Leukemia & Lymphoma, July 2005; 46(7): 973–992

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Comparative animal models for the study of lymphohematopoietic tumors: strengths and limitations of present approaches

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Abstract

The lymphomas probably represent the most complex and heterogenous set of malignancies known to cancer medicine. Underneath the single term lymphoma exist some of the fastest growing cancers known to science (i.e Burkitt's and lymphoblastic lymphoma), as well as some of the slowest growing (i.e. small lymphocytic lymphoma [SLL] and follicular lymphoma). It is this very biology that can dictate the selection of drugs and treatment approaches for managing these patients, strategies that can range from very aggressive combination chemotherapy administered in an intensive care unit (for example, patients with Burkitt's lymphoma), to watch and wait approaches that may go on for years in patients with SLL. This impressive spectrum of biology emerges from a relatively restricted number of molecular defects. The importance of these different molecular defects is of course greatly influenced by the intrinsic biology that defines the lymphocyte at its different stages of differentiation and maturation. It is precisely this molecular understanding that is beginning to form the basis for a new approach to thinking about lymphoma, and novel approaches to its management. Unfortunately, while our understanding of human lymphoma has blossomed, our ability to generate appropriate animal models reflective of this biology has not. Most preclinical models of these diseases still rely upon sub-cutaneous xenograft models of only the most aggressive lymphomas like Burkitt's lymphoma. While these models clearly serve an important role in understanding biology, and perhaps more importantly, in identifying promising new drugs for these diseases, they fall short in truly representing the broader, more heterogenous biology found in patients. Clearly, depending upon the questions being posed, or the types of drugs being studied, the best model to employ may vary from situation to situation. In this article, we will review the numerous complexities associated with various animal models of lymphoma, and will try to explore several alternative models which might serve as better *in vivo* tools for to study these interesting diseases.

Keywords: *lymphoma, dog models, mouse models, comparative animal models*

Background

Non-Hodgkin's lymphomas (NHL) are presently the fifth most common cause of cancer-related death in the USA. Approximately 54,370 new cases of NHL will be diagnosed in the United States in 2004 [1]. Collectively, they account for over 19,410 deaths, making up for approximately 4–5% of all cancer-related deaths. However, because the NHL tends to afflict a younger population, the years of life lost are greater than in most other malignancies. This ranks NHL fourth among all cancers with regard to their economic impact in the USA. Thus, the case-fatality rate for NHL (i.e. the number of deaths attributed to the disease/the incidence of the disease) is approximately 36%. As with most haematologic malignancies, there is a slight male predominance, with approximately 53% of all cases developing in males. Hodgkin's disease (HD) is a biologically different disease from NHL, being characterized predominantly by the presence of the Reed-Sternberg cell, with a marked local lymphocytosis which accounts for the bulk of the tumor. Mortality rates have been steadily declining since the late 1960s, and in 1994 accounted for 1440 deaths in the USA. Approximately 6% of all

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Received for publication 15 February 2005.

ISSN 1042-8194 print/ISSN 1029-2403 online © 2005 Taylor & Francis Group Ltd
DOI: 10.1080/10428190500083193

lymphoma related deaths can be attributed to HD [2].

One of the most concerning aspects of NHL epidemiology concerns its rising incidence. Recently, the American Cancer Society reported that NHLs have increased 50% over the last 15 years. A steadily increasing trend can be traced back to 1950, when the disease incidence was 5.9 cases per 100,000 people [3]. At present, the incidence of this disease appears to be increasing at a rate of approximately 3–4% per year though this may be falling in recent years. If this rate continues, nearly 80,000 cases of NHL/year can be expected by the end of the next decade. This increase represents one of the largest noted for any malignancy over the last decade. Although the etiology for this increase is largely unknown, AIDS-related lymphomas are thought to contribute modestly to the observed trends.

During the past decade, we have witnessed a rapid and important evolution of novel treatment strategies for malignant diseases. However, successful translation of these innovative therapeutic strategies from drug development laboratories to the treatment of human cancer has been wrought with many challenges. Some of the obstacles specific for drug development in lymphohematopoietic tumors include the highly heterogeneous nature of these diseases [4], their under-representation in drug development laboratories [5] and the lack of appropriate animal models within which clinical investigators can develop and refine these novel therapeutic approaches. Rodent-based animal models have proven to be a valuable tool in the preclinical assessment of many antineoplastic strategies, but sometimes fail to reliably predict the observed response in humans. Therefore, there is a clear need to improve these rodent models of lymphohematopoietic tumors and to develop other animal models that may more accurately serve as pre-clinical tools for these diseases.

Xenogeneic animal models of lymphoma

The transplantation of human tumor cells into immunodeficient mice has been used extensively for the study of tumor biology and its response to treatment since the late 1960s. Athymic nude mice (nu/nu) were among the first murine models used to accept human tumors as a xenograft [6,7]. Human tumor xenografts generally retain the characteristics of the original tumor, including cellular morphology [8,9], tumor markers [10], oncogene and antigen expression [11–14], expression of receptors for growth factors and hormones [15–17], and some chemotherapy response characteristics [10]. Maintenance of these characteristics has made the nude mouse model a major tool in oncology research, especially for the preclinical testing of the new drugs and immunotherapy.

Factors influencing xenograft survival

The probability of xenograft acceptance varies considerably among the different mouse strains, tumor type, route of tumor cell administration, and alteration of the mouse immune system by immunosuppressive agents. Presently, there are at least 75 different congenic strains of nude mice. The different genetic backgrounds of these strains have been found to influence the xenograft transplantability and tumor growth [18]. Human leukemia and lymphoma cell lines are amongst the most difficult tumors to implant and grow in nude mice [19–25]. Sublethal irradiation of mice is often used before tumor implantation as a means of eradicating host immune effector cell function. It has been shown that irradiation improves tumor take rates and dissemination [26]. However, in select cases, radiotherapy has been shown to partially restore basic immunological function in SCID mice, potentially complicating the response of these mice, and their xenografted tumors, to chemotherapy and immunotherapy treatment [27].

The presence of enhanced natural killer (NK) cell function [28–35], macrophage activity [36,37] and naturally occurring anti-tumor antibodies in nude mice have been thought to affect the rejection of the transplanted human tumors [38,39]. Initially, xenograft rejection was felt to be primarily restricted to malignancies of the lymphohematopoietic system [40]. Subsequent studies have shown that a variety of other human tumors, and even normal cells, are susceptible to NK cell mediated activity. Although the data regarding the association between susceptibility to NK cell mediated activity and tumorigenicity are sometimes equivocal [33–37], several studies have explored ways to reduce the host immune effect against xenotransplanted tissue. Administration of anti-thymocyte/anti-lymphocyte serum [41–43], splenectomy, thymectomy [10], whole body irradiation, or various combinations of these modalities, have been shown to improve xenograft take rates and *in vivo* tumor growth [26,27,44–53]. Similarly, cyclophosphamide has been used not only for increasing the tumor take rates [54], but also for abrogating host immune responses against the murine antibody in immunotoxin-treated animals [55,56]. Specific NK cell depletion strategies have been employed using antibodies specifically directed against antigens expressed by NK cells [anti-asialo-GM1 (AA-GM1) and anti-NK1.1 antibodies]. Although AA-GM1 can inhibit NK cell activity *in vitro* and *in vivo* [57–59],

its influence on the survival of NK-resistant lymphoma cells in nude mice is controversial [60]. Other studies have shown very little additional benefit of immunosuppression with the addition of anti-asialo-GM1 antibodies in irradiated mice, especially in the profoundly immunosuppressed NOD/SCID strain [28].

Routes of xenograft implantation

The subcutaneous (s.c.) route has been the most commonly used route for tumor implantation; however, the growth of s.c. xenografts can be associated with profound differences in regional invasion, and can limit the metastatic potential of many tumor cell lines. Tumor cell suspensions can also be injected by a variety of other routes, including intravenous (i.v.), intraperitoneal (i.p.), intradermal, intra-arterial, intrabronchial, intracranial, intraventricular, intrasplenic, intrarenal, or via the foot-pad [21,60–69]. Tumor take rates can be increased after 'orthotopic' injection (i.e. placement of the tumor cells in the analogous organ of origin in the mouse) of the tumor cells, which can result in a greater metastatic potential [70–72]. Typically, the s.c. xenografts are not suitable for large-scale drug screening because the tumor take rates can be sub-optimal and, in certain instances, it can take 4–6 months to establish a palpable tumor. Sub-renal capsular implantation provides a rich vascular bed for drug delivery and represents a suitable method for assessing the *in vivo* response of a tumor to chemotherapeutic agents [73]. Similar to s.c. xenografts, subrenal capsular implants have been shown to behave like the original human tumor in terms of maintaining the original morphologic characteristics, natural history [62,74] and chemotherapeutic response characteristics [75–77]. Although this approach appears to more closely approximate clinical scenarios, the take rate for human lymphoma cell lines is still poor compared to other solid tumor xenografts [78]. Although some human lymphohematopoietic tumors have been found to survive in immunodeficient mice when implanted by the s.c. route, they do not spread through the murine lymphohematopoietic tissues like spontaneous lymphomas [23]. Intraperitoneal implantation is typically followed by local intraperitoneal tumor growth and ascites, and generally does not resemble the natural history of the corresponding haematologic disease [55,79–82]. Neoplastic cell involvement of the bone marrow, peripheral blood, liver, lung, spleen and central nervous system are observed more commonly following intravenous administration of human lymphohematopoietic tumors [81–84].

Primary central nervous system lymphomas (PCNSL) pose unique challenges not characteristic of other malignancies. Their growth and response to therapy may be significantly different from the results obtained in *in vitro* experiments, and typically do not resemble the results observed using systemic routes of administration of the same disease. Lymphomas and leukemias have been reported to demonstrate preferential growth in immunological sanctuary sites, such as brain and testes. One of the first lymphohematopoietic transplant models of PCNSL was developed after intracranial inoculation of the cells into nude mice [21–25]. Recently, a reproducible model of primary lymphoma of the central nervous system has been established in nude rats [85]. Human B-cell lymphoma cells (BL2) were implanted by a surgical procedure in the frontal area of the rats brain through a special silastic device sealed to the skull. The animals were sacrificed after 15 and 30 days and the analysis of the brain tissue showed tumor growth in 14 out of 16 animals (88% take rate). Such models may be more realistic approximations of the human disease (i.e PCNSL), given the fact that these diseases are growing in similar organ structures and microenvironment, unlike the usual flank s.c. approaches.

Immunodeficient murine models

Because many tumors are difficult to grow in nude mice, investigation into alternative mouse strains with other immunodeficiencies has blossomed (Table I). The mutant murine C.B-17 strain manifests a severe combined immunodeficiency (SCID) which was first described by Bosma et al. [86]. Mice homozygous for this mutation have impaired differentiation of both T- and B-lymphocytes resulting in profound lymphopenia. In addition, they are hypogammaglobulinemic and deficient for immune effector functions mediated by T- and B-lymphocytes. Subsequently, SCID mouse models have demonstrated several advantages over nude mouse models with regard to their ability to support the growth of human solid and lymphohematopoietic tumors [16,28,83,86–91].

The non-obese diabetic (NOD-SCID) mice have a spontaneous autoimmune T-cell defect with insulin-dependent diabetes mellitus, and are profoundly deficient in NK cell activity [92]. By crossing the *SCID* mutation from C.B-17 strains (SCID/SCID mice) onto the NOD background, the NOD/*LtSz-scid* strain was generated, which lacks mature lymphocytes and serum immunoglobulins. Irradiated NOD/*LtSz*-scid mice are capable of supporting 5- to 10-fold higher levels of human cell burden in their bone marrow compared to the

Table I. Strains of immunodeficient mice.

Strain	Description	References
Nude mouse (BALB/c nu/nu)	Chromosome 11 nu/nu gene, autosomal recessive. Athymic mice. Primarily a defect in T-cell functions, but consequently B-cell functions are also altered. Immunoglobulin production is sparse and IgM is the only immunoglobulin that is produced *in vivo* in high amounts. Macrophage system and natural killer (NK) cells in nude mice are active	[31,94,95]
Beige mouse (C.B-*Igh-1*^{b}GbmsTac-*Prkdc*^{scid}-*Lyst*^{bg} N7)	Chromosome 13 bg/bg gene, autosomal recessive. Impairment of NK activity, altered generation of cytotoxic T-cells in response to alloimmune challenge. Somewhat analogous to the Chediak–Higashi syndrome. Extensively used for evaluating the cytotoxic and anti-metastatic mechanisms of NK cells towards syngeneic tumor cells	[97,98]
Lozzio asplenic athymic mouse- (lasat)	Both chromosome 1 (Dh)-semidominant hemimelia and asplenia and the nu mutations. Agenesis of both spleen and thymus. Transplantation rates into lasat mice are at least as good as in nude mice and occasionally may be higher	[99,100]
X-linked immune deficiency mouse- (xid)	Chromosome X, recessive. B-cell defect in CBA/N mice characterized by low complement receptor, low Mls determinants, high surface IgM, low surface IgD, and low IgG3 production	[101]
Nude-Xid mouse-	The combination of the nu and xid mutation, resulting in a mouse with both T- and B-cell deficiency	[102]
Beige-nude mouse/Beige–xid mouse/ Beige-xid-nude mouse	Defects in two (beige-nude, beige-xid) or three (beige-xid-nude) loci obtained by crossing of beige, nude and xid mice. NK cells and macrophages are intact. They still mount immune responses, animals with even mild subclinical infections are extremely resistant to xenografting. They have been used to study haematopoiesis after engraftment of normal human haematopoietic tissues	[103,104]
Severe combined immunodeficiency mouse- (SCID)	Chromosome 16 scid/scid gene, autosomal recessive. Loss of B- and T-cell immunity. Extensively used as a xenograft model and human haematopoietic cell transplant model (hu-SCID, SCID repopulating cells-SRC). Remarkably sensitive to irradiation. (For nude approximately 600–900 cGy, but for SCID 300–350 cGy wipes out lymphohematopoietic system)	[88]
Non-obese diabetic/scid mouse- (NOD-LtSz-SCID)	Generated by crossing the SCID mutation from C.B-17-scid mice onto NOD background, which provided a new mice strain with B-and T-cell deficiency, depressed NK activity and less prone to develop 'leakiness' in comparison to SCID mice and lack of detectable haemolytic component. Major disadvantage; mean life span is only 8 months due to thymic lymphomas, which occur in 70% of this mice strain. The presence of NOD mouse-unique endogenous ecotropic murine leukemia provirus locus (Emv30) leads to activation on SCID background, ending up with thymic lymphoma. For this reason, Emv30^{null} NOD/LtSz-scid mice strain is generated which retains the ability of human haematopoietic support but develops thymic lymphomas in a delayed manner. Beta2 microglobulin-deficient (B2mnull) NOD/scid mice strain has been recently established and shown to support human haematopoiesis better than NOD/scid mice; however, this strain has been observed to be more radiosensitive, and had increased incidence of thymic lymphomas than both NOD/scid and SCID mice	[104,105,106]
Recombination activation gene (RAG-1 or RAG-2) deficient mice	Loss of B- and T-cell immunity, but still has NK cell activity. In comparison to SCID and NOD/SCID models, those strains are not proven to be better as human lymphohematopoietic xenograft models. Recently, NOD/LtSz-Rag1null strain has been generated with increased mean life span and more radioresistant than NOD/scid	[28,108,109]

C.B-17*scid* [93]. With or without additional immunosuppression, these strains are considered by many to possess several advantages over the nude mouse models, especially for lymphohematopoietic tumors [28,94].

To date, at least two immunodeficient murine models have been used to study engraftment of human haematopoietic stem cells. The NOD-SCID and the beige/nude/X-linked (*bnx*) immunodeficient mice are known to support long-term multi lineage engraftment of human stem cells in a murine bone marrow microenvironment [95]. Interestingly, in the *bnx* murine model, stable engraftment of T lymphoid cells, but not B lymphocytes, has been shown for over 12 months. In the NOD/SCID model, high levels of human haematopoietic stem cell engraftment can be obtained by injection of 5 $\times$ 10^4 cord blood, or 2 $\times$ 10^6 bone marrow CD34+ cells in irradiated mice (300–400 cGy). Under these conditions, up to 50% of the bone marrow is comprised of human CD45+ cells after 5–6 weeks [96]. However, this model is compli-

cated by the fact that these animals develop a very high incidence of spontaneous lymphoma, which typically develops at approximately 8 months of age. These models are particularly valuable in the study of genetically modified human stem cells in that they allow determination of whether true stem cell modification has been achieved because long-term engraftment will not be possible if more differentiated cells are transplanted.

Cell stromal factors influencing growth

Human tumors growing in immunodeficient mice eventually become a hybrid of cells composed of human malignant cells and murine stromal cells (blood vessels, mesenchymal elements). The relationship between the mesenchymal compartment and the malignant cells is well known as an important determinant of tumor behaviour. The stroma not only serves as a physical support for malignant cells, but also provides the ingredients for neovascularization and secreted factors that can affect tumor growth signals. Based on these observations, experiments using irradiated fibroblasts or sarcoma cells co-injected s.c. with lymphohematopoietic cell lines were shown to have a significant favourable effect on tumor take and growth rates [28,40,54,97–99]. Furthermore, increased rates of growth for haematopoietic-derived cells were achieved with co-transplantation of fetal bone marrow, thymus fragments, or fetal bone fragments (each containing stromal elements) under the renal capsule [92,100,101]. A logical extension of these studies has also included the administration of various human haematopoietic growth factors and cytokines. However, these data are generally inconsistent and the role of supplemental growth factors in facilitating lymphoma xenograft growth is unclear [84,102].

Adhesion molecules, bone marrow stromal cells and cytokines have a very important role in the regulation of human multiple myeloma (MM) cell growth and survival. Murine models of MM that support the growth of human cells in the context of a murine stromal micro-environment in SCID mice have been unable to discern the relative importance of the human bone marrow stromal cells on the growth of the human myeloma cells. Recently, an *in vivo* model of human MM using SCID mice implanted with bilateral human fetal bone grafts (SCID-hu mice) has been established [103]. In this model, the human fetal bone is implanted into irradiated SCID mice, where the bone eventually becomes engrafted with the development of its own blood supply. Human MM derived cell lines (ARH-77, OCI-My5, U-266 or RPMI-8226) are typically injected directly into the BM cavity of one of the bone implants. Over a 4-week period, the myeloma cells engraft and begin to proliferate in the implanted fetal bone. If left long enough, engraftment on the contralateral bone can also be achieved, whereas no metastasis to the murine stromal microenvironment is observed. This model has also been used for the study of primary cell lines obtained directly from patients. One such study has demonstrated successful engraftment of myeloma cells from over 80% of the patients studied [104]. What makes this study so elegant is that the paraproteinemia associated with the myeloma can be quantified from the murine plasma. This model allows the successful screening of agents for multiple myeloma, with fairly straightforward monitoring of a disease surrogate. In addition, the mice develop the classic osteopenia and osteoclastic lesions indicative of the human disease, with commensurate hypercalcemia. This model exhibits the importance of the stromal environment on myeloma engraftment and growth.

Lymphohematopoietic cell lines and the influence of exogenous factors

The very first reliable human lymphoma xenograft models were mainly established from Burkitt's lymphoma cell lines [24,105]. Many of the B- and T- cell NHLs have been successfully grown as xenografts, although models of indolent lymphomas and Hodgkin's Disease have been far less successful than models employing very aggressive large cell lymphomas [96,106–113]. However, the individual tumor take rates still vary considerably between the different immunodeficient mouse strains. The SCID mouse model supports different Hodgkin's cell lines better than the nude and the bg/nu/xid mice [114]. One of the difficulties with the well established murine models of human lymphoma is that they primarily focus on the most aggressive lymphoproliferative malignancies, such as Burkitt's or immunoblastic lymphoma, because these diseases are historically the easiest to grow under the broadest range of conditions. Therefore, there is a bias built into these murine models for sub-types of lymphoma that may not reflect the common biologies most frequently encountered in the clinic. Hence, there is an obvious and emergent need to try and develop models of the various lymphoma sub-types, so that drug screening and development initiatives can be more focused on specific biological questions and relevant targets.

When primary human lymphoma cells are grown in SCID mice, some animals develop lymphomas distinct from the original phenotype. These new phenotypes are often Epstein–Barr virus (EBV) positive and are thought to derive from EBV-

transformed SCID mouse B-cells [90]. This observation has necessitated validation of the original lymphoma cell line from the immunocompromised animals following implantation of the primary human lymphomas. Although there are a number of difficulties associated with human lymphoma xenograft models, many lymphoma cell lines retain the characteristics of the original lymphoma [40,115], and therefore can provide a useful model for the study of human lymphomas and their treatment.

The tumorigenicity of many human lymphoma cell lines in xenograft models is dependent upon the expression of certain adhesion molecules. Molecules such as the 80–90 kDa isoform of CD44 [116], the functional fibronectin receptor alpha 5-β1 (CD49e/CD29) [117], low lectin binding proteins [118], the production of vascular endothelial growth factor [119], interleukin (IL)- 6 [120–124] or IL-10 [125] can all affect tumorigenicity of the cell lines and EBV-immortalized human B-lymphocytes. Expression of leukocyte function antigen-1α and β by human EBV transformed lymphoblastoid cell lines was proposed to have a role in the homing of these cells to the central nervous system, based upon interactions with ICAM-1 expressed by endothelial cells within the vasculature of the brain [126]. Contrary to its normal B-cell growth and differentiation promoting effect, CD40 stimulation can inhibit the growth of various aggressive human B-cell lymphomas *in vivo*, and also prevents the occurrence of EBV-induced B-cell lymphomas in SCID mice [127–128]. *Ex vivo* systems using CD40L transfected Chinese hamster ovary cells may augment the growth of certain indolent NHL.

The presence or absence of cytokines is another important factor that influences tumorigenicity in xenograft models. EBV-infected B-cell tumors taken from immunocompromised patients are known to be very heterogenous with respect to their requirements for IL-6. Some of these cell lines are dependent upon the presence of IL-6, while others have no such requirement [120,129–131]. Interestingly, coadministration of IL-6 expressing EBV-immortalized cells with IL-6 non-expressing cells results in increased tumorigenicity of the IL-6 non-expressing cells [132]. These and other studies have suggested that production of IL-6 by immortalized cells can help them escape immune surveillance by inhibiting NK cell cytotoxicity at the tumor site [132]. Another example of an important cytokine influence has been observed in Burkitt's lymphoma cells. When highly tumorigenic Burkitt's lymphoma cells are transfected with different human and murine cytokine genes, only murine IL-4 transfectants suppressed the tumorigenicity of co-inoculated non-transfected lymphoma cells. This observation supports the notion that murine IL-4 administration could induce an *in vivo* antitumor effect against human B-cell lymphoma in SCID mice [133].

Hepatocyte growth factor (HGF) has been shown to produce a number of effects on lymphoma cells. It has been shown to increase the adhesion of c-MET positive B-cell lymphoma cells (BJAM) to the extracellular matrix, and to promote migration by increasing the invasion of the lymphoma in to the lung, liver and lymph nodes. However, this effect may be limited to specific cell types because the behaviour of c-MET transduced Ramos cells did not change significantly by HGF administration [134].

In addition to adhesion molecules and cytokine influences, a host of other biological factors have been shown to be important determinants of xenograft tumorigenicity. One such study correlated the presence of certain chromosomal aberrations like t(8:22) and t(2:8) with increased tumorigenicity in xenograft models. Other examples include the SCID-human thymus graft model, in which co-transplantation of human thymus was found to enhance the growth of primary T-cell NHL in SCID mice. Although the precise mechanism for this phenomenon remains to be elucidated, it points to the importance of human lymphoid microenvironments in malignant T-cell lymphogenesis [135]. The influence of cell cycle and death regulatory pathways on the *in vivo* tumorigenicity and chemosensitivity of both Hodgkin's disease and NHLs has also been evaluated in a number of different xenograft models. For example, transfection of wild-type tumor suppressor genes, such as retinoblastoma [136] or p53 [137], delayed or decreased the tumorigenicity of several lymphoma cell lines in mice. The expression of apoptotic genes such as Bik/Nbk, CD95/Fas [138] enhanced the *in vivo* chemosensitivity of lymphomas. Treatment of Raji lymphoma xenografts with methylprednisolone resulted in decreased expression of c-MYC and bcl-2 and, consequently, resulted in significant growth inhibition [139]. Transcriptional factors like NF-κB have been shown to prevent apoptosis in Hodgkin's lymphoma cells under a variety of different conditions, while depletion of constitutive nuclear NF-κB strongly impaired tumor growth in SCID mice [120]. These observations are consistent with the fact that a complex myriad of host and donor related genetic determinants govern the natural history of those transplanted cells in xenograft models.

Human T-cell leukemia virus type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia lymphoma (ATLL). Inoculation of SCID mice with HTLV-transformed cell lines and ATLL tumor cells was employed to investigate the tumorigenic potential of HTLV-1 [125]. HTLV-1 infected cell lines of

nonleukemic cells did not acquire tumorigenic potential in SCID mice. The authors noted that the IL-2 autocrine mechanism was not directly involved in the tumor cell growth, and viral gene expression was not required for the maintenance of neoplastic cell growth [140]. Enhanced NK cell activity was successful in eliminating the HTLV-1 infected cell lines but not the adult T-cell leukemia cell lines [129,130], while blockage of NK activity with anti-asialo GM1 antibody enhanced the engraftment of the HTLV-1 infected lines [132]. Because HIV-1 infection of already immortalized B-cell lines from EBV-positive donors lead to an up-regulation of EBV and c-myc transcripts, they readily formed invasive tumors of a Burkitt lymphoma phenotype after s.c. injection into SCID mice. Hence, HIV infection was considered to play a role in the pathogenesis of B-cell lymphoma in AIDS, apart from inducing immune suppression [131].

Spontaneous mouse models of lymphoma

Spontaneous mouse tumor models and genetically engineered mice

Genetically-engineered mice (GEMs) are animals with induced mutations including mice with transgenes, mice with targeted mutations (knockouts), and mice with retroviral or chemically induced mutations [141]. Transgenic mice carry a segment of foreign DNA that has been incorporated into the genome via non-homologous recombination following insertion by infection with a retroviral vector or, in some cases, by homologous insertion [142]. Mice with targeted mutations (knockouts) are created by first introducing gene disruptions, replacements, or duplications into embryonic stem cells by homologous recombination between the exogenous (targeting) DNA and the endogenous (target) gene. Genetically-modified embryonic stem cells are then microinjected into host embryos at the 8-cell blastocyst stage. Microinjected embryos are transferred into pseudopregnant host females that bear chimeric progeny. The chimeric progeny that carry the targeted mutation (i.e. the 'knocked out' gene) in their germ line are then bred to establish the line [143]. Mice with chemically induced gene mutations can be created using a variety of chemicals. For example, ethylnitrosourea (ENU) is used to induce point mutations [144]. ENU mutagenesis involves exposing male mice to ENU and then breeding the treated males with untreated females. The resultant progeny, many of which carry point mutations, are screened for phenotypes of interest.

GEMs are useful tools to elucidate basic biological processes, to study relationships between disease phenotypes and discrete genetic mutations, and as models of human disease. Because many human lymphoproliferative malignancies have been well described with respect to specific genetic lesions, there is an obvious potential to model these discrete molecular lesions in murine models mimicking the human disease [145,146]. Over the years, a large number of GEMs have been shown to develop lymphoproliferative malignancies. Transgenic mice with altered c-myc or bcl-2 have been developed, although again they appear more representative of the high grade aggressive lymphoid malignancies. It is well beyond the scope of this article to comprehensively review all strains of genetically engineered mice; however, some examples of mouse strains associated with particular genetic events and their subsequent propensity to develop lymphoma are presented in Table II. Increasingly, new GEM strains are becoming available, possessing a number features that make them an attractive or even complimentary alternatives to culture-based assays or human xenotransplant models. Of course, there are several liabilities associated with these sorts of models. For the most part, human cancer is felt to be the consequence of several 'genetic hits'. Although allowing the study of the impact of a discrete genetic event, or the importance of that event in various drug screening initiatives, these types of monogenic models are likely to be poor surrogates for the disease occurring spontaneously in patients given the more heterogenous nature of genetic lesions that are more commonly found in most human cancers.

As mentioned above, Table II shows some of the commercially available GEM strains that have been associated with an increased incidence of lymphoma, and their targeted genes. These animals develop tumors whose genetic profiles and histopathology appear similar to the molecular signatures and natural behaviour of human malignancies. Therefore, GEMs may be used to define the role of particular genes in response to new agents. Because GEMs are immunocompetent animals, they may be more realistic models from the viewpoint that the role of the immune system may more closely resemble the intact immune system in humans, allowing for a better assessment of the influence of secreted cytokines and effector cell function. Furthermore, unlike ectopic tumor cell transplants, spontaneously developed primary transgenic malignancies are never exposed to selective pressure by artificial growth conditions, allowing tumors to be treated in their natural microenvironmental context [147]. GEMs may also allow testing of single or multiple agents at various stages of tumor progression, including the very early manifestations of malignancy. Human tumor cell lines or xenografts are often not repre-

Table II. Some commercially available genetically engineered mice strains with increased incidence of lymphoma.

Strain name	Targeted gene	Description	References
129S6/SvEvTac-*Atm*^{tm1Awb}	Atm	Mice homozygous for the *Atm*^{tm1Awb} targeted mutation display many of the characteristics of ataxia telangiectasia. Most homozygotes develop thymic lymphoma between 2 – 4 months of age	[164]
C3H/He-TgN(LCKprBCL2)36Sjk	BCL2	Hemizygotes carrying the human LCKprBCL2 transgene display normal architecture of all lymphoid organs to 10 weeks of age. CD8 + cells and the total percentage of T-cells are increased in the spleen and lymph nodes. Malignant lymphoma develop in hemizygotes at approximately 18 months of age	[165]
STOCK TgN(MMTV-Cdc37)1Stp	Cdc37	In wild-type mice *Cdc37* is expressed primarily in proliferative tissues. These transgenic mice express *Cdc37* under the direction of an MMTV promoter. As a result, levels of transgene mRNA are significantly higher than levels of endogenous *Cdc37*. By 18 months of age, females exhibit proliferative disorders, including mammary tumors and lymphomas. By 22 months of age, 100% of transgenic females develop mammary or lymphoid tumors	[166]
CD1-TgN(Igh-HOX11)11Idd	*TLX1*	Heterozygous mice appear normal and healthy at birth but die in their second year of life. More than 85% of these mice die from mature B-cell lymphoma. No homozygous *TLX1* mice were identified in offspring of heterozygous mating, suggesting that homozygotes are not viable	[167]
C57BL/6J-TgN(IghMyc)22Bri	Myc	Expression of the mouse *Myc* transgene is restricted to the B-cell lineage. Hemizygotes show increased pre-B-cells in the bone marrow throughout life and a transient increase in large pre-B-cells in the blood at 3 – 4 weeks of age. Spontaneous pre-B and B-cell lymphomas reach an incidence of 50% at 15 – 20 weeks in hemizygous progeny of a wild-type female mated with a hemizygous male. The transgene synergizes with an TgN(BCL2)22Wehi transgene to produce primitive lymphoid tumors within 5 weeks of birth, and with an Emu-v-*abl* transgene to produce plasmacytomas by 8 weeks	[168]
NOD.Cg-*Prkdc*^{scid} *Emv30*^{b}/Dvs	Prkdc	Mice homozygous for the severe combined immune deficiency spontaneous mutation (*Prkdc*^{scid}, commonly referred to as *SCID*) are characterized by an absence of functional T-cells and B-cells, lymphopenia, hypogammaglobulinemia, and a normal haematopoietic microenvironment. There is a high incidence of thymic lymphomas in this congenic stock limiting the mean lifespan to only 8.5 months under specific pathogen-free conditions	[170]
129-*Trp53*^{tm1Tyj}	Trp53	Mice homozygous for the *Trp53*^{tm1Tyj} mutation show no visible phenotype but most develop tumors (principally lymphomas and osteosarcoma) at 3 – 6 months of age. Heterozygous mice develop tumors at approximately 10 months of age	[171]

sentative of pre-malignant or early lesions whose response to therapy may differ substantially from tumors that have accumulated substantial stochastic genetic changes.

There are other examples of GEMs that effectively mimic the clinical course of response to therapy and development of chemotherapy resistance. Subsequent analysis of non-responding mice or those that eventually became resistant may reveal additional genetic lesions or other changes that account for the observed differences. Non-responding mice may be useful for testing of new classes of agents to overcome resistance. Because these cancer models are developed on various strains of inbred mice or on mixed genetic backgrounds, they may also be valuable to delineate the genetic determinants of response or resistance to therapy. However, although initiated by a comparable genetic event, many tumor-suppressor knockout mice and oncogene-expressing transgenic mice do not precisely recapitulate human malignancies [148]. Furthermore, the secondary genetic events acquired during the process of tumor development in transgenic mice are often poorly characterized. The biological complexity of tumor progression can itself be viewed as a confounding factor in models seeking to control many variables. Although this variability recapitulates the diversity of patients diagnosed with

the same cancer entity, it can make tumors more difficult to compare [149,150].

In conclusion, using GEMs as drug screening models allows the effectiveness of anticancer therapies to be related to defined genetic lesions in naturally developed tumors. These models will not replace assays using human cancer samples, but rather will complement existing preclinical models by adding a more physiological layer of *in vivo* interactions

Spontaneous lymphoma in dogs

Spontaneous lymphoma (LSA) is one of the most common neoplasms seen in the dog. The annual incidence of canine lymphoma is estimated to be approximately 24 per 100,000 dogs at risk [151]. Lymphoma is the most common haematopoietic malignancy in dogs, and comprises approximately 16 – 24% of all canine neoplasia [152]. This neoplasm is a disease of predominately older animals; however, the disease has been reported in dogs ranging in age from 3 months to 18 years [153,154]. Genetic predispositions have been previously reported in a variety of pedigrees [155,156] and certain breeds such as Bernese Mountain dog, boxers, bassets, Scottish Terriers and bulldogs have the highest risks of lymphoma [157,158].

The etiology of canine lymphoma is presently unknown. Based on the mounting evidence implicating certain herbicides in the development of human NHL [159 – 161], two epidemiological studies have suggested that the use of such lawn herbicides may increase the risk for canine lymphoma development [162 – 164]. Characteristic non-random chromosomal abnormalities have been described in people with NHL; however, no consistent abnormalities have been noted in a single study performed in dogs with lymphoma [165]. Similar to some cases of impaired immunity-associated human NHL, diminished immune function has been described in dogs with lymphoma [166,167] and immune-mediated thrombocytopenia is associated with an increased risk of canine lymphoma development [168]. Histological criteria and anatomic location are the two predominate criteria for classification of canine spontaneous malignant lymphoma. The most common anatomic forms of lymphoma are multicentric, cranial mediastinal, cutaneous, gastrointestinal and extranodal. The most common presentation for dogs with lymphoma is with superficial lymphadenopathy with or without hepatosplenomegaly (i.e. multicentric). A multitude of histological classification systems has been previously used to describe canine lymphoma. The most readily adaptable human lymphoma to canine lymphoma classification schemes are the Working Formulation (NIH) and the Kiel system [169 – 173]. By contrast to human NHL, there are relatively few cases of follicular lymphoma in dogs; however, this may be due to dogs presenting in a more advanced stages of disease that could have been initially follicular (Table III). In addition, most canine cases of lymphoma are intermediate to high-grade and are usually all large cell tumors. Approxi-

Table III. Canine and human lymphomas (percentage) classified by the working formula.

Grade	Category	Canine[171]	Canine[176]	Human[4]
Low	Small lymphocytic	–	10.0	4.0
	Follicular small cleaved	12.0	–	26.0
	Follicular mixed small cleaved	4.3	1.0	9.0
Intermediate	Follicular large cell	31.0	3.4	4.0
	Diffuse small cleaved cell	8.6	3.4	8.0
	Diffuse mixed small and large	5.0	5.1	7.0
	Diffuse large cell	30.0	48.0	22.0
High	Diffuse immunoblast	6.0	25.6	9.0
	Diffuse lymphoblast	–	0.6	5.0
	Diffuse small noncleaved	–	3.2	6.0

Grade	Category	Canine[171]	Canine[176]	Human[4]
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High	Diffuse immunoblast	6.0	25.6	9.0
	Diffuse lymphoblast	–	0.6	5.0
	Diffuse small noncleaved	–	3.2	6.0

mately two-thirds to three-quarters of canine lymphoma are B-cell in origin based on immunophenotyping [175,196], and recent reports suggest greater percentage of remissions and longer remission/survival times in dogs with B-cell lymphoma [176,177].

The diagnostic evaluation of dogs suspected of having LSA should include history and thorough physical examination, blood count and serum biochemistry, urinalysis, bone marrow aspiration and lymph node biopsy. Additional diagnostics can include chest radiographs, abdominal radiographs and/or abdominal ultrasonography. Cerebrospinal fluid analysis, skin biopsy or other tests may be indicated based on the site of involvement. Based on the results of these tests, the extent of disease may be determined and a World Health Organization (WHO) clinical stage and substage delineated. The approach to therapy of dogs with lymphoma is determined by a variety of factors, including WHO stage/substage, anatomic location, financial limitations of the clients, as well as many other patient-specific factors.

With generally very few exceptions, lymphoma in dogs is considered to be a systemic disease and therefore systemic therapy is the treatment of choice. In rare cases where the lymphoma is in a single site, surgery and/or radiation therapy may be employed. Most dogs will die of their lymphoma in approximately 4 weeks if left untreated [169,178]. A variety of chemotherapy protocols for dogs with lymphoma have been developed over the last 20 – 25 years. Most multi-agent chemotherapy protocols will induce a complete remission in 65 – 85% of dogs with lymphoma, and the average remission and survival times are 6 – 12 and 9 – 15 months, respectively [177 – 181]. Most dogs tolerate chemotherapy well and, based on the percentage of response, it can be a gratifying disease to treat. The agents showing the most efficacy include L-asparaginase, vincristine, cyclophosphamide, prednisone and doxorubicin.

The prognosis for dogs with lymphoma is extremely variable and dependent on a growing number of factors including stage/substage, grade, anatomic location, immunophenotype and presence or absence of hypercalcemia. Recently, proliferative assays utilizing argyrophilic nucleolar organizing regions, proliferating cell nuclear antigen and bromodeoxyuridine have shown promise as prognostic indicators [169,182 – 184]. In addition, several investigators have shown the prognostic significance and predictability for remission/survival times via the expression of P-glycoprotein (Pgp) in dogs with LSA [185,186]. Based on the vast majority of efficacious chemotherapy agents in veterinary medicine being P-glycoprotein substrates, this would suggest that the use of non-Pgp substrate chemotherapeutics in Pgp-over expressing dogs with lymphoma might be therapeutically beneficial.

Previous authors have surmised that dogs with lymphoma appear to be good clinical models for human NHL [187 – 199]. The recent addition of more molecular-based prognostic factors in canine lymphoma argues that this disease may also represent a good molecular model for human NHL. Because lymphoma in dogs is a spontaneous malignancy, and dogs are generally an outbred species that live in an environment similar to humans, there is a strong argument for using dogs with lymphoma as an appropriate model of human NHL compared to murine xenograft models.

Use of animal models for evaluating novel treatments for human lymphoma

The most commonly exploited application for human lymphoma xenograft models has been in the evaluation of experimental therapeutic modalities.

Chemotherapy

Establishment of human lymphoma xenograft models by using different strains of immunocompromised mice has led investigators to test different therapeutic approaches in these models. However, the sensitivity of different lymphomas is known to be effected by the mice strain, route of drug and tumor administration, and the degree of irradiation of the mice employed [28,29,128,191]. In spite of these factors, drug sensitivity of the human haematological malignancies needs to be evaluated in the context of an *in vivo* model. Results obtained from *in vivo* SCID models and *in vitro* assays typically reveal remarkable differences in the patterns of resistance and sensitivity of the cell lines to many drugs, including daunorubicin, idarubicin, ifosfamide and etoposide [81].

Immunotherapy: monoclonal antibodies, immunotoxins and radioimmunotherapy

To date, an exhaustive literature list has been compiled evaluating the activity of a host of new anti-lymphoma therapies, some of which have proceeded onto successful clinical trials, others of which have not. For example, the therapeutic merits of several antigenic targets have been firmly established in many xenograft models. Unfortunately, many monoclonal antibodies are weak in provoking anti-tumor activity when used in their native form, save the promising activity of rituximab. Thus, antibodies conjugated to chemotherapeutic agents,

biological toxins or radioisotopes are designed for delivering intracellular poisons in a targeted manner. Bacterial toxins, such as diphtheria toxin and *Pseudomonas exotoxin* (PE), and plant toxins that are called ribosome inactivating proteins, such as pokeweed antiviral protein, gelonin, ricin, saporin and abronin, are conjugated to different antibodies for developing immunotoxins (ITs) [192]. These agents have been tested in xenograft models for determining the therapeutic window of ITs have been used to refine many of these IT strategies. First-generation ITs conjugated to native Ricin A (RTA), were cleared from the bloodstream rapidly and their entrapment in the liver caused marked liver damage [193]. Second-generation ITs used deglycosylated RTA (dgRTA) which were less toxic with longer half-lives [194,195]. After the cloning of the cDNA of the ricin precursor, recombinant RTA immunotoxins became available [174]. In SCID L540Cy-HD and SCID Daudi-Burkitt's lymphoma xenograft models using dgRTA conjugated monoclonal antibodies (CD25/Irac and CD19/CD22, respectively), prominent anti-tumor effects, such as prolonged remission and/or cure, were achieved with well-tolerated doses [187,196–198]. Comparison of ITs that bind to different epitopes have shown that the affinity of the antibody and possibly the epitope that it recognizes could affect the cytotoxicity [199]. In a disseminated Burkitt's lymphoma SCID model, dgRTA-anti-CD22 was also effective for extranodal disease [200]. A mutant form of the Pseudomonas exotoxin conjugated to anti-CD22 has also exhibited a remarkable response in SCID Burkitt's lymphoma model at doses well-tolerated in cynomolgus monkeys [201]. In a s.c. human B-cell lymphoma nude mouse model, PE conjugated LL2 or LL2-Fab′ induced tumor regression [202]. A variety of specific antibodies conjugated to different modified toxin molecules, such as blocked ricin [203], pokeweed antiviral protein [204], saporin [205,206], or PE [207,208] have also been tested in human T-, B-cell lymphomas, HD and anaplastic large cell lymphoma with promising activity. For example Intrathecal IT administration for central nervous system involvement was more effective than intrathecal methotrexate and well-tolerated in a scid-lymphoma model [209].

Considering the biological heterogeneity of the human lymphomas, combination therapy models have also been developed. The combination of chemotherapeutics such as doxorubicin, cyclophosphamide or campothecin, with ITs has been shown to improve the anti-tumor effect, with the best response being achieved when an IT-based therapy was given before or at the same time as the chemotherapy [210]. Combinations of IT to multidrug regimens may help to eliminate mdr expressing, drug-resistant lymphoma xenografts [211,212]. CD40L in combination with an IT has also been tested. In experimental animals, the selection of antigen-deficient mutants was observed to cause late relapses after monoclonal antibody-based therapies [213]. Combinations of ITs that bind to different epitopes on the tumor cells improved the therapeutic index of ITs both for HD and NHL [214–216].

In human Burkitt's lymphoma models, combinations of human recombinant IL-2 to Lym-1, anti-CD19 or anti-CD20 increased the efficacy of treatment by increasing the antibody-dependent cell-mediated cytotoxicity, and consequently anti-tumor activity [217–220]. Although other cytokines, such as TNF-α and IFN-γ [221], were also tried in combination with monoclonal antibodies for potentiating the anti-tumor effects, the use of IL-2 with anti-tumor antibodies was notably more active [222].

Bispecific monoclonal antibodies (Bi-MAbs) are able to accumulate and activate human effector cells at the tumor site because they have both an effector binding (Cd16 or CD3) and a target binding (CD30 or CD19) domain. Peripheral NK- or T-cells targeted by appropriate Bi-MAbs to tumor cells expressing a tumor-associated antigen display multiple signs of activation, including proliferation, cytokine secretion, up-regulation of cytotoxic peptides and enzymes and induce an efficient tumor cell lysis *in vivo*. Tumor-bearing SCID mice that were treated by effector cell-triggering Bi-MAbs were mostly cured [223–227]. Lymphoma-specific monoclonal antibodies conjugated to β-emitting radionuclides offer the possibility of delivering their energy not only to the lymphoma cells, but also to the surrounding or 'bystander' cells. Administration of radioiodinated antibodies specific for B-cell NHL, chronic lymphocytic leukemia, T-cell NHL or HD [228–231] have been studied extensively in xenograft models, providing the evidence that radioimmunotherapy alone or in combination with different chemotherapeutic agents, or cytokines, or immunotoxins, was effective both in an adjuvant setting for eliminating the minimal residual disease and in tumor reduction for disseminated/or bulky disease [213,214,232–235]. Although the concept of radioimmunotherapy-delivering radiotherapy in a site and tumor specific manner was simple, the observations in xenograft models and phase I trials showed that the choice and dose of optimal radionuclide, such as ^{125}I, ^{131}I, ^{212}Bib [200], ^{90}Y ^{269} or ^{67}Cu [236], use of 'cold antibody' predosing for optimal biodistribution [237], choice of linker [238] and antibody construct was critical in determining the efficacy and toxicity profile of the radioimmuno-

conjugates. The problem with the xenograft models for testing novel radioimmunotherapeutic agents was the difference in side-effect profile between mice and human. In murine models, myelotoxicity and hepatoxicity were observed less often than they actually occurred in humans. The results seen in canine models were considered to be closer to the observations in humans with regard to the side-effect spectrum [239].

Adoptive immunotherapy

Adoptive immunotherapy models using human lymphoma/scid xenografts have been used for understanding the role of cytokine or antigen induced T- or NK cells in eliminating the lymphoma burden.

Stimulation of human peripheral blood T-lymphocytes either *in vitro* or *in vivo* with a Burkitt's lymphoma (Daudi) cell line had led to induction of a cytotoxic T-cell line against Daudi cells. Adoptive transfer of this cytotoxic cell line increased the survival of SCID mice that were inoculated lethal dose of Daudi cells [240].

Immune surveillance of human B-cell Su-DHL-4 lymphoma cell line carrying translocation t(14;18) has also been evaluated in a SCID mice model by co-inoculation of IL-2 stimulated peripheral blood human leukocytes. This strategy demonstrated the efficacy of cellular therapy after autologous stem cell transplantation [241], which was effective for *in vivo* elimination of the disease.

As an adoptive immunotherapy model, SU-DHL-4 contaminated murine bone marrow samples were incubated with cytokine-induced killer cells (IFN-γ anti-CD3 mAb, and IL-2) and transplanted to SCID mice. This strategy proved to be effective in terms of graft purging [242].

Other therapy modalities

Antisense oligonucleotide therapy against bcl-2 and telomerase had some success in controlling tumor growth in Burkitt's lymphoma xenograft model [243–245]. In addition to these, gene therapy modalities have been recently evaluated in human lymphoma SCID model by using an immunoglobulin-regulated diphtheria toxin gene delivered by a novel adenovirus-polylysine conjugate [246], and EBV immediate-early protein genes delivered by adenovirus vectors [228].

Conclusions

The development of novel small molecules for the treatment of the lymphoproliferative malignancies has been hampered by the lack of available animal models reflective of the broader biology. These diseases represent a vast diversity of biological heterogeneity that is often not well represented in standard preclinical models of lymphoma. In addition, the presently available cell lines and models typically employ, for convenience sake, rapidly growing Burkitt's lymphomas, which do not represent most kinds of lymphoma, and certainly not some of the more clinically relevant forms of NHL. Many of these lines are also transfected by a number of different viruses (mostly EBV), which can cause them to behave in ways markedly different from their wild-type counterparts, typically imparting a more aggressive phenotype and better growth characteristics in the *in vivo* models. Hence, there is a growing need to identify those cell lines and *in vivo* models that may best represent the majority of lymphomas afflicting patients being cared for in the clinic.

Following the development of xenograft mouse models in the late 1960s, their application to understanding human malignancies has become indispensable. However, lymphomas are markedly more vulnerable to residual host NK cell activity. As a result, more fastidious and immunocompromised murine models have had to be developed. These mice are vulnerable to infections under standard housing conditions, and this often makes an understanding of the role of various biological therapies (such as monoclonal antibodies) very difficult to assess given the multitude of immunological defects. In addition, and as with any xenograft models, differences in the intrinsic sensitivity of the host and the implanted tumor cells may make evaluation of dose–response and cytotoxic effects difficult, especially when the intrinsic sensitivity for the host is greater than the implanted xenogeneic cells. Presumptions regarding the dose–response relationship for virtually any variable, from toxicity to cytocidal effects, varies significantly across species boundaries. Although xenograft models have formed the backbone of present day drug screening approaches, it is clear that some of the new generation genetically-engineered mouse models offer a new venue for circumventing this difficulty. Of course, the impractical feature of these models revolves around the fact that they do not adequately represent the sometimes enormous biological diversity and heterogeneity that often comprises a typical human tumor. This difficulty may be addressed through the use of other spontaneous models of human cancer, including those found in outbred animals such as dogs and cats. These models, while allowing us to embrace the heterogeneity of the tumor biology, suffer from the lack of reagents that might allow us to more thoroughly understand

mechanism, especially in regard to several of the immunologically-based treatment strategies. Although there is no such thing as the perfect model, it is clear that each model possesses its own strengths and liabilities. Identifying the best model to answer the questions at hand is likely to involve a multitude of different approaches to validate observations across the model systems and, hopefully, to increase the probability of success in translating laboratory approaches to the clinic.

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