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T-CELL AND OTHER LYMPHOPROLIFERATIVE MALIGNANCIES (J ZAIN, SECTION EDITOR)

Development and Significance of Mouse Models in Lymphoma Research

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Abstract

Purpose of Review Animal models have played an indispensable role in interpreting cancer gene functions, pathogenesis of disease, and in the development of innovative therapeutic approaches targeting aberrant biological pathways in human cancers.
Recent Findings These models have guided the therapeutic targeting of cancer-causing mutations and paved the way for assessing anti-cancer drug responses and the preclinical development of immunotherapies. The mammalian models of cancer utilize genetically edited or transplanted mice that develop fairly accurate disease histopathology. The mouse model also allows us to study the effect of tumor microenvironment in the development of lymphoma. The emergence of patient-derived xenografts provides a better opportunity for recapitulating primary lymphoma characteristics and researching personalized drug therapy.
Summary In conclusion, the refinement and advancement of available mouse models in lymphoma significantly minimize the therapeutic translational failures in patients.

Keywords Mouse models · Xenograft · Syngeneic · Genetically engineered · Lymphoma · Treatment

Introduction

Research into the molecular mechanisms of cancer pathogenesis and progression and the discovery of novel anti-cancer therapeutics has long relied on the evolution and use of animal models. From drosophila, zebrafish, canine, feline, equine, murine, and non-human primate, there are a variety of animal models available in cancer research and each has its own advantages and disadvantages [1–5]. For example, the species drosophila exhibits characteristics that result in an animal model well-suited for rapid results and ease of genetic modification, i.e., a short life span, high fertility, external embryo clutches, and brisk maturation (growth) [6]. However, this feasibility of genetic modification is counterintuitive to natural oncogenesis. Natural oncogenesis is a complex, chronic processes requiring time, the recruitment of host cells and nutrients, and evasion of a functional immune system. The combination of these factors and the nuances of host individuality (DNA, gene expression, environmental circumstances) result in cancer heterogeneity that may confound current therapeutics. In 2018, the expected number of all-site cancer diagnoses is 1,735,350 and the expected mortality is 609,640 persons [7]. New therapeutics are mandated and animal models are the authority behind therapeutic discovery with their targeted approach to identifying key pathways in oncogenesis.

One area of cancer research necessitating further inquiry is lymphoma, the cancer of lymphocytes (T, B, NK cells). In 2018, there will be approximately 83,180 newly diagnosed patients with lymphoma [7]. Their 5-year survival depends on the subtype of lymphoma they have developed. If diagnosed with Hodgkin's lymphoma (defined as the presence of Reed-Sternberg cells), a patient has an 86% chance for 5-year

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survival [7, 8]. If diagnosed with Non-Hodgkin's, their prognosis is even worse at 71% [7]. The current treatment options for lymphoma include chemotherapy, radiation, stem cell transplantation, and targeted therapies, e.g., monoclonal antibodies [9]. The reason for existing lymphoma mortality is linked to poor drug response, resistance, and relapse. Thus, further insight into lymphomagenesis is necessary for identifying novel molecular targets for drug development. *Mus musculus*, or the mouse, has served as the model organism of lymphoma studies by establishing multiple perspectives to view disease progression and later preclinical drug trials. This has been accomplished in the mouse model by either injecting cancerous cells in syngeneic/immunocompromised mice (transplantable mouse model) or through genome editing approaches (genetically engineered mouse model) (Fig. 1 and Table 1).

Syngeneic and Xenograft Transplantable Mouse Models

The implantation of tumorous material requires a systematic approach. For instance, these cells can be administered via subcutaneous, orthotopic, intraperitoneal, or intravascular routes. Each route translates to different benefits and lymphoma presentation [25–28]. For example, an intravascular injection (via the tail vein) is advantageous for studying disseminated, or widely distributed, disease, e.g., diffuse large B cell lymphoma [29]. Transplantable models of lymphoma involve the implantation of histocompatible allografts (syngeneic) or foreign xenografts into immunocompetent or immunodeficient mice.

Syngeneic mouse models are one of the oldest preclinical models [30•]. The term syngeneic implies similar or identical genetics, i.e., murine cell lines into mouse models. The main advantage of this model is the ability to permit the study lymphoma in presence of an intact immune system. However, not all murine tumor cells will engraft in the presence of an immune system and cells with fewer aggressive characteristics may require some degree of immunosuppression for successful engraftment. Commonly used lymphoma cell lines utilized in syngeneic model are EL4, A20, H11, BL3750, and S49 derived from spontaneous tumors. After establishing a tumor, the effect of drugs on lymphoma growth can be studied [29, 30•, 31–34]. Recently, the engineering of human antigens, e.g., CD20 on the surface of murine cells, has allowed for the testing of novel monoclonal antibodies directed against these antigens [35, 36]. Another application of syngeneic models is observation on the role of the tumor microenvironment on lymphoma progression [37]. For example, the

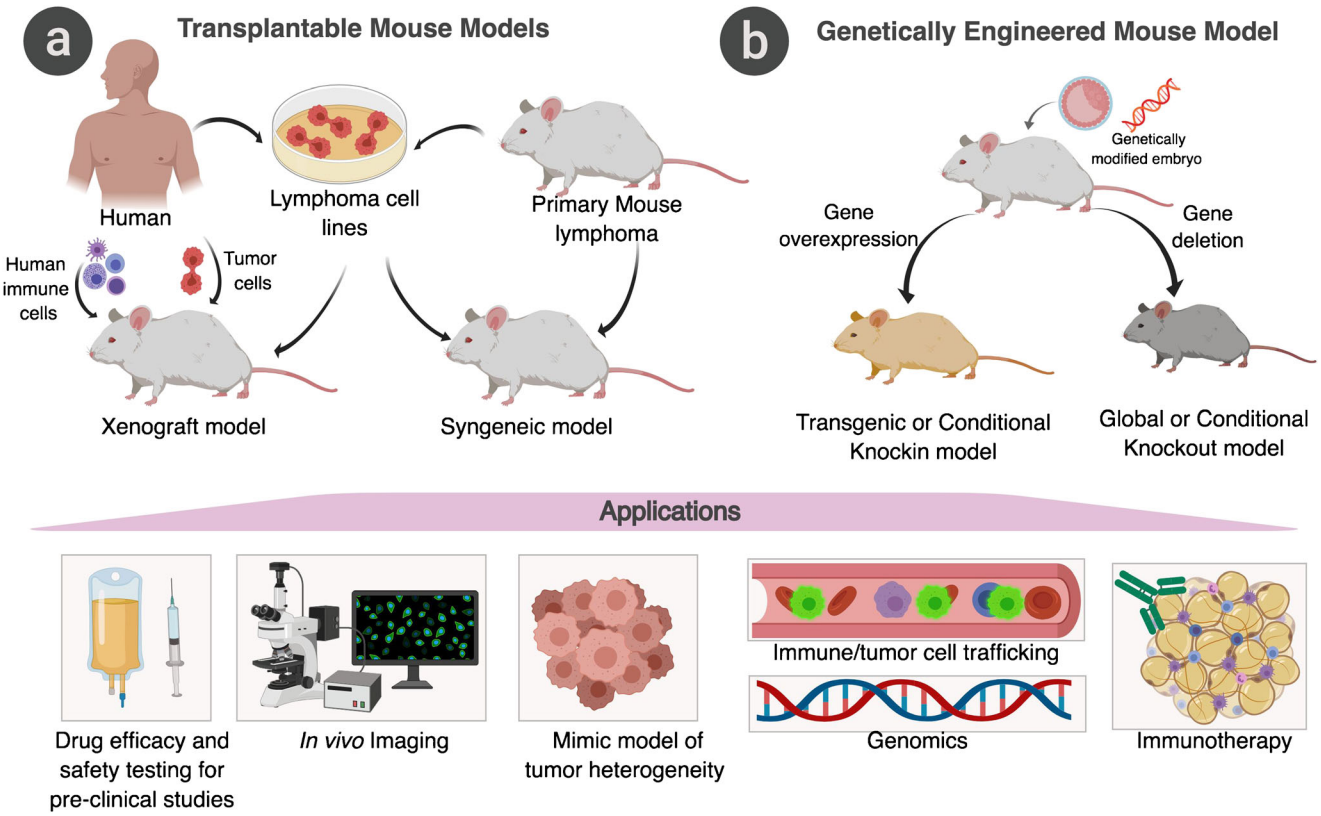

Fig. 1 Approaches for developing pre-clinical mouse models for **a** transplantable xenograft mouse models and **b** genetically engineered transgenic and knockout mouse models and **c** the in vitro and in vivo applications of different mouse models in understanding lymphoma biology

Table 1 Approval of novel therapies for lymphoma with insights from mouse model

Drug name (generic name)	Approved	Used for	Mechanism of action	Reference
Acalabrutinib (Calquence)	2017	Mantle cell lymphoma; chronic lymphocytic leukemia	Bruton tyrosine kinase (BTK) inhibitor	[10, 11]
Axicabtagene ciloleucel (YESCARTA)	2017	B cell lymphoma	Anti-CD19 CAR T cell therapy	[11–13]
Copanlisib (ALIQOPA)	2017	Follicular lymphoma	Inhibitor of PI3Kα and PI3K-δ	[14, 15]
Venetoclax (VENCLEXTA)	2016	B cell lymphoma, mantle cell lymphoma	BCL-2 inhibitor	[16–19]
Belinostat (Beleodaq)	2014	peripheral T cell lymphoma (PTCL)	Histone deacetylase inhibitor	[20, 21]
Brentuximab vedotin (Adcetris)	2011	Primary effusion lymphoma	CD30-directed antibody-drug conjugate	[22–24]

injection of irradiated BCL1 lymphoma cells (acting as a vaccine) can activate and boost the effects of the host's adaptive immune system against future invasion of functional lymphoma cells [26]. The activation of immune cells via engineered cells, e.g., chimeric antigen receptor (CAR) T cells, is the basis of immunologic therapy, and color-coded fluorescent protein-based imaging can allow real-time observation of cell recruitment in the tumor microenvironment [38, 39]. While syngeneic models of the tumor microenvironment are promising, the use of murine-based therapies in a murine system does not guarantee the human equivalent of these therapies will show similar effects [40, 41] and research into xenograft models more accurately reflects human lymphoma and drug response.

Xenograft mouse models are the transplantation of human lymphoma cells into immunodeficient mouse strains, i.e., NOD/SCID and Nude [42]. These lymphoma cells can be of primary tumor origin (patient-derived) or from an existing cell line. Cell lines demonstrate aggressive in vitro growth patterns that allows them to be exploited for in vivo studies due to an increased engraftment rate (Table 2). Nevertheless, since transplant requires an immunodeficient host to avoid rejection of the foreign human tissue and cell lines, it can be disadvantageous when compared to patient-derived xenografts. For example, cell line models of lymphoma contain the occasional mutation and these aberrations may not be observed in the comparative human lymphoma [43]. The primary utilization of cell lines is for initial screening of drug evaluation, i.e., efficacy, resistance, and cytotoxicity [30•, 44–51].

Patient-derived xenografts (PDX) refer to transplant of freshly harvested lymphoma cells from patients into immuno-compromised mice. The retention of primary lymphoma characteristics is the main benefit of PDX model [43, 52]. For example, if a patient has refractory lymphoma, or is unresponsive to treatment, a PDX model of their disease recapitulates this refractory character [42]. The applications of this recapitulation are diverse and consequential for developing new treatments. Models of rarer lymphoma subtypes (e.g., intravascular large B cell lymphoma—IVLBCL) can be recreated with fidelity even if the mechanisms of its progression are not yet understood [53]. There are three major advantages to testing drugs in PDX models. Of note, testing is defined here as the application of drugs in these models. The first advantage relates to personalized drug therapy. The retention of primary lymphoma characteristics permits the study and manipulation of a refractory patient's lymphoma in a PDX model. This provides insight into the optimal therapeutic regimen for future lymphomas displaying similar drug resistance [54, 55]. This model also allows for the robust testing of novel therapeutics and validation of molecular targets in in vivo settings. Both academia and pharmaceutical industries rely heavily on PDX models to ascertain drug efficacy and safety prior to clinical trials in patients. Finally, the application of drugs in rare lymphoma PDX models (e.g., IVLBCL) is a method used to research key pathways of lymphoma regulation and thus, possible targets for drug intervention [53, 56]. Xenograft patient-derived mouse models are not easily obtained, but certain methods can improve successful engraftment rates [42, 52]. One example is serial engraftment. This refers to taking samples of a successfully engrafted lymphoma and injecting it into another mouse. One consequence of this approach is the gradual loss of primary tumor characteristics [52]. Overall, PDX models are limited due to their necessity for an immunosuppressed host. To overcome this disadvantage, the humanized mouse model is an alternate method with its functional immune system.

Humanized Mice

A humanized mouse is the innovation of an immunodeficient mouse populated with a human immune system and the methods behind the exact transformation have been previously described [57••, 58, 59]. The manufacture of a miniature model of human lymphoma in a functional human immune system permits the observation and manipulation of a variety of human diseases and this opportunity to expand current knowledge on pathogenesis is paramount to establishing alternative therapeutic options [60, 61]. One area of research that has capitalized on this model is the continuous investigation into the transition of Epstein-Barr virus (EBV) to B cell lymphomas, e.g., Hodgkin's [62–64]. These studies have

Table 2 Current xenograft cell-lines of lymphoma

B cell lymphoma	BC-1, BC-2, BC-3, BCBL-1, CI-1, CRO-AP2, CRO-AP3, CRO-AP5, CRO-AP6, DB, DOHH-2, GRANTA-519, HT, JEKO-1, JIYOYE, MAVER-1, MC-116, MHH-PREB-1, MINO, NCEB-1, NU-DHL-1, NU-DUL-1, OCI-LY1, OCI-LY18, OCI-LY19, OCI-LY3, OCI-LY7, RC-K8, REC-1, RI-1, RL, SC-1, SU-DHL-10, SU-DHL-16, SU-DHL-4, SU-DHL-5, SU-DHL-6, SU-DHL-8, U-2904, U-2932, U-2940, U-2946, U-2973, U-698-M, ULA, VAL, WILL-1, WILL-2, WSU-DLCL, WSU-DLCL2, WSU-FSCCL, WSU-NHL
Burkitt lymphoma	BJAB, BL-100, BL-2, BL-41, BL-70, BLUE-1, CA-46, DAUDI, DG-75, DND-39, DOGKIT, DOGUM, EB-1, GUMBUS, NAMALWA, NAMALWA.CSN/70, NAMALWA.IPN/45, NAMALWA.KN2, NAMALWA.PNT, RAJI, RAMOS
B lymphoblastoid cells	232A4, BD-215, COLO-720 L, I83-LCL, IM-9, L-591, LCL-HO, LCL-WEI, NC-NC, PG-EBV, RO, SD-1, TMM
Hairy cell lymphoma	BONNA-12, HAIR-M, HC-1
Diffuse large B cell lymphoma	CARNAVAL, TOLEDO
Chronic B cell leukemia	CI, CII, EHEB, HG-3, I83-E95, JVM-13, JVM-2, JVM-3, MEC-1, MEC-2, PCL-12, PGA-1, WA-C3CD5+, WA-OSEL
Hodgkin lymphoma	HD-MY-Z, HDLM-2, KM-H2, L-1236, L-428, L-540, RPMI 6666, SUP-HD1, U-HO1
T cell lymphoma	DERL-2, DERL-7, SUP-T1
Cutaneous T cell lymphoma	HH, H-9, HUT-78, HUT-102, SEAX, MYLA, MJ
Anaplastic large T cell lymphoma	SR-786
Histiocytic lymphoma	JOSK-I, JOSK-M, U-937
T and NK cell leukemia	NK-92, YT
Mantle cell lymphoma	MINO, MAVER-1, JVM-2

addressed the role of various modalities, e.g., EBV nuclear proteins (e.g., EBNA3C), latent membrane proteins (e.g., LMP1, LMP2A), and inhibitory receptors (e.g., T cell CTLA-4 and PD-1) [62–64]. Overall, humanized mouse models are a developing field of research that have the potential to elicit novel cancer therapies that rely on a functional immune response. Other models pursue understanding of lymphoma and drug application through the genetic engineering of mice.

Genetically Engineered Transgenic and Knockout Mouse Models

Genetically engineered mouse models are transgenic or knockout manipulation of a target gene in a wild-type mouse and have been useful in defining the genetic causes of lymphoma. A transgenic mouse model is defined as the addition or upregulation of a target gene and this process has been previously described [65]. A classic example of transgenic model of lymphoma is the Eμ-Myc model created with the DNA construct of a c-myc gene in combination with a IgH enhancer. Ninety percent of the heterogenetic mice offspring will develop spontaneous lymphomas, primarily of B cell origin [66]. This model has enhanced our understanding of B cell lymphomagenesis and the effect of novel therapeutics on the lymphoma progression [67]. Transgenic mouse models have also been used to understand the pathogenesis of a variety of other lymphomas [68–70]. For example, IL-15 is implicated in cutaneous T cell lymphoma (CTCL) and transgenic upregulation of IL-15 results in a spontaneous CTCL model [70, 71]. Once established, transgenic models of lymphoma can aid in the development of preclinical drug testing, e.g., killer cell immunoglobulin-like receptor (KIR) transgenic mice [72, 73]. KIRs are found on the surface of NK cells and regulate negative feedback (diminished signaling). NK cells are critical to the innate immune system and may have a role in preventing lymphoma growth. Using KIR transgenic mice to test the efficacy of anti-KIR antibodies can be instrumental in understanding the effects of harnessing the microenvironment against lymphoma development and radiotracers can be incorporated to observe these effects [73, 74].

An additional mouse model related to transgenic is the conditional knockin, where a gene of interest is inserted into the embryo genome but prevented from expression with the inclusion of a STOP cassette. The STOP cassette can be inactivated at any time, and once removed, gene expression occurs. The conditional knockin method is advantageous for studying the effect of gain in function mutations in lymphoma development. For example, conditional expression of ITK-

SYK, chromosomal translocation of t(5;9)(q33;q22), in mice results in peripheral T cell lymphomas [75]. Loss of function mutations can be observed in knockout mouse models.

Within the knockout model, there is global knockout and conditional knockout. Global knockout is the deletion of a gene of interest and the process has previously been described [76]. There are numerous potential targets of knockout studies, but the primary focus is on identifying key signaling pathways in lymphomagenesis [77, 78]. For example, observing the effect of removing a cell-surface receptor implicated in EBV transformation [79]. Significantly, if the gene of interest is necessary for embryological development, its deletion results in embryonic lethality. Therefore, in order to study these genes, conditional knockout mice are essential [80, 81]. For example, RORC is a nuclear hormone critical for the development of a functional immune system. Global RORC knockout mice develop spontaneous lymphoma with 50% frequency, yet because RORC is required in fetal development for an intact immune system, global knockouts do not capitulate real life lymphomagenesis. A conditional RORC knockout permits the study of hormone deficiency and lymphomagenesis in the context of a functional immune system [82]. Another method of conditional knockout is the CRISPR-Cas9 system. The process has previously been described, but it utilizes the premise of bacterial CRISPR arrays to cut DNA, permitting genetic editing [83]. This method is advantageous for studying the effects of interrupted signaling upon lymphoma development and for the identification of lymphoma essential genes and suppressors [84, 85–87]. CRISPR systems have been beneficial in exploring the potential therapeutic targets for mantle cell lymphoma, a lymphoma with poor prognosis and resistance to standard therapies [84, 88]. The applications of CRISPR in mouse models are a developing field of study with promising results for lymphoma patients.

Significance of Mouse Models

Mouse models are significant in the development of new lymphoma treatments, because they are used to identify key drug targets and serve as models for preclinical drug testing. For example, while the FDA has recently approved immunotherapies for treatment of lymphoma, any new immunotherapy drug must undergo rigorous preclinical drug testing to ensure drug efficacy, limited drug toxicity, and any beneficial or negative drug-on-drug interactions [89, 90]. This can be simplified as understanding the pharmacokinetic and pharmacodynamic properties of drugs and there have been numerous studies detailing this process [29, 30•, 31–34, 44–51, 67]. Several studies have used murine models to focus on CAR T cell therapies and their associated toxicity cytokine release syndrome (CRS), characterized by systemic symptoms, e.g., hemodynamic instability [91–93]. Signaling molecules IL-1 and IL-6 have been implicated in CRS, but the pathogenesis is not yet fully understood. Further research using mouse models is necessary to improve therapeutic outcomes for lymphoma patients [91–94].

Conclusion

There are a variety of mouse models applicable in the study of lymphomagenesis and in the development of new treatment options. Syngeneic models were the first step into creating a model organism and subsequent technological advancements have permitted genetic editing for the benefit of a more in-depth understanding of the pathogenesis of lymphoma and its resistance to current therapies. Eradicating lymphoma mortality is a priority and the utilization of mouse models and their development is the pivotal approach to accomplishing this.

Compliance with Ethical Standards

Conflict of Interest Anjali Mishra reports grants from Galderma, grants from Kura Oncology, outside the submitted work. Jordan N Noble declares that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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