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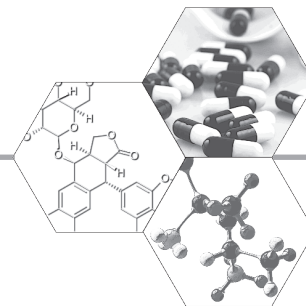
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Lab reports and cat scans: can veterinary oncology guide our way to new treatments for human cancers?

“There is a wealth of knowledge and experience to be gained from our veterinary oncology colleagues due to the synergy that often exists between our species and that of companion animals, concentrating particularly on cancers such as lymphomalleukemia, osteosarcoma, melanoma and mammary carcinoma.”

Keywords: cancer ■ clinical trials ■ comparative oncology ■ synergy ■ tyrosine kinase inhibitor ■ veterinary

The development of veterinary oncology as a speciality has benefited from the changing role of companion animals in society, and the accessibility to treatment afforded by pet insurance schemes now means that, at least in financial terms, a diagnosis of cancer in our pets is no longer an automatic death sentence. Veterinary oncology is making significant inroads as a specialist field of veterinary internal medicine, reflected by the work of referral practices around the USA and Europe. Many are affiliated with veterinary schools, which are leading the way in the development and optimization of treatments for a range of veterinary cancers. The Veterinary Cancer Society and the European Association of Veterinary Oncology have grown into vibrant professional organizations to promote advances in veterinary oncology. What is particularly illuminating is that studies involving spontaneous veterinary cancers are now appearing in the mainstream cancer research journals – in fact, a recent issue of this journal dedicated a mini-focus to veterinary pharmaceuticals [1].

Historically, efforts to merge the medical and veterinary professions towards mutual benefit of human and animal species began in the mid 19th century with the observations of Rudolf Virchow; who, being the son of a butcher, was well-placed to observe that the similarities between man and beast might lead to the transmission of infection. Inspired by these observations, Virchow became the first to describe the concept of zoonoses. It was his colleague, William Osler, however, who used these initial concepts and his interests in comparative pathology to turn veterinary pathology into a major discipline of the clinical sciences. In the process, he was advocating a ‘One Medicine’ philosophy that would encourage advances in

public health and increase our understanding of human and veterinary disease. The implications are still felt today, where the unravelling of the molecular pathogenesis of cross-species diseases, such as HIV and cancer, the evolution of drug resistance and the use of genetically manipulated animal models in biomedical research may be directly attributed to our understanding of comparative pathology. In recognition of the continuing need for cooperation and a shared platform for veterinary and medical research, The American Medical Association and the American Veterinary Medical Association have approved resolutions supporting the bridging between the two professions [2].

As we move into the second decade of the new millennium, comparative pathology is morphing into comparative ‘omics’, where, for example, canine cross-species genomics has been used to identify gene signatures expressed in human and canine osteosarcoma as a means of validating canine osteosarcoma as a model for the human disease [3]. Organizations such as the Veterinary Cancer Registry provide a resource for those studying the epidemiology of veterinary cancers, whereas sequencing projects such as the Canine Genome Project, a collaboration between the University of California, Berkeley (CA, USA), the University of Oregon (OR, USA), and the Fred Hutchinson Cancer Research Center, Seattle, Washington (DC, USA); and the Cat Genome Project, based at the Laboratory of Genomic Diversity at the National Cancer Institute (USA), have also provided comprehensive data on the expression of genes and, therefore, drug targets influential in tumorigenesis. This will help initiate studies to find new biomarkers, gene signatures and drug targets all available for bioinformatic analysis



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and comparison with data from the Human Genome Project.

The development of molecular cytogenetics has revealed chromosomal aberrations linked to malignant transformation; these have proven to be powerful prognostic indicators and a means of rationally applying chemotherapy with targeted anticancer agents in animal and human species. An early example is the Philadelphia chromosome, a translocation mutation that leads to overexpression of the fusion protein bcr–abl, a tyrosine kinase linked with tumor cell survival and proliferative pathways in chronic myelogenous leukemia that is expressed in both human and canine versions of the disease. This has enabled the leveraging of the bcr–abl inhibitor imatinib (Glivec®) for human to veterinary use [4].

There is a wealth of knowledge and experience to be gained from our veterinary oncology colleagues due to the synergy that often exists between our species and that of companion animals, concentrating particularly on cancers such as lymphoma/leukemia, osteosarcoma, melanoma and mammary carcinoma [5]. The Comparative Oncology Program, a division of the US National Institute of Health, proposes a scheme whereby studies involving cats and dogs are used as an additional layer of preclinical data to inform human cancer trials, alongside preclinical experimental animal models such as xenograft, transgenic or gene-targeted mice [6]. There are clear ethical advantages to using spontaneous veterinary cancers as models of human cancer – decreased reliance on genetically manipulated rodent models is in keeping with the reduction, refinement and replacement ethos in research involving laboratory animals. Ethical issues aside, however, we have greater genetic homology with dogs than with mice, they share our environment and therefore our risk of exposure to carcinogens unlike transgenic mice, there is a degree of genetic heterogeneity in the canine and our population. Like our cancers, veterinary cancers also occur naturally rather than by experimental induction. The biological similarities, such as the size, physiology and natural history of tumors in cats and dogs arguably provide a more relevant model; however, there are some double-edged swords. Companion animals and humans show similar size and tumor volumes, potentially providing a clinically valid predictive model for pharmacokinetic and toxicological studies. Whereas this offers the clear advantage of being able to use dose ranges directly translatable to subsequent

Phase I dose escalation studies carried out in humans, the flipside is the consequent increased cost of the drug formulations used.

Another issue to circumvent is that the average lifespan of the dog allows ‘clinical trials’ to take place over a shorter time span than in humans, where follow-up times of around 1–3 years are typically cited. These studies, however, will still take longer to complete than those involving mouse models [7,8]. That said, in contrast to the xenografted tumors often used for *in vivo* testing of anticancer agents, spontaneous veterinary cancers are syngeneic, that is, tumor and host are matched [9]. In a field where much of the scientific workforce is focused on developing agents that target the interaction between tumor cell and the host tissue environment, it is crucial that we have models where the molecular pathways being targeted are not purely restricted to malignant cells, but also to the host systems that heavily influence the path of cancer progression, such as the vasculature, inflammation and host immunity.

Veterinary oncology research initially lagged behind the rapid pace of human experimental and clinical oncology in terms of drug discovery and development. For instance, there has been a significant amount of catch-up to be done to optimize treatment regimens involving classical anticancer agents and radiation. These treatment modalities are reasonably well established in human oncology. Where veterinary oncology is coming into its own, however, is that first-in-dog studies care now a viable route for the preclinical development of novel targeted agents.

Where veterinary oncology potentially comes into its own as a model is for rare human cancers, about which we know relatively little. For instance, the incidence of osteosarcoma, a high-grade primary bone tumor, is only 1–3 cases per million worldwide and tends to affect teenagers and young adults. In contrast, osteosarcoma is a relatively common type of cancer in dogs, where approximately 8000 dogs per year are registered with the disease in the USA. While osteosarcoma is a disease of older dogs, as in humans the tumor tends to occur in the metaphyseal section of long bones. The underlying molecular pathogenesis is similar in part – p53 mutations arise in both canine and human osteosarcoma and, just as HER-2 overexpression is an indicator of poor prognosis in the human disease, the related *erb-b2* gene is overexpressed in the canine disease. The similarity extends to the expression of PDGFR, the IGF-1 receptor and oncogenes

such as c-myc. In terms of the natural history of the disease, the pattern of metastasis also shows similarity, most commonly occurring in the lung [8]. A canine brief-pain inventory has proven to be a reliable device when measuring pain constructs and interference with normal activity, showing potential for use in pain studies that will optimize how we clinically manage bone pain and assess quality of life in the palliative care of human patients with the disease [10].

Canine mammary gland cancers are also considered to be models of human breast cancer and, accordingly, biomarker studies have revealed shared molecular pathways involving the overexpression of steroid receptors, proliferation markers, mutated p53 and microenvironmental targets, such as the matrix metalloproteinases and cyclooxygenases. Human and canine diseases have a similar clinical course, hormone-dependent etiology and relative age of onset [11]. Some important comparative studies taking place at the veterinary school at the Freie Universität Berlin (Germany) have looked at the shared characteristics of metastatic breast disease at the genomic, proteomic and transcriptomic level. In particular, the transcriptomic study revealed a metastatic 'cascade' of pathways relating to cell division and matrix invasion. Again, upregulation of matrix metalloproteinases was observed in metastatic tumors alongside downregulation of adhesion proteins such as PECAM1, demonstrating an overlap with gene expression signatures in human breast cancer [12].

To be able to realistically integrate clinical trial data from veterinary patients with human studies depends upon the use of comparable clinical end points and being able to 'scale' these appropriately. Response Evaluation Criteria in Solid Tumors guidelines are continually updated in both human and veterinary cancers by consensus, considering parameters such as the measurable size of the lesion and how this relates to the extent of response and disease progression after treatment. Although, of course, timescales involved and the point at which response is evaluated differs between veterinary and human patients, the approach is similar, where time to progression may be used as a parameter for evaluation of clinical response in trials [13]. The diagnostic approaches typically used in human oncology trials, such as ¹⁸F-DG PET, are also gaining acceptance in veterinary oncology; a good example being its use to assess response to the tyrosine kinase inhibitor toceranib, a newly approved

targeted anticancer agent specifically licensed for the treatment of canine mast cell tumors [14].

The development of tyrosine kinase inhibitors is perhaps the biggest success story for targeted anticancer agents in both veterinary and human oncology. As well as promising data coming out of trials of imatinib in dogs and cats with mast cell tumors and sarcomas, the recent approval of toceranib (Palladia®) and masitinib (Masivet®), also for the treatment of canine mast cell tumors, is testament to the investment in veterinary oncology by the pharmaceutical industry and the laying of groundwork for future trials as part of multimodality treatments in companion animals. Imatinib was originally developed as a novel treatment for bcr-abl-expressing chronic myelogenous leukemia, subsequent studies highlighted its activity against the oncogene c-Kit in gastrointestinal stromal tumors [15] and melanomas arising in humans [16]. Crucially, however, toceranib and masitinib were developed for veterinary patients. Kit is a mast cell receptor, where its mutation leads to excessive signalling and loss of growth control. Toceranib is a multi-kinase inhibitor, targeting Kit, but also VEGFR, PDGFR and Flt-3; and, aside from its current use for canine mast cell tumors, the drug has been evaluated in a range of other tumor types such as sarcomas, carcinomas, melanoma and myeloma [17]. What is particularly interesting here is that the uptake of these agents demonstrates that angiogenic growth factor receptors, such as EGFR and VEGF, are of shared prominence in human and veterinary research, and that there is scope for leveraging trials involving novel tyrosine kinase inhibitors from veterinary to human medicines and *vice versa*. As far as Kit goes, however, the relevance of the target relates to the differences in tumor pathology existing between man and companion animals. Mast cell tumors are a relatively common malignancy in dogs, particularly Boxers, that tend to develop in the skin and intestines; whereas, the most closely related condition in man is mastocytosis, a condition that may manifest cutaneously as mastocytoma of the skin, but has mainly systemic effects affecting mast cell function throughout the body. Both mast cell tumors in companion animals and mastocytosis as it occurs in humans are mediated via activation of Kit. Masitinib, like toceranib and imatinib, targets Kit. Accordingly, masitinib is now being transferred to human oncology, where it is undergoing evaluation as a treatment for mast cell leukemia, which is one manifestation of mastocytosis [18,19].

Although it has taken decades of human oncology research to produce the targeted agents, this knowledge has been rapidly taken up by the veterinary oncology field and we have seen tyrosine kinase inhibitors for veterinary use developed in parallel with their human equivalents. In a similar fashion, 'hot topics' currently on the human oncology research circuit, such as the tumor microenvironment, metabolism and radiation oncology, are experiencing a knowledge surge in veterinary oncology. For instance, work is currently taking place at the Comparative Oncology Program to bring inhibitors of the mammalian target of rapamycin (mTOR) into clinical use for canine osteosarcoma [20]. We are also seeing clinical trials to evaluate novel agents targeting the molecular chaperone Hsp90 in dogs with a range of spontaneous tumors, which is parallel to

the development of Hsp90 inhibitors in human oncology research [21].

While to any pet owner, the successful treatment and prolongation of life for our canine and feline family members is a valuable end point in itself, there is increasing recognition that by treating our pets, we stand to gain valuable insight into how we treat cancer in our own species.

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References

- Martinez MN. Welcome to the animal pharmaceuticals special focus. *Future Med. Chem.* 3(7), 845–846 (2011).
- Cardiff RD, Ward JM, Barthold SW. 'One medicine – one pathology': are veterinary and human pathology prepared? *Lab. Invest.* 88(1), 18–26 (2008).
- Paoloni M, Davis S, Lana S *et al.* Canine tumor cross-species genomics uncovers targets linked to osteosarcoma progression. *BMC Genomics* 10, 625 (2009).
- Breen M. Update on genomics in veterinary oncology. *Top Companion Anim. Med.* 24(3), 113–121 (2009).
- Vail DM, MacEwen EG. Spontaneously occurring tumors of companion animals as models for human cancer. *Cancer Invest.* 18(8), 781–792 (2000).
- Khanna C, Vail DM. Targeting the lung: preclinical and comparative evaluation of anticancer aerosols in dogs with naturally occurring cancers. *Curr. Cancer Drug Targets* 3(4), 265–273 (2003).
- Pinho SS, Carvalho S, Cabral J, Reis CA, Gärtner F. Canine tumors: a spontaneous animal model of human carcinogenesis. *Transl. Res.* 159(3), 165–172 (2012).
- Mueller F, Fuchs B, Kaser-Hotz B. Comparative biology of human and canine osteosarcoma. *Anticancer Res.* 27(1A), 155–164 (2007).
- Rankin KS, Starkey M, Lunec J, Gerrand CH, Murphy S, Biswas S. Of dogs and men: comparative biology as a tool for the discovery of novel biomarkers and drug development targets in osteosarcoma. *Pediatr. Blood Cancer* 58(3), 327–333 (2012).
- Brown DC, Boston R, Coyne JC, Farrar JT. A novel approach to the use of animals in studies of pain: validation of the canine brief pain inventory in canine bone cancer. *Pain Med.* 10(1), 133–142 (2009).
- Queiroga FL, Raposo T, Carvalho MI, Prada J, Pires I. Canine mammary tumours as a model to study human breast cancer: most recent findings. *In Vivo* 25(3), 455–465 (2011).
- Klopfleisch R, Lenze D, Hummel M, Gruber AD. The metastatic cascade is reflected in the transcriptome of metastatic canine mammary carcinomas. *Vet. J.* 190(2), 236–243 (2011).
- Vail DM, Michels GM, Khanna C *et al.* Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0) – a Veterinary Cooperative Oncology Group (VCOG) consensus document. *Vet. Comp. Oncol.* 8(1), 28–37 (2010).
- Leblanc AK, Miller AN, Galyon GD *et al.* Preliminary evaluation of serial 18FDG-PET/CT to assess response to toceranib phosphate therapy in canine cancer. *Vet. Radiol. Ultrasound* 53(3), 348–357 (2012).
- Croom KF, Perry CM. Imatinib mesylate: in the treatment of gastrointestinal stromal tumours. *Drugs* 63(5) 513–522; discussion 523–524 (2003).
- Postow MA, Carvajal RD. Therapeutic Implications of KIT in Melanoma. *Cancer J.* 18(2), 137–141 (2012).
- London CA. Tyrosine kinase inhibitors in veterinary medicine. *Top. Companion Anim. Med.* 24(3), 106–112 (2009).
- Misdorp W. Mast cells and canine mast cell tumours. A review. *Vet. Q.* 26(4), 156–169 (2004).
- Metcalf DD. Regulation of normal and neoplastic human mast cell development in mastocytosis. *Trans. Am. Clin. Climatol. Assoc.* 116, 185–203; discussion 203–204 (2005).
- Paoloni MC, Mazcko C, Fox E *et al.* Rapamycin pharmacokinetic and pharmacodynamic relationships in osteosarcoma: a comparative oncology study in dogs. *PLoS ONE* 5(6), e11013 (2010).
- London CA, Bear MD, McCleese J *et al.* Phase I evaluation of STA-1474, a prodrug of the novel Hsp90 inhibitor ganetespib, in dogs with spontaneous cancer. *PLoS ONE* 6(11), e27018 (2011).