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Animal Models in Immunotherapy: Potential and Limitations

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Abstract This study studys the potential and limitations of various animal models used in immunotherapy research, with a focus on genetically engineered immunodeficient mice, patient-derived xenografts (PDXs), and humanized mouse models. These models are instrumental in understanding the interactions between the immune system and tumors, and in preclinical testing of new immunotherapeutic agents. However, significant challenges remain, including species-specific differences that limit the translational relevance of these models to human clinical outcomes. Advances in humanized mouse models, which incorporate human immune cells and tumor tissues, offer promising avenues for more accurate preclinical assessments. Despite their potential, these models also face limitations such as incomplete immune system reconstitution and high costs. This study highlights the need for continued refinement of animal models to enhance their predictive power and translational applicability in cancer immunotherapy research.

Keywords Animal models; Cancer immunotherapy; Humanized mice; Patient-Derived xenografts (PDXs); Preclinical studies

1 Introduction

Immunotherapy has revolutionized the landscape of cancer treatment by harnessing the body's immune system to combat malignancies. This therapeutic approach includes a variety of strategies such as immune checkpoint inhibitors, adoptive cell transfer, and cancer vaccines, all aimed at enhancing the immune response against tumor cells (Zhang and Zhang, 2020; Duan and Luo, 2021). Immune checkpoint inhibitors, for instance, target molecules like CTLA-4, PD-1, and PD-L1 to prevent cancer cells from evading immune detection (Sau et al., 2018). Despite the significant advancements, the efficacy of immunotherapy varies among patients, and only a subset of cancer patients benefit from these treatments. This variability underscores the need for a deeper understanding of the tumor microenvironment (TME) and the immune system's interactions with cancer cells (Poeta et al., 2017; Zhang and Zhang, 2020).

Animal models play a crucial role in the development and evaluation of immunotherapies. They provide a platform to study the complex interactions between the immune system and cancer cells in a controlled environment. Traditional transplantation tumor systems have been largely replaced by more sophisticated models, such as transgenic mice, which better mimic human malignancies (Ostrand-Rosenberg, 2004). These models include genetically engineered mice with spontaneous tumor development and humanized mice with a functioning human immune system, which are essential for preclinical testing of immunotherapeutic strategies (Choi et al., 2018; Olson et al., 2018). Additionally, patient-derived xenografts (PDXs) and organoid models have emerged as valuable tools for studying the tumor immune microenvironment (TIME) and testing personalized cancer immunotherapies (Choi et al., 2018; Sun et al., 2022). Despite these advancements, there is a continuous need for more realistic and predictive animal models to improve the translation of preclinical findings to clinical success.

By studying the current state of animal models, including transgenic mice, humanized mice, PDXs, and organoid models, this study identifies the strengths and weaknesses of each model in replicating human cancer and immune responses. Furthermore, the study seeks to highlight the advancements needed to develop more accurate and predictive models that can enhance the efficacy and reliability of immunotherapy trials. Ultimately, this research aims to contribute to the optimization of preclinical testing platforms, thereby facilitating the development of more effective cancer immunotherapies.

2 Overview of Animal Models Used in Immunotherapy

2.1 Rodent models

Rodent models, particularly mice, are the most commonly used animal models in immunotherapy research due to their low cost, short reproductive cycles, and ease of genetic manipulation. Mice have been instrumental in the development of various immunotherapeutics, including chimeric antigen receptor (CAR) T-cells and immune checkpoint inhibitors (Chulpanova et al., 2020). Humanized mice, which are engineered to have a functional human immune system, have become increasingly sophisticated and are used to model human cancer immunotherapies more accurately (Sun et al., 2020; Tian et al., 2020; Jin et al., 2021). These models allow for the in vivo exploration of human cancer immunology and immunotherapy, providing a platform to evaluate the efficacy of immunotherapeutic agents (Buqué and Galluzzi, 2018; Choi et al., 2018). However, significant differences between rodent and human immune systems often limit the translational applicability of findings from mouse models to human clinical settings (Rochere et al., 2018; Chulpanova et al., 2020; Sun et al., 2020). Rats, although less commonly used than mice, offer certain advantages such as larger size and a more active complement system (Ostrand-Rosenberg, 2004; Olson et al., 2018). Immunodeficient rats have been developed to study human immune responses, including graft versus host disease (GVHD) and tumor rejection, making them valuable complementary models to mice (Ménoret et al., 2019).

2.2 Non-human primate models

Non-human primates (NHPs) are considered the gold standard for preclinical immunotherapy studies due to their close genetic and immunological similarities to humans. These models are particularly useful for evaluating the safety and efficacy of new immunotherapeutic agents before clinical trials.

NHPs can provide insights into the pharmacokinetics, pharmacodynamics, and potential toxicities of immunotherapies, which are crucial for predicting human responses (Choi et al., 2018). However, the use of NHPs is limited by ethical considerations, high costs, and longer reproductive cycles compared to rodent models.

2.3 Zebrafish models

Zebrafish have emerged as a valuable model for studying cancer biology and immunotherapy due to their transparent embryos, which allow for real-time visualization of tumor growth and immune cell interactions. Zebrafish models are particularly useful for high-throughput drug screening and studying the effects of genetic modifications on tumor development and immune responses (Sun et al., 2020). Despite their advantages, zebrafish models have limitations, including differences in immune system complexity and tumor microenvironment compared to mammals.

2.4 Other emerging animal models

Canine and porcine models are gaining attention in immunotherapy research due to their physiological and immunological similarities to humans. Canine models, in particular, are valuable for studying spontaneous tumors that closely resemble human cancers in terms of histopathology and genetic mutations. These models can provide insights into the natural progression of cancer and the efficacy of immunotherapeutic agents in a clinically relevant setting (Duan and Luo, 2021).

Porcine models offer advantages such as larger size and longer lifespan, which allow for more extensive longitudinal studies. Pigs have been used to study various aspects of immunotherapy, including organ transplantation and immune responses to infectious diseases. However, the use of these models is still in its early stages, and further research is needed to fully establish their potential in immunotherapy studies (Chulpanova et al., 2020).

While rodent models, particularly mice, remain the cornerstone of immunotherapy research, the use of non-human primates, zebrafish, and emerging models like canine and porcine is expanding. Each model offers unique advantages and limitations, and their combined use can provide a more comprehensive understanding of immunotherapeutic strategies (Spitzer et al., 2016).

3 Role of Animal Models in Understanding Immune Responses

Animal models have been indispensable in advancing our understanding of immune responses, particularly in the context of immunotherapy. These models provide a controlled environment to study the complex interactions between the immune system and various diseases, including cancer and viral infections. This section delves into the mechanistic insights gained from animal studies, the comparative immunology between human and animal immune systems, and the contribution of these models to the development of immune-based therapies.

3.1 Mechanistic insights gained from animal studies

Animal models have been pivotal in elucidating the mechanisms underlying immune responses. For instance, genetically modified mouse models have been extensively used to study the function of the Rel/NF-κB/IκB family of transcription factors, which are crucial for immune responses and inflammation. These models allow researchers to manipulate specific genes and observe the resultant effects on immune function, providing valuable insights into the roles of these genes in health and disease (Overgaard et al., 2018).

Moreover, the Oncopig model, which involves genetically induced tumors, has been instrumental in understanding the tumor microenvironment and T-cell responses. This model has shown pronounced intratumoral T-cell infiltration, with a strong predominance of cytotoxic CD8β+ T cells and differentiated γδ T cells, alongside a regulatory response mediated by FOXP3+ T cells (Overgaard et al., 2018). Additionally, the Oncopig model closely mimics key aspects of human tumor heterogeneity, stromal interactions, and immune evasion mechanisms, making it a valuable tool for studying tumor-immune dynamics. Such findings highlight the potential of the Oncopig model for preclinical testing of cancer immunotherapies, including checkpoint inhibitors, adoptive T-cell therapies, and personalized treatment strategies.

3.2 Comparative immunology: human vs. animal immune systems

Comparative immunology studies have revealed significant differences and similarities between human and animal immune systems, which are crucial for the translation of preclinical findings to clinical settings. For example, while murine models are widely used, their immune responses often differ significantly from those of humans, leading to challenges in translating findings. This has led to the exploration of alternative models, such as porcine and canine models, which are more closely related to humans in terms of immune system architecture and function (Overgaard et al., 2018).

Humanized mouse models, which are engrafted with human tissues or express human genes, offer another approach to bridge this gap. These models have been used to study human immune responses to viral infections, cancer, and autoimmune diseases, providing a more accurate representation of human immunology (Douam et al., 2018). However, challenges remain in fully recapitulating the complexity of human immune responses, as these models often exhibit incomplete immune cell maturation, species-specific differences in cytokine signaling, and limitations in replicating the full human immune microenvironment. Further refinements are needed to improve their physiological relevance and translational value in biomedical research.

3.3 Contribution to the development of immune-based therapies

Animal models have significantly contributed to the development of immune-based therapies. For instance, patient-derived xenografts (PDXs) in humanized mice have been used to test immunotherapeutic strategies, improving the chances of finding novel biomarkers for drug development (Choi et al., 2018). These models allow for the study of diverse cancers in environments that closely mimic human conditions, thereby enhancing the precision of new drugs. Additionally, systemic immunity has been shown to be crucial for effective cancer immunotherapy. Studies using genetically engineered cancer models have demonstrated that immune activation occurs both locally in the tumor and systemically, with peripheral immune cells playing a key role in sustaining the immune response and driving tumor rejection (Spitzer et al., 2016). These findings underscore the importance of considering systemic immune responses in the development of immunotherapies (Figure 1) (Zhang and Zhang, 2020).

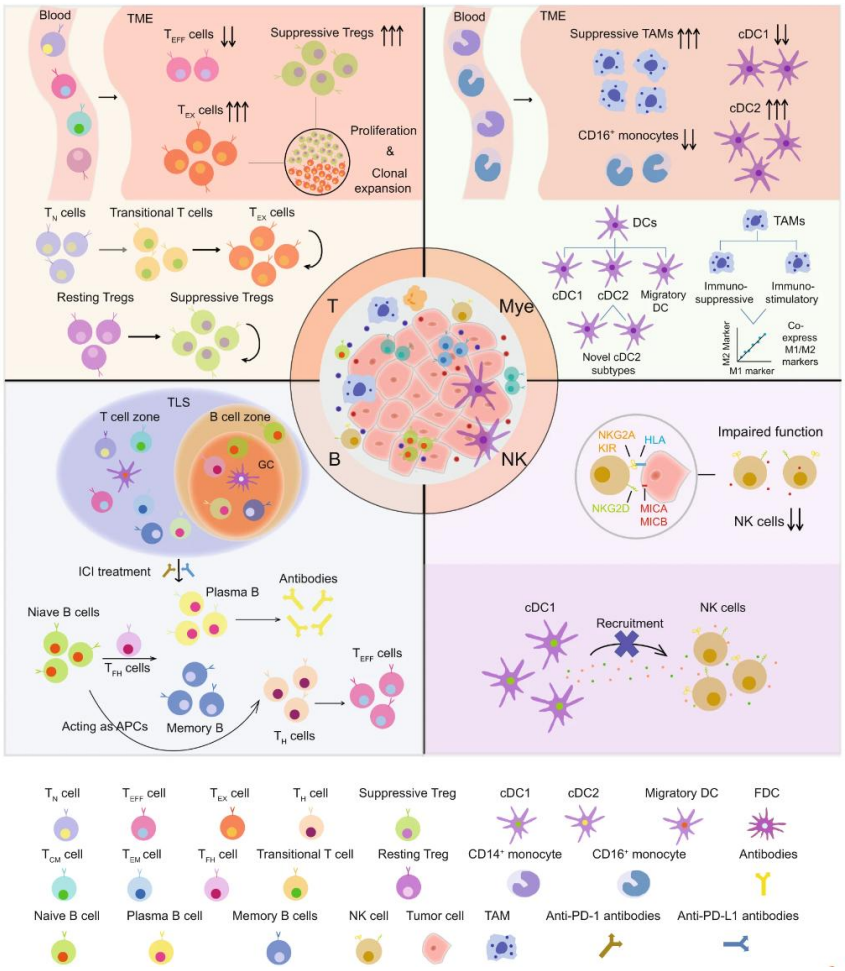

Figure 1 Functional properties and dynamic changes of immune cells in the tumor microenvironment (Adopted from Zhang and Zhang, 2020)

Image caption: The image provided appears to be a comprehensive schematic representation of the functional properties and dynamic changes of immune cells within the tumor microenvironment (Adopted from Zhang and Zhang, 2020)

4 Case Study: Animal Models in CAR-T Cell Therapy

4.1 Use of mice in CAR-T cell therapy research

Mice have been extensively used in CAR-T cell therapy research due to their cost-effectiveness, short reproductive cycles, and the ability to be easily genetically modified. These characteristics make them ideal for creating complex tumor models that can reliably reflect the tumor microenvironment and its interactions with immunotherapeutic agents (Chulpanova et al., 2020). Humanized mouse models, in particular, have been instrumental in advancing CAR-T cell therapy. These models involve engrafting human immune cells and tumor tissues into immunodeficient mice, allowing researchers to study human immune responses and the efficacy of CAR-T cells in a controlled environment (Jin et al., 2018; Wu et al., 2019). For instance, demonstrated the use of a humanized mouse model to test CD19-targeted CAR-T cells against primary acute B-lymphoblastic leukemia (B-ALL), showing promising results that mirrored clinical outcomes (Wu et al., 2019).

4.2 Translational challenges from animal models to human trials

Despite the successes in preclinical studies using mouse models, there are significant translational challenges when moving from animal models to human trials. One major issue is the high failure rate observed in human clinical trials after promising results in mouse models(Chulpanova et al., 2020). This discrepancy is often due to differences in the tumor microenvironment and immune system between mice and humans. For example, while mouse models can provide insights into the mechanisms of CAR-T cell action and resistance, they may not fully replicate the complexity of human tumors and immune responses (Figure 2) (Zhou et al., 2023). Additionally, toxicities such as cytokine release syndrome (CRS) and neurologic toxicity observed in human trials are not

always accurately predicted by mouse models (Jiao et al., 2020; Yue and Bai, 2023). These challenges highlight the need for more sophisticated models and better predictive tools to bridge the gap between preclinical and clinical research.

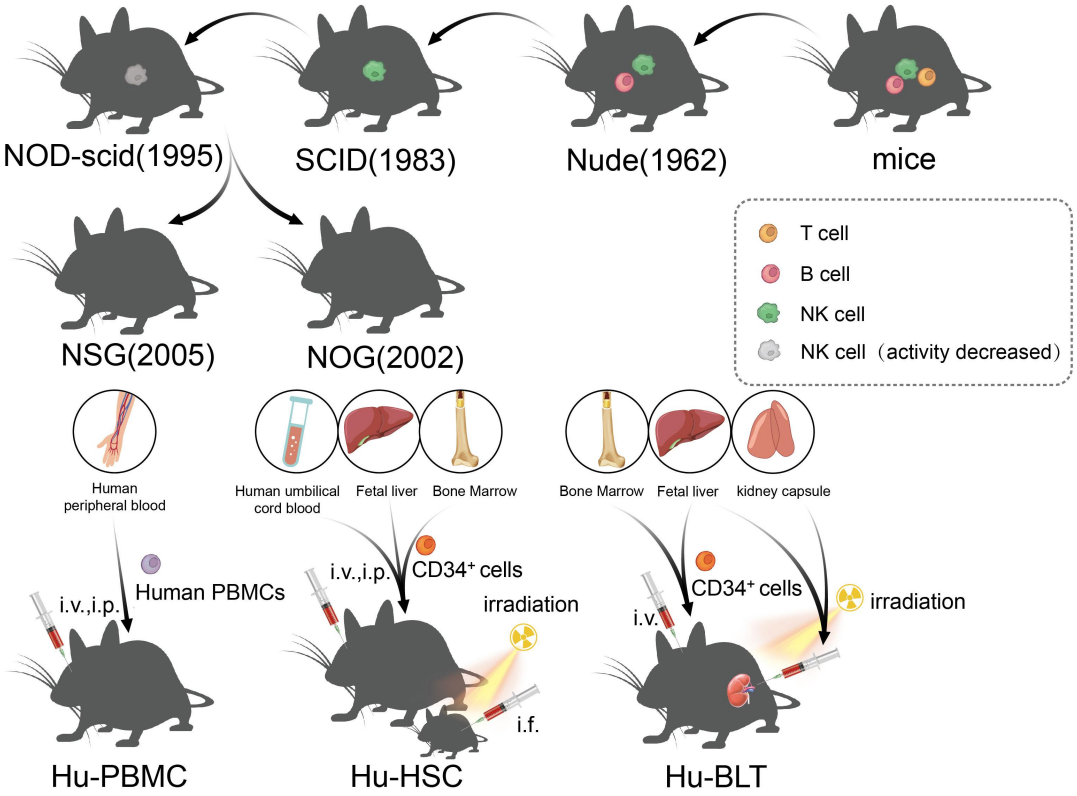

Figure 2 The development of immunodeficient mice and the construction method of the humanized mice model (Adopted from Zhou et al., 2023)

Image Caption: This image provides a chronological overview of the development of immunodeficient mouse models and outlines the construction methods for different types of humanized mice models (Adopted from Zhou et al., 2023)

4.3 Lessons learned and future directions

The use of animal models in CAR-T cell therapy research has provided valuable insights but also underscored the limitations and challenges in translating findings to human patients. One key lesson is the importance of developing more advanced and representative models, such as humanized mice, which better mimic the human immune system and tumor microenvironment (Mhaidly and Verhoeyen, 2020; Yue and Bai, 2023). These models have shown potential in improving the predictability of preclinical studies and facilitating the design of new CAR-T cell therapies with enhanced efficacy and reduced toxicities (Jin et al., 2018; Mhaidly and Verhoeyen, 2020). Future research should focus on refining these models, incorporating patient-derived xenografts (PDX), and exploring combination therapies to overcome resistance mechanisms and improve therapeutic outcomes (Li et al., 2019; Wu et al., 2019). Additionally, efforts to understand and mitigate the side effects of CAR-T therapy, such as CRS and immune suppression, are crucial for the successful translation of these therapies to clinical practice (Jiao et al., 2020; Yue and Bai, 2023).

5 Limitations of Animal Models in Immunotherapy

5.1 Genetic and physiological differences

One of the primary limitations of using animal models in immunotherapy research is the genetic and physiological differences between animals and humans. These differences can significantly impact the translatability of preclinical findings to clinical settings. For instance, mouse models, which are commonly used due to their low cost and ease of genetic manipulation, often fail to accurately replicate the human immune system and tumor microenvironment. This discrepancy can lead to promising results in animal studies that do not translate into successful human treatments (Buqué and Galluzzi, 2018; Wege, 2018; Chulpanova et al., 2020). Non-human

primates (NHPs) offer a closer approximation to human physiology and immune responses, but they are not without their own limitations, including ethical concerns and high costs (Ceppi et al., 2020).

5.2 Ethical considerations

The use of animal models in immunotherapy research raises significant ethical concerns. The welfare of animals used in experiments is a critical issue, particularly when it involves inducing diseases such as cancer. Ethical guidelines and regulations are in place to ensure humane treatment, but the moral implications of using animals for research purposes remain a topic of debate. Additionally, the high failure rate of translating animal model results to human clinical trials further exacerbates these ethical concerns, as it questions the justification for the use of animals in such studies (Wege, 2018; Buqué and Galluzzi, 2018).

5.3 Challenges in translational research

Translational research, which aims to move findings from the laboratory to clinical applications, faces numerous challenges when relying on animal models. One major issue is the high rate of failure in clinical trials despite promising preclinical results. This is often due to the inability of animal models to fully mimic the complexity of human diseases and immune responses. For example, immunodeficient mice used in patient-derived xenografts (PDXs) lack a fully functional immune system, which is crucial for studying immunotherapies (Buqué and Galluzzi, 2018; Choi et al., 2018). Moreover, the differences in tumor biology between species can lead to misleading conclusions about the efficacy and safety of new treatments (Wege, 2018; Buqué and Galluzzi, 2018).

5.4 Alternatives and complementary approaches

Given the limitations of animal models, researchers are increasingly exploring alternative and complementary approaches to study immunotherapy. In vitro models, such as organoids and 3D cell cultures, offer a more controlled environment to study specific aspects of tumor biology and immune interactions. Computational models and simulations are also being developed to predict immune responses and treatment outcomes, potentially reducing the reliance on animal testing (Kim et al., 2021; Costello et al., 2018).

These alternatives can provide valuable insights and help bridge the gap between preclinical and clinical research, although they too have their own set of limitations and challenges. While animal models have been instrumental in advancing our understanding of immunotherapy, their limitations necessitate the development and integration of alternative approaches to improve the translatability of research findings to human clinical settings.

6 Case Study in Place: Tumor Models in Immunotherapy

6.1 Example of a successful animal model in tumor immunotherapy

Genetically engineered mouse models (GEMMs) have been pivotal in advancing cancer research, particularly in the field of immunotherapy. One notable example is the use of GEMMs to study prostate cancer. These models, such as the PTEN null and Kras G12D; Pten null mouse prostate cancer models, closely mimic the histopathological and molecular features of human prostate cancer. They have been instrumental in evaluating the efficacy of combinatory immunotherapies, including immune checkpoint inhibitors and mTOR inhibitors. These models have shown that while prostate tumors are resistant to androgen depletion and certain chemotherapies, they respond to specific immunotherapeutic strategies, thereby providing a robust platform for preclinical studies (Kersten et al., 2016; Wang et al., 2019).

6.2 Limitations of the selected model

Despite their success, GEMMs have several limitations. One significant drawback is the spontaneous nature of tumor onset and progression, which can make it challenging to synchronize studies and evaluate therapeutic interventions consistently. Additionally, the cost and complexity of breeding compound mutant mice can be prohibitive. Furthermore, while GEMMs can recapitulate many aspects of human cancer, they may not fully capture the genetic and immunological diversity seen in human tumors. This can limit the translatability of findings from mouse models to human clinical outcomes (Kersten et al., 2016; Wang et al., 2019; Chulpanova et al., 2020).

6.3 Comparison with human clinical outcomes

The translation of findings from GEMMs to human clinical outcomes has been mixed. While GEMMs have been successful in identifying potential therapeutic targets and understanding tumor biology, the high failure rate of promising treatments in human clinical trials remains a significant challenge. This discrepancy is often due to differences in tumor microenvironment, immune system interactions, and genetic heterogeneity between mice and humans. For instance, while GEMMs have shown promising results with immune checkpoint inhibitors, the same treatments have not always yielded robust responses in human patients, highlighting the need for more predictive preclinical models (Figure 3) (Olson et al., 2018; Chulpanova et al., 2020; Cogels et al., 2021).

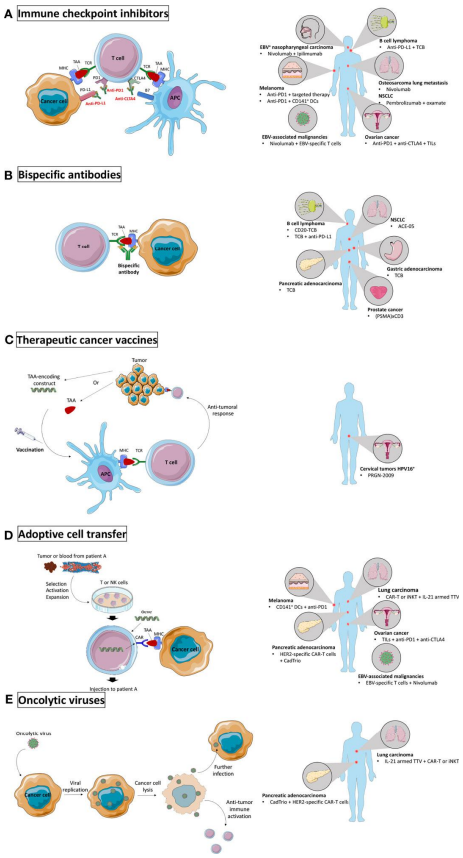

Figure 3 Novel immunotherapy settings tested in humanized mice (Adopted from Cogels et al., 2021)

Image caption: The image provided appears to be a detailed illustration of various novel immunotherapy approaches tested in humanized mice, showcasing different methods and their applications in cancer treatment (Adopted from Cogels et al., 2021)

6.4 Potential improvements in model design

To enhance the predictive power of animal models in immunotherapy, several improvements can be made. One approach is the development of humanized mouse models, which can bear both human immune systems and human tumors. These models offer a more accurate representation of human tumor-immune interactions and can provide valuable insights into the efficacy and safety of immunotherapeutic agents. Additionally, integrating patient-derived xenografts (PDXs) with humanized immune systems can further improve the relevance of preclinical studies. Advances in genetic engineering, such as CRISPR, can also be utilized to create more precise and customizable models that better mimic the genetic and immunological landscape of human cancers (Choi et al., 2018; Moyes et al., 2019; Cogels et al., 2021).

7 Future Perspectives

7.1 Innovations in animal model development

The development of animal models has been significantly advanced by the advent of CRISPR/Cas9 technology. This gene-editing tool has enabled the creation of more accurate and sophisticated models that closely mimic human diseases. For instance, CRISPR/Cas9 has been used to generate large animal models, such as non-human

primates and pigs, which are more representative of human physiology compared to traditional rodent models (Barazesh et al., 2020; Lin et al., 2022). These advancements are crucial for studying disease mechanisms and testing new therapies. However, challenges such as off-target effects and ethical considerations remain and need to be addressed to fully harness the potential of these models (Chen et al., 2019; Khalaf et al., 2020).

7.2 Integration of multi-omics approaches

The integration of multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, with animal models is poised to revolutionize immunotherapy research. By combining these comprehensive datasets, researchers can gain a holistic understanding of the molecular and cellular mechanisms underlying immune responses and disease progression. CRISPR/Cas9 technology facilitates this integration by enabling precise genetic modifications that can be studied across different omics layers (Khalaf et al., 2020; Ou et al., 2021). This approach not only enhances the accuracy of animal models but also aids in the identification of novel therapeutic targets and biomarkers (Xia et al., 2018; Chen et al., 2019).

7.3 Moving towards personalized animal models

Personalized medicine is an emerging paradigm in healthcare, and its principles are now being applied to the development of animal models. Personalized animal models are created by introducing patient-specific genetic mutations into animals using CRISPR/Cas9 technology. This allows for the study of individual variations in disease and treatment responses, providing a more tailored approach to therapy development (Ren and Zhao, 2017; Zhi et al., 2021). For example, CRISPR/Cas9 has been used to create models with specific cancer mutations, enabling the testing of targeted therapies and the study of resistance mechanisms (Chen et al., 2019; Khalaf et al., 2020). This personalized approach holds great promise for improving the efficacy and safety of immunotherapies.

7.4 Ethical and regulatory considerations

The use of CRISPR/Cas9 in developing animal models raises several ethical and regulatory issues that must be carefully considered. The potential for off-target effects and unintended consequences necessitates rigorous risk assessment and mitigation strategies (Khalaf et al., 2020; Sharma et al., 2020). Additionally, the creation of genetically modified animals, especially large animals, poses ethical dilemmas related to animal welfare and the justification of their use in research (Barazesh et al., 2020; Lin et al., 2022). Regulatory frameworks need to evolve to address these concerns, ensuring that the benefits of CRISPR/Cas9 technology are realized while minimizing harm. Transparent and inclusive discussions involving scientists, ethicists, and the public are essential to navigate these complex issues responsibly.

8 Concluding Remarks

Animal models have been instrumental in advancing our understanding of tumor immunology and the development of immunotherapies. Traditional mouse models, including immunodeficient mice xenografted with human cancer cell lines and patient-derived xenografts (PDXs), have provided foundational insights but come with limitations, particularly in studying tumor immunology and immunotherapy due to the lack of a functional immune system. Humanized mouse models have emerged as a significant advancement, allowing for the study of human immune responses in a more relevant context. These models have shown promise in preclinical evaluations of immunotherapies, such as PD-1-targeted treatments, and have highlighted the importance of human immune cell reconstitution for translational research. Additionally, transgenic and knockin mouse models have been crucial in understanding the tumor-host relationship and the mechanisms of immune activation and tolerance. Despite these advancements, there remain challenges in replicating the complexity of human malignancies and immune interactions within the tumor microenvironment.

The development and refinement of animal models are critical for the continued progress of immunotherapy research. Future research should focus on improving the translational power of these models by enhancing the humanization of immune components and addressing the limitations of current models, such as the lack of immune-related adverse events (irAEs) observed in clinical settings. The integration of quantitative systems pharmacology (QSP) models with humanized mice can facilitate more accurate preclinical assessments and optimize study designs. Additionally, the exploration of alternative animal models, such as immunodeficient rats,

may offer complementary advantages and provide new insights into human immune responses. The development of more sophisticated in vitro models, such as hydrogel-based 3D cancer models, can also serve as valuable tools for predicting therapeutic benefits and personalizing treatment strategies.

Animal models will continue to play a pivotal role in the advancement of immunotherapy. The ongoing efforts to enhance the fidelity of these models to human biology are essential for bridging the gap between preclinical research and clinical applications. As we move forward, the combination of advanced animal models with innovative in vitro systems and computational approaches will likely yield more predictive and efficient tools for immunotherapy development. The ultimate goal is to create models that not only replicate the human immune system and tumor microenvironment with high accuracy but also provide reliable platforms for testing and optimizing new therapeutic interventions. The future of immunotherapy research depends on our ability to refine these models and translate their findings into effective clinical treatments.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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