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Naturally occurring canine cancers: powerful models for stimulating pharmacogenomic advancement in human medicine

“...research into canine cancer may offer a wealth of insight into driver mechanisms of human carcinogenesis and provide a more representative model for testing new therapies.”

KEYWORDS: cancer ■ canine model ■ chemotherapy ■ clinical trials

An estimated 1.6 million new cases of cancer were diagnosed in the USA in 2012 [101]. The pharmaceutical industry is working furiously to develop new efficacious chemotherapeutics; however, the vast majority of compounds that show anticancer activity in preclinical studies fail during subsequent human clinical trials, hindering progress in patient care and further increasing costs for drug development [1–3]. Modern cancer research places a heavy emphasis on murine models for investigating cancer etiology and for driving the development of new therapies. Mice represent excellent models for studying cancer due to their short lifespans, ease of maintenance and opportunities for genetic manipulation [4]. While their attributes have led to numerous fundamental advances in identifying novel therapies, several important limitations exist. Murine models of cancer are generally induced by genetic engineering, or by subcutaneous xenografts. The limitations and advantages of various methods of inducing neoplasms in mice are well reviewed elsewhere [4,5]. Induced murine neoplasms are developed in a short period of time and they lack heterogeneity in the tumor cell population, the microenvironment and the stroma, all of which are inconsistent with most human cancers. Furthermore, human cancers typically display increased genomic instability compared with their induced murine counterparts, which limits their utility as tools for pharmacogenomics [6]. Many of these limitations may be addressed by using the domestic dog as a complementary model system. Canines share our environment and develop many age-related diseases with similar pathologies to humans. Perhaps most importantly, dogs exhibit a wide variety of spontaneous cancers that share extensive clinicopathologic features with those of human patients, offering a unique opportunity for comparative analysis of

naturally occurring cancers towards advancing treatment strategies in both species.

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Why canines make promising models of human cancer

A survey conducted from 2011–2012 indicates that approximately 78 million domestic dogs currently reside in the USA [102]. The domestic dog suffers from more than 450 spontaneous diseases, approximately 360 of which have a human analog [7]. Cancer is the leading cause of death in several of the most popular dog breeds, such as golden retrievers, Labrador retrievers and boxers, which succumb to cancer with frequencies of 50, 34 and 44%, respectively [8]. When evaluated by breed, there are clear differences in predispositions for a variety of cancers. In turn, several canine cancers exhibit breed-associated profiles of tumor-associated genomic aberrations, including lymphoma, osteosarcoma (OS) and intracranial malignancies. Moreover, comparative studies have revealed conserved genomic signatures in canine and human counterparts of the same cancer [9–12]. Based on the large population of dogs that develop cancer and the clinical and pathological similarity between many dog and human cancers, research into canine cancer may offer a wealth of insight into driver mechanisms of human carcinogenesis and provide a more representative model for testing new therapies.

Canine pharmacogenomics

The availability of a high-quality canine genome sequence assembly [13] has opened the door for identifying key drivers of disease that may also

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impact human patients. In an effort to identify putative drivers of OS, Angstadt *et al.* combined bioinformatics and experimental methods to conduct a genome-wide assessment of tumor-associated DNA copy number aberrations in spontaneous canine and human OS [10]. OS in both species exhibits extensive genomic instability and a similar pathophysiological profile. Critically, however, human OS represents <1000 new diagnoses per year in the USA compared with >10,000/year in canines, thus providing tremendous sources of clinical materials [10]. Comparative analysis of recurrent copy number aberrations in human and canine OS revealed discrete gene sets that were common to both species, disrupting fundamental cellular functions such as osteoblast fate commitment, regulation of organ growth, telomerase activity and homophilic cell adhesion, among others [10]. These results shed new light on gene candidates that may play a role in OS development and progression in both species [10], reinforcing the enormous potential for advancement through cross-species approaches.

Clinical potential of canines

In addition to using tumor-bearing canines as preclinical models, methods for incorporating dogs into the existing clinical testing framework have been proposed, and a logical integrated approach has been well described by Paoloni and Khanna [6]. Since canine clinical management strategies utilize similar diagnostic and therapeutic modalities to those in human medicine, the diagnostic nomenclature of canine cancers broadly follows that of their human counterparts. Canine chemotherapy protocols focus on more palliative approaches and are therefore prescribed at lower doses than the equivalent human protocols [6]. For example, the standard protocol for canine B-cell non-Hodgkin's lymphoma (NHL) is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), which, until recently, was also the first-line treatment for humans with B-cell NHL. In human patients, the recent addition of the monoclonal antibody rituximab to the CHOP regimen (i.e., R-CHOP) has become the first-line treatment for humans with B-cell NHL.

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In the search for targeted lymphoma and autoimmune-related therapies, activation of the B-cell antigen receptor signaling pathway has

become a high priority since being identified as critical for the survival of B-cell NHL cells [14]. Btk represents a key component for B-cell antigen receptor activation, making the recent discovery of ibrutinib, the small-molecule irreversible inhibitor of Btk, a promising advance in the search for new and effective therapies for NHL [14,15]. In a recent study by Honigberg *et al.*, murine models were used to demonstrate ibrutinib's efficacy for treating lupus and arthritis, and dogs with spontaneous B-cell NHL were enrolled in a trial to test whether ibrutinib would affect disease progression [15]. At the time the study was published, eight dogs had been treated, with three partial responses (one dog with a 77% reduction in tumor burden) and three incidences of stable disease [15]. Upon these findings, a human clinical trial was promptly conducted on patients with refractory and relapsed B-cell NHL. Promising results were achieved, with a complete response in 16% of patients, while 60% of patients reached the objective response rate, and the median progression-free survival at the end of the trial for all patients was 13.6 months [16]. The US FDA has granted ibrutinib three ‘breakthrough’ designations and it is currently pending FDA approval. Hopes are high that it will see approval by the end of the year.

“...companion animal studies are subject to strict regulatory oversight that is highly comparable to that enforced for human patients.”

Ethics of the canine model

While the use of companion animals has enormous potential for comparative medicine, it is important to recognize that these canine patients are presenting with naturally occurring disorders and are receiving medical care for their own well-being with informed owner consent. Any time that research is performed in a clinical setting (rather than a laboratory setting), there are a number of additional factors that must be considered. These include the patient environment, owners of animals and the perspective of the general public.

Many of the ethical concerns regarding involving companion animals in clinical research studies are shared with basic principles of human subjects, including autonomy (informed consent, in this case of the owners) and non-maleficence (an absence of any sort of fraud or harmful deceit, as well as avoiding harm to the animal). Research conducted

in this setting requires rigorous protection of confidential patient/owner data and must be performed to a high ethical standard. As such, companion animal studies are subject to strict regulatory oversight that is highly comparable to that enforced for human patients. These principles will inevitably impact the design of canine studies, but are also critical for assuaging concerns.

Conclusion

The murine model will continue to be an indispensable resource for cancer research and is deserving of enormous credit for the advancements in cancer therapy over previous decades. We believe that the large numbers of available canine patients with spontaneous cancers can offer an unequalled opportunity for stimulating advancement in the clinical management of human and companion animal cancers. We propose that, for applicable diseases, the canine model should be integrated into existing pre-clinical and clinical frameworks (including pharmacogenomics studies) in a way that not only benefits human drug development and

disease understanding, but also improves the quality of treatment for our four-legged friends. Although we have focused primarily on cancer, it should also be noted that dogs are successfully used to study and develop treatments for many other diseases and disorders, such as wound healing, blindness and other vision disorders, heart disease, epilepsy, autoimmune diseases and narcolepsy [17,18]. It is our hope that with continued integration in these areas, we can expedite both the identification of druggable targets and improve the efficiency of the drug development system, for the benefit of both humans and canines.

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