, cannot be appropriately mimicked in tumours developed in animal models, such as genetically engineered mice. This also illustrates the limitation of using animals for research when predicting the effectiveness of therapy, because though treatments appear to be efficacious in animals, they often do not quite translate to a similar level of efficacy in humans. It may be difficult to assess the effectiveness of therapies, particularly those targeted towards the immune system or new drug delivery systems, because the microenvironment of cancer in animals may not mimic that in humans.

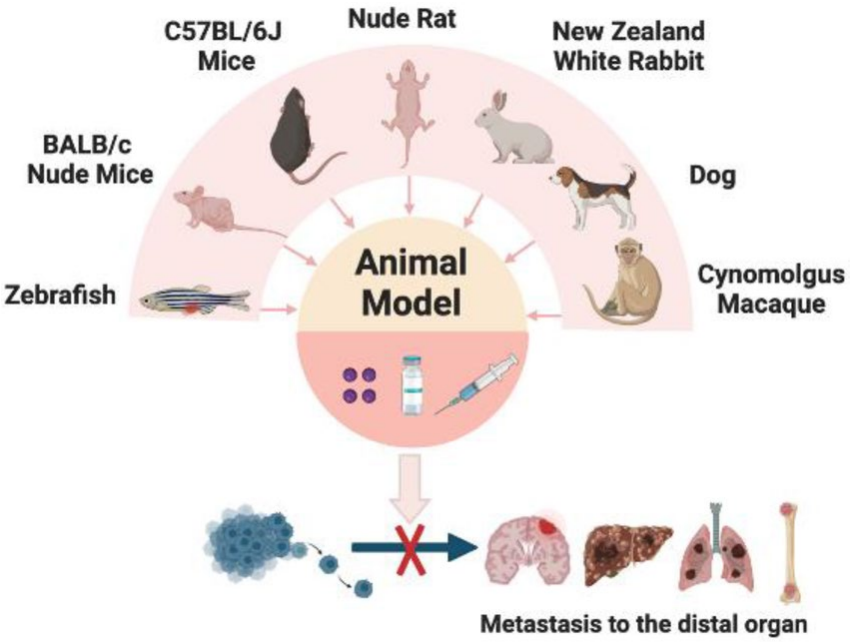

Figure 1: Treatment of cancer metastases and administration location using animal models [2]

Another reason the use of animal models in research on cancer treatment is criticized is because of inherent limits in extrapolating findings from animal models to people. Even though animal models have proved quite useful in testing the fundaments of cancer biology and methods of treatment, it has often been observed that many drugs that are effective in animals—this is particularly so when looking at tumour shrinkage or early

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ISSN: 3049-3757 | Vol. 01 Issue 01, February 2025 | pp. 60-79

responses—have failed to produce long-lasting remission or increased survival in human clinical trials. Different species' biological characteristics, such as genetic makeup, immunological response, and the tumour microenvironment, may significantly affect the distribution, metabolism, and interaction of anticancer drugs with the tumour [3]. The limited genetic diversity exhibited by most animal models, such as inbred mouse strains, does not reflect the diverse genetic changes found in human cancers, which are critical for understanding the processes of tumour progression and resistance to treatment. This lack of diversity may be able to provide a partial image of the efficacy of possible treatments, which might distort results. There has also been a reevaluation of the continuing reliance on animal-based research as a result of ethical concerns over the use of animals in testing and increasing awareness about the need for more human-relevant models. That is, now, the focus is on making more complex, human-like systems that can bridge the gap between preclinical discoveries and clinical application, even though animal models of cancer may continue to be used.

1.1. Background Information

Over the past decades, proper approaches to treating cancers have witnessed significant development. Such treatments include immunotherapy, radiation therapy, and chemotherapy, which are now all part of cancer care. Still, their effectiveness is limited by the disease's progression. The main reason behind such a limitation is the complexity and heterogeneity of malignant tumors, including characteristics like genetic instability, rapid mutation, and responsiveness to treatment [4].

Preclinical cancer research has heavily relied on animal models, including murine models, which allow researchers to explore the biology of tumours and evaluate potential therapies. Yet it has become increasingly clear that results of findings from these models are not directly transferable to humans. While informative, tumors in animal models often do not recapitulate all the conditions of cancers in humans. Animal models thus remain an important component of cancer research but have many limitations.

1.2. Objectives of the Review

- To assess the key challenges faced in using animal models for cancer treatment development [5].
- To critically evaluate the methodologies employed in cancer research using animal models.
- To explore future research directions to improve the utility of animal models in oncology.

1.3. Importance of the Topic

Closing the gap between animal-based cancer research and human clinical applications is an aspect that cannot be overestimated; one of the biggest barriers in the development of cancer treatments remains the failure to convert promising animal model results into human medicines. Although animal models have provided invaluable information about tumour biology, mechanisms of therapy, and drug efficacy, a significant proportion of clinical trial failures has been due to the

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inability of animal models to faithfully recapitulate the complexity of human cancer, including genetic heterogeneity, immune system differences, and variations in the tumour microenvironment [6]. By recognizing and reconciling the fundamental limitations of research in animals, this review seeks to outline what these factors are in creating disparities, along with any potential paths towards increasing the usefulness and forecasting abilities of preclinical models. From these understanding issues and looking for new methods by which animal models may be improved, scientists could create more effective therapy regimens against cancer, enhance the association of laboratory studies with human oncology practice, and better serve the needs of the patients.

2. KEY RESEARCH STUDIES ON CANCER TREATMENT CHALLENGES IN ANIMAL MODELS

This includes some of the studies which have raised some of the substantial difficulties in using animal models to create efficient cancer treatments. Such problems are significant in cases where preclinical research needs to be converted into effective clinical treatment. Chemosensitivity and drug resistance, tumour heterogeneity and tumour microenvironment are currently trending topics within the study of cancer [7].

Table 1: Reference Table

References	Title	Topic Covered	Research Study
Hegde and Chen (2020) [8]	Top 10 challenges in cancer immunotherapy	Immunotherapy challenges, immune evasion, immune checkpoint regulation, tumor heterogeneity, and immune suppression	The study focused on the challenges in cancer immunotherapy, particularly issues like immune evasion by tumors, checkpoint regulation, and translating animal model findings into human therapies.
Hoarau-Véchot et al. (2018) [9]	Halfway between 2D and animal models: Are 3D cultures the ideal tool to study cancer-microenvironment interactions?	Limitations of 2D and animal models, advantages of 3D cell cultures for mimicking tumor microenvironment (TME)	This study explored the use of 3D cultures as more accurate models to study cancer progression, tumor biology, and drug responses, addressing the limitations of traditional 2D and animal models.
Hua et al. (2018) [10]	Current trends and challenges in the	Clinical translation of nanomedicines,	This research focused on the challenges of

	clinical translation of nanoparticulate nanomedicines	nanoparticle optimization, drug delivery, species differences in metabolism	translating animal model findings on nanoparticulate nanomedicines to clinical use, highlighting issues like drug metabolism differences and immune response.
Kashyap et al. (2021) [11]	Natural product-based nanoformulations for cancer therapy: Opportunities and challenges	Natural product-based therapies, bioavailability, toxicity, regulatory hurdles in clinical translation	This study reviewed the use of natural product-based nanoformulations in cancer therapy, identifying challenges in their clinical translation, such as bioavailability, toxicity, and regulatory hurdles.
Khan et al. (2019) [12]	Anticancer plants: A review of the active phytochemicals, applications in animal models, and regulatory aspects	Plant-derived compounds, anticancer properties, regulatory concerns, variability in chemical composition	This review focused on plant-derived anticancer compounds, their efficacy in animal models, and the challenges of translating these therapies into clinical practice due to regulatory and safety concerns.

- **Tumor Heterogeneity**

Tumour heterogeneity remains one major barrier to cancer research. Human tumors, even of the same kind of cancer, are notoriously variable in terms of both phenotype and genetic composition. The effects of the tumor microenvironment, epigenetic modifications, and genetic abnormalities all contribute to this heterogeneity. Predicting how a treatment will work is difficult because the cells of tumors frequently have unique molecular profiles and functional behaviors. Nevertheless, most animal models—especially inbred mouse strains—cannot adequately reflect this diversity. Inbred mouse strains cannot represent the genetic heterogeneity present in human populations since they are genetically similar [13]. This constraint may then lead to an oversimplification of cancer dynamics in animal models by not being able to mimic the

numerous mutations and changes observed in human tumours because they cannot. For instance, a genetically engineered mouse model may not have the genetic diversity present within human tumors. Yet it may be showing encouraging outcomes in terms of tumor regression. But this could lead to inappropriate assumptions in larger patient populations about how the individual treatment would actually work. Lack of genetic variation, which makes animal models unable to satisfactorily reflect the complexity of human tumors is another factor that makes these systems ineffective to evaluate the efficacy of treatments.

- **Chemoresistance and Drug Resistance**

The other significant problem in cancer therapy is chemoresistance, or the ability of tumours to become resistant to chemotherapy and other forms of cancer treatment. While many animal models exhibit initial drug sensitivity, resistance mechanisms can rapidly be acquired by tumours, rendering previously effective treatments useless. Lung, breast, and colorectal cancers are among the types of cancers that show this pattern. Indeed, studies have shown that in the initial stages of treatment, mice models, be it for lung or breast cancer, commonly indicate tumor shrinking or slowed growth with chemotherapy or targeted drugs. Like in real patients, the tumors within these models tend to eventually become resistant as well. For example, in one study that examined how chemoresistance develops in mouse models of lung cancer, tumours initially responded to chemotherapy drugs such as cisplatin [14]. However, these tumours rapidly developed Defence mechanisms against the drug's effects, including increased drug efflux, altered drug metabolism, and DNA repair mechanisms. Since the resistant strains that arise in animals may not precisely mimic the resistance mechanisms which have been noticed in human patients, such resistance mechanisms in animal models often fail to predict the long-term success of chemotherapy in humans. This is also the reason behind the high clinical trial failure rates despite promising preclinical results highlight just how hard it is to translate research findings from animal models into successful treatments in humans.

- **Tumor Microenvironment**

Tumour cells, stromal cells, immune cells, blood vessels and extracellular matrix constituents comprise this complex and dynamic TME, which has made it a promising target for different therapeutic approaches considering its involvement with the process of tumour growth, metastasis, and chemoresistance among others. Though, in particular, the majority of animal models fail to realistically replicate the multifaceted connection between the tumor and its microenvironment. More particularly, animal models often do not mimic the hypoxic conditions, immunosuppression, and vascular dysmorphias commonly observed in human cancers [15]. For instance, hypoxic areas in human tumors can lead to poor drug delivery and increased radio- and chemo-resistance. Other immune suppressive elements include tumor associated macrophages, regulatory T cells, and myeloid derived suppressor cells

(MDSCs). However, these features of the human TME are not fully recapitulated by many animal models, particularly those employing xenografts or genetically engineered mice. It is hard to test immune checkpoint inhibitors and other immunotherapies since, while numerous mouse models of breast cancer manifest immune suppression in the TME, they commonly fail to manifest the extent of immune evasion typical of human cancers. The inability to predict how therapies will function in humans limits their ability to use animal models, especially in the case of immunotherapies and treatments that target elements of the tumour microenvironment, because no completely functional TME exists.

2.1. Methodologies Used in Animal-Based Cancer Research

Animal models are still heavily used for preclinical cancer research, as they provide fundamental information on the biology of cancer, its treatment processes, and possible therapeutic efficacy. Despite these limitations, animal models are crucial in finding a feasible therapeutic opportunity, understanding tumour progression, and exploring novel therapeutic modalities. A wide range of approaches have been developed to make cancer research on animals more precise and applicable. Following are some of the most popular methods in the field:

- **Xenograft Models**

In xenograft models, human tumour cells or tissues are transplanted into immunocompromised mice, who are extremely vulnerable to engraftment because they lack functional T cells, B cells, and sometimes natural killer (NK) cells. These models are crucial in understanding the biology of human cancer and evaluating possible treatments because they enable researchers to see how real tumors grow and behave in a living creature [16]. Xenograft models are often used to evaluate the effectiveness of immunotherapies, targeted treatments, and chemotherapy. The major advantage of xenograft models is that they allow for the direct assessment of human tumours in an in vivo environment, providing more biologically meaningful data than conventional cell culture models. For example, because a xenograft accurately reproduces a situation found in real tumors, such as the response of a tumor to therapy, drug absorption, distribution, metabolism, and excretion (ADME) in a living organism, it is often used when testing anti-cancer therapy candidates.

Xenograft models, however, have several important disadvantages. Probably the most significant disadvantage is that such models cannot replicate human immunological responses faithfully. The immune system responds to xenografted human tumours differently from how it would in a human body because these are usually transplanted in immunocompromised mice. This is a very serious disadvantage, especially for immunotherapies that rely on the body's defenses to fight the cancer cells. Further, since xenografts do not possess the full range of stromal cells, vascular networks, and immune cells that are responsible for tumor

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progression and drug resistance in humans, they cannot truly reflect the complexity of human tumor biology. Thus, xenograft models fail to represent the complexity of actual malignancies, mainly in terms of immune interactions and variables in the tumour microenvironment, though they provide useful information relating to tumour growth and efficacy in therapy [17].

- **Genetically Modified Mouse Models**

Genetically modified mice models are utilized for inducing particular cancers, typically by the elimination of tumor-suppressor genes or mutation induction. This calls for these models to research the genetic pathways of cancer underlying this condition as well as the role particular mutations play in the development of this cancer. One of the most popular genetically engineered models is the spontaneous cancer model, such as the p53 knockout mouse, which develops lung cancer after the p53 gene that is an important tumour suppressor gene. More additional genetically engineered models include conditional knockout models that allow manipulating gene expression location and time or transgenic mice with mutations to either oncogene or tumour suppressor genes. This also results in the frequent genetic changes noted in human tumours, so these models represent a more realistic depiction of the genetics and carcinogenesis of human cancer.

Another one of its strengths lies in the replication of the human genetic abnormalities and oncogenic pathways responsible for inducing cancer by the genetically modified mouse models. Because of this reason, it is highly suitable for tumor biology, metastasis, and therapeutic resistance research studies. For instance, the mutant mouse model K-Ras has often been applied to study the case of pancreatic cancer, wherein the KRAS gene alterations have often been implicated. In addition, the HER2-overexpressing mouse model is used for studying breast cancer because HER2 amplification represents a common cause of human breast cancer. Using such models, one could assess new medicines and identify possible therapeutic targets within a genetic environment that closely approximates human disease [18].

Genetically modified mouse models have several disadvantages, however. They often fail to represent the complexity of human tumors, although they are genetically more specific than xenograft models. For example, the genetic background of inbred mouse strains might limit studies of tumor heterogeneity, and tumors grown in mice may be more uniform even though the genetic mutations may be the same as those reported in human cancers. Moreover, while genetically engineered mice can mimic many aspects of the biology of human cancer, they often fail to duplicate all the complexity of the human immune response. For instance, the immunological profiles of murine models, which are generally disparate from those of humans, may well influence the results of immunotherapy trials. Besides, these models do not necessarily portray the entire range of human cancer subtypes, especially when multiple mutations or environmental variables are in question, even though they

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ISSN: 3049-3757 | Vol. 01 Issue 01, February 2025 | pp. 60-79

might allow the investigation of specific genetic mutations.

- **Patient-Derived Tumor Xenografts (PDTXs)**

Compared to the traditional xenografts, patient-derived tumour xenografts, or PDTXs, directly introduce human tumors into immunocompromised mice, which provides a more biologically accurate model of cancer. The direct collection of samples from human patients, usually through biopsies or surgical resections, followed by implantation into mice where they proliferate and spread throughout a living body, comprises the PDTX models. This approach has become increasingly popular as it offers a more realistic image of human cancer and retains the genetic and histological features of the original tumor. Since PDTXs retain the heterogeneity of the original tumor, including the cellular components and genetic profiles, they are extremely useful for research into cancer subtypes [19].

The capacity of PDTX models to mimic the biochemical and genetic diversity found in human tumours is one of their main advantages; this makes the model more clinically relevant for therapy testing. The effectiveness of targeted therapies, immunotherapies, and combination treatments is frequently assessed using PDTXs because they offer a clearer picture of how these treatments function in tumour environments that are similar to those of humans. In addition, PDTXs allow for the study of cancer metastasis as the tumors grown in mice contain the capability of metastasizing and producing secondary growths, thus researchers can follow the process of metastasis in real-time in vivo.

However, although these models offer some advantages, there are still various limitations in PDTX models. One main limitation is related to interspecies variation in metabolism and immune response. The metabolic profile of mice, particularly the immunocompromised mice that are often used in PDTX studies, varies significantly from that of humans. Such variation might be able to influence drug absorption, distribution, and elimination. Furthermore, the immune systems of mice are highly divergent from that of human and since the immunodeficient mice's immune systems are not well developed, the immunological-related reactions of cancer treatment could not be represented correctly. Finally, as the PDTX models require real patient tumour tissue and the tumors often take much longer to engraft and grow than the xenografts, they are cost and time-intensive to establish.

2.2. Limitations of Animal Models in Translating to Human Treatment

The main reliance of cancer research has been on animal models, such as mice and rat models. However, these models have several shortcomings that explain why it is quite challenging to transform the preclinical findings into human treatments. The main limitation is the physiological and genetic differences between humans and animals. For instance, how drugs interact with the tumour itself and its reaction to a treatment are influenced by the way rats metabolize drugs, have unique immune system responses, and

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have diverse tumour biology. Such species-specific differences may cause a drug that had very promising effects in the mouse model to not have similar promise in human clinical trials [20]. Rodents' immune responses, especially in immunocompromised models, are significantly weaker than those of humans. Because of this, immune-based therapies, such as checkpoint inhibitors, which are increasingly employed as a key component of cancer therapy, often do not work as well in mice. The complexity of human cancers, which typically constitute a rich and heterogeneous tumor microenvironment (TME) containing immune cells, fibroblasts, blood vessels, and extracellular matrix components, may also be hard for tumors in animal models to mimic. These interactions are often not completely reproduced in animal models even though they are crucial for medication resistance and cancer progression, especially in genetically homogeneous strains or tumour cell lines.

One major limitation of animal models is that they cannot accurately mimic the complete spectrum of heterogeneity seen in human tumors. The genetic diversity of human cancers often underlies tumor development and drug resistance. However, this diversity is not captured by most animal models, which instead utilize genetically uniform tumour cell lines or genetically altered mice. This means that in actual patients, for example who frequently have tumours with a variety of mutations, a cancer medication that works well in a genetically homogeneous tumor model might not work. Furthermore, the vast array of mutations and epigenetic changes seen in human tumors are usually not reproducible in animal models. Because human tumors are genetically complex and adaptive, drugs that appear effective in preclinical studies may fail in human trials due to the absence of tumour heterogeneity. In addition, differences in enzyme profiles, absorption, distribution, and excretion processes limit the predictive validity of animal models for human drug metabolism. The toxins of drugs may be different, and their potencies may vary when administered to humans because the metabolic methods of drugs are different in animals. Chemotherapy drugs, for example, which work well in animal models, may metabolize too quickly or too slowly in people, possibly limiting its therapeutic effectiveness. These metabolic variances and shifts in the gut microbiota may make animal models less predictive. While highly species-specific, the influence of the microbiome on drug metabolism is seldom considered in conventional animal model research despite increasingly being recognized as an important aspect of cancer therapy outcomes [21].

The given above further highlights the constraints in the easy translation of results from animal models into effective treatment practices in humans. Animal models do not accurately reproduce human cancer experience as a result of species variation and metabolic abnormalities or heterogeneity. This remains to be a persistent challenge to devising effective therapies, though essential in the exploration of cancer today. Researchers are trying more complex models, including organoid systems, patient-derived

ISSN: 3049-3757 | Vol. 01 Issue 01, February 2025 | pp. 60-79

xenografts, and humanized animals, to overcome the challenges. Such models may provide a better predictive value of the preclinical outcomes and give a more accurate representation of the biology of human cancer. Nonetheless, the existing disparity between clinical success and animal-based research emphasizes the necessity of more reliable and human-relevant models to close the gap between preclinical research and clinical cancer therapeutic application.

2.3. Advances and Alternatives in Animal-Based Cancer Research

Recent advances in the field of cancer research have yielded more complex models of animals overcoming some of the major drawbacks in conventional models. One of these innovations is in the development of genetically engineered models (GEMs) made possible through CRISPR-type gene-editing technology. Through GEMs, researchers may make more accurate imitations of genetic alterations that exist in actual cancers, because particular mutations can now be introduced exactly. GEMs are especially useful in personalized medicine, where they can predict human treatment outcomes more accurately by revealing how specific mutations affect the development of cancer and how tumors respond to treatments. By genetically engineering animals to develop cancers that closely resemble human tumors, scientists can better study the effects of therapeutic interventions on particular genetic drivers and design more targeted and effective treatments [22].

Other viable alternatives to traditional 2D cell cultures are organoids and 3D cell cultures. Organoids are relatively small in size, similar in shape, and functional to human tissues. They are produced from human cells. These models include genetic and cellular heterogeneity seen in human cancers as well as better recapitulating TME. Because organoids more biologically realistically mimic the interactions of tumors with surrounding cells and tissues, they enable more reliable testing of treatment responses. This paradigm has further potential as the ability to produce patient-derived organoids provides a platform for individualized cancer treatment and the chance to test treatments that are specific to the genetic composition of a patient's tumor. Similarly, 3D cell cultures that culture cells in a scaffold to mimic the in vivo environment also help in improving the predictability of drug efficacy by mimicking important aspects of human tumors.

Developments in immunocompetent models, or mice with completely functional immune systems, have furthered the improvement of research in tumor-immune interactions, which is necessary for developing immunotherapies. The environment of human immune responses can be closely emulated in these models, in which the interaction between the immune system and cancer may be studied as well as the efficiency of the different immunotherapies such as checkpoint inhibitors. Immunocompetent models are an absolute must for researching how tumors avoid immune detection and eventually become resistant to immunotherapies. To improve techniques in immunotherapy and address problems with immune suppression in the tumor microenvironment, the link between the tumor and the immune system

ISSN: 3049-3757 | Vol. 01 Issue 01, February 2025 | pp. 60-79

should also be studied in these models. Even larger, more complex models, such as non-human primates, are now under development for even better representations of human immunology [23]. These models will help test new immunotherapeutic strategies and provide deeper insights into the immune response to cancer. Together, these advancements represent a significant leap forward in cancer research, providing more accurate, human-relevant platforms for studying tumor biology, testing therapies, and improving treatment outcomes.

3. ISSUES WITH DRUG TESTING AND RESPONSE IN ANIMAL MODELS

There are still some problems in the evaluation of effective novel cancer treatments and in predicting their success in human patients despite the use of animal models in preclinical cancer research [24]. Among these issues, difficulties stand out during the assessment of immunotherapies, radiation, and chemotherapy because they have variable resistance levels, unpredictable outcomes, and inconsistent reactions in animal models.

Figure 2: Investigating substitutes for animal experimentation in medication development [25]

3.1. Chemotherapy and Radiation Resistance in Animal Models

While radiation and chemotherapy remain the cornerstones of treatment for most cancer types, mechanisms of tumour resistance often limit their effectiveness. For decades, animal models have been used to study the efficacy of these treatments, but one of the major limitations of these models is their inability to accurately recapitulate the resistance mechanisms observed in human patients. Tumours in many animal models initially respond to radiation or chemotherapy but often become resistant with time. These can occur through mechanisms such as the

ISSN: 3049-3757 | Vol. 01 Issue 01, February 2025 | pp. 60-79

overexpression of genes involved in cell survival and proliferation, the activation of drug efflux pumps that remove chemotherapeutic chemicals from the cells, and improved DNA repair [26].

Translation of these findings to people is difficult because animal models, especially genetically homogeneous mouse strains, cannot necessarily represent the whole spectrum of resistance mechanisms that exist in human tumours. Although rodent models of specific cancers, such as lung or breast cancer, might offer critical information on how a particular type of cancer responds to treatment at an initial stage, they might not be able to mimic the adaptive resistance that eventually develops in human patients. The difference is particularly alarming when chemotherapy and radiation are the primary treatments for malignancies. Even though preclinical results were promising, chemotherapy's poor success in clinical trials underlines the challenges of overcoming resistance and improving outcome predictability. Moreover, factors such as hypoxia, immunological suppression, and altered blood supply contribute to resistance and failure of treatment in human tumours, which are more complex than the TME in animal models [27].

3.2. Immunotherapy Challenges in Animal Systems

Patients with cancers that are not responsive to standard treatments now have new hope thanks to the revolutionary advancement of immunotherapy. However, the study of immunotherapies through animal models poses special challenges. The principle of immunotherapies such as CAR-T cell therapy and immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors) lies in the capacity to induce the immune system to recognize and destroy tumor cells. Results of such treatments in patients are often erratic, although critical insights into basic mechanisms underlying the tumor-immune interaction came from animal models, particularly from immunocompetent mice [28].

One of the biggest issues with animal models is that there is significant variation in the function of the immune system between species. Mice and other common animal models have immune systems that are very different from humans in terms of regulation of immunological checkpoints and the types of immune cells involved in the response. Because of variations in the expression and function of immune checkpoint proteins, for example, some immune checkpoint inhibitors may work well in mice but not as well in clinical trials including humans. Most often, animal models do not serve very well to realistically replicate the complexity of the immune context within human cancers, where a sophisticated immune system environment is also compromised by strategies for immune escape, tumor immunosuppression, and more, through defective functions of a dysfunctional tumour microenvironment [29].

This is further evidenced by the possibility that the dynamic nature of the human immune responses cannot be captured in animal models in their interactions with tumors. While immunocompetent animal models better approximate the human immune system

ISSN: 3049-3757 | Vol. 01 Issue 01, February 2025 | pp. 60-79

than those whose immunity is weakened, they are not fully representative of human immunological responses. Human cancer patients' immunological profiles are usually complex, and other factors, including genetic predispositions, innate immune disorders underlying the disease, and the content of the tumour microenvironment, can modulate the success of immunotherapy. The failure of immunotherapy in the clinical environment arises from the significant gap between the translation of preclinical immunotherapy findings to human therapies due to the lack of human-specific immune system interactions in the use of animal models [30].

3.3. Inconsistent Predictability of Treatment Outcomes in Humans

This can be perhaps considered one of the biggest drawbacks with drug testing in animal models because the variable predictability of the outcome of a treatment when extrapolated to human clinical trials. Animals can often predict an important part of the biology behind the tumors but very rarely will a model for how a certain drug will actually function in a person. There could be many reasons for this variability, such as differences in the biology of the tumour, immunological response, metabolism of medication, and the complexity of the human body interacting with therapeutic agents.

Human tumor biology is very complex, reflecting not only the genetic content of tumor cells but also the complex relationships between tumors and their microenvironment, including blood vessels, immune cells, and stromal cells. These interactions, which are often under-represented in animal models, can greatly impact how effectively therapies work. In addition, the dosing and duration of treatment in animal models are generally different from what is used for humans. Differences in drug pharmacokinetics and pharmacodynamics can be significant between individuals and animals, which means the perceived safety and efficacy of treatments can also be different [31].

Another important issue that contributes to the different effects of treatment is the inability to adequately mimic the entire variability of human tumours in models using animals. Human malignancies are often characterized by the presence of many cell subpopulations with both heterogeneous genetic alterations and responses to the same therapy. However, they are generally genetic engineered animal strains or homogeneous cell lines for a tumour which may not completely represent the complexity and diversity of a human tumor. For this reason, drugs with promise in preclinical studies may not work in clinicals because they often fail to kill the more diverse and resistant human tumor populations contained within patients [32]. This discrepancy between preclinical and clinical results highlights the need for more dependable models that more accurately mimic human tumour biology and treatment responses, as high failure rates in cancer medication development are caused by this.

4. DISCUSSION

This study underlines the limitations of animal models in cancer research, but the necessity for advanced substitutes like organoids, humanized mouse models, and computational techniques that would allow

ISSN: 3049-3757 | Vol. 01 Issue 01, February 2025 | pp. 60-79

improvement in translational accuracy with solutions to ethical concerns. Future efforts should focus on multimodal approaches, tailored models, and legislation supporting non-animal techniques [33].

4.1. Interpretation of Findings

The conclusions of this review draw significant attention to serious drawbacks in employing animal models within cancer research. Although animal models, especially murine systems, have been crucial to improving our knowledge of cancer biology and evaluating the approaches of treatment, their prognostic usefulness remains limited by an incapacity to accurately mimic the complexity of human tumours and tumour microenvironments. It is very challenging to translate preclinical successes into effective human drugs because of the differences in genetic makeup, immunological response, and tumour heterogeneity between humans and animals. Although chemoresistance and drug resistance mechanisms have been studied in animal models, they do not fully capture the adaptive character of resistance in human tumors. Moreover, the tumour microenvironment of human cancers is often missing conditions such as hypoxia, immunosuppression, and vascular abnormalities seen in animal models. These considerations are important when determining the efficiency of current therapies like immunotherapy [34].

4.2. Implications for Conservation

The results point to the need to maintain and improve the validity of animal models while exploring other approaches. The failure of animal models to predict human responses with certainty underscores the importance of developing human-relevant systems, even though they are still indispensable tools in oncology research [35]. The translational gap can be closed to some extent with the inventions and use of advanced techniques, such as organoids, genetically modified mice models, known as GEMs, or patient-derived tumour xenografts, PDTXs. Such surrogates provide a more realistic milieu for drug testing and therapy assessment because of their better recapitulation of the complexity of human malignancies, including their heterogeneity and immunological interactions. Additionally, the preservation of resources by giving priority to the most humane and predictive models will improve the effectiveness of cancer research while resolving ethical issues related to animal testing [36].

4.3. Future Directions

Future research should focus on the following areas to address the limitations of current approaches:

1. **Advanced Models Development**
    - Increase the use of functioning human immune systems in humanized mouse models to study tumor-immune interactions and evaluate immunotherapies [37].
    - Use 3D cultures and patient-derived organoids to more closely mimic the tumour microenvironment and better

reflect the genetic heterogeneity of actual cancers

2. **Multimodal Approaches Integration**
   - Incorporate state-of-the-art technologies such as artificial intelligence (AI) and CRISPR-based genetic editing in conventional animal models to reproduce the course of human cancer and the response of that disease to therapy.
   - Apply computer models for predicting the action of medications and optimizing the therapeutic plan before actually embarking on clinical or animal experiments [38].
3. **Personalized Cancer Research:**
   - Develop patient-specific preclinical models, including PDTXs generated from individual patients, to assess and optimize therapy strategies tailored to specific tumor phenotypes and genomic signatures.
4. **Emphasize Ethical and Regulatory Developments:**
   - Invest in the development of alternative to animal methods of research, like in silico models, that would reduce animal testing and overcome ethical concerns.
   - Encourage the development of regulatory frameworks that support the integration of alternative models into drug development pipelines and recognize their value.

5. CONCLUSION

This study stresses how hard it is to reproduce the complexities of human tumors, including genetic heterogeneity, immune system interactions, and tumour microenvironments, using animal models in cancer research [39]. These constraints have partly contributed to the failure of many treatments in human clinical trials, thus resulting in considerable discrepancies between preclinical findings and clinical outcomes. Although animal models have disadvantages, they are still essential tools for studying the biology of cancer and assessing treatment strategies. More predictive and human-relevant systems are urgently needed to bridge the gap between preclinical research and successful human therapeutics, as their translational limitations demonstrate.

Using cutting-edge techniques such as organoids, GEMs, and PDTXs in the future allows for the possibility to increase the accuracy of cancer research. While customized preclinical models tailored to patient profiles can improve the approaches of treatments, the use of computer models and artificial intelligence can further strengthen predictive capacities. This would include

prioritizing ethical developments, such as a lack of dependency on animal techniques for drug development. Alleviating growing worries and enhancing research procedures would also serve to benefit the discipline of oncology, which can develop validity in preclinical research and speed up the production of effective cancer medicines by focusing on these future directions [40]

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