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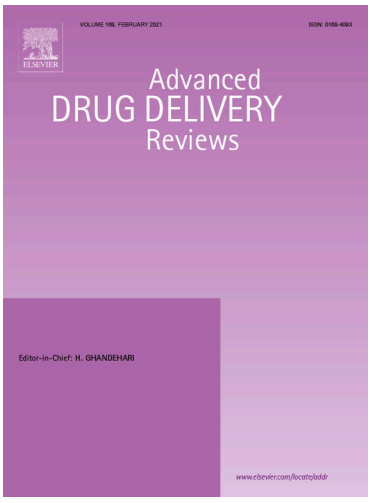

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Translational oncotargets for immunotherapy: from pet dogs to humans

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List of abbreviations

AKT1 and 2 – serine/threonine kinase 1 and 2
ARID1A – AT-Rich Interaction Domain 1A
BCL2 – B-cell lymphoma 2
BRAF – encodes the serine/threonine-protein kinase B-Raf
BRCA 2 – breast cancer 2
BUB1B – mitotic checkpoint serine/threonine-protein kinase BUB1 beta gene
CDK4 – cyclin-dependent kinase 4
CDKN2A/B – cyclin-dependent kinase inhibitor 2A and B
CGA – cancer-germline antigens
CSPG4 – chondroitin sulfate proteoglycan-4
DLG2 – disks large homolog 2
DMD – Duchenne muscular dystrophy
dTERT – dog telomerase reverse transcriptase
EGFR – epidermal growth factor receptor

ERK – extracellular signal-regulated kinase

FAT4 – gene encoding protocadherin Fat 4

GM-CSF – granulocyte-macrophage colony-stimulating factor

HLA – human leukocyte antigen

KRAS – gene encoding K-Ras protein

LRP1B – gene encoding low-density lipoprotein receptor-related protein 1B

MAPK – gene encoding mitogen-activated protein kinase

MDM2 – gene encoding mouse double minute 2 homolog

MHC – major histocompatibility complex

MYC – family of regulator genes and proto-oncogenes that code for transcription factors

NF-κB – gene encoding nuclear factor-kappa B

NF1 – gene encoding nuclear factor-1

NK – natural killer

NRAS – gene encoding N-Ras protein

PIK3 – gene encoding phosphoinositide-3-kinase

PIK3CA – gene encoding phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha

PLCG1 – gene encoding phospholipase C Gamma 1

POT1 – gene encoding protection of telomeres 1

PTEN – gene encoding phosphatase and tensin homolog

PTPN11 – gene encoding protein tyrosine phosphatase non-receptor type 11

PTPRJ – gene encoding protein tyrosine phosphatase receptor type J

RB1 – gene encoding retinoblastoma transcriptional corepressor 1

S100A8/9 – gene encoding S100 calcium-binding protein A8

SETD2 – SET domain containing 2 encodes the Histone-lysine N-methyltransferase

SPRED1 – gene encoding Sprouty related EVH1 domain containing 1

STK11 – gene encoding serine/threonine-protein kinase 11

TAA – tumor-associated antigens

TERT – telomerase reverse transcriptase

TRAF3 – gene encoding tumor necrosis factor receptor associated factor 3 protein

TSA – tumor-specific antigens

WNT/β-catenin – gene encoding wingless-type ligand/β-catenin

Abstract

Pre-clinical studies in rodent models have been important for human clinical research, but many of them failed in the translational process. Spontaneous tumors in pet dogs have the potential to bridge the gap between preclinical models and human clinical trials. Their natural occurrence in an immunocompetent system overcome the limitations of pre-clinical rodent models. Due to its reasonable cellular, molecular, and genetic homology to humans, pet dog represents a valuable model to accelerate the translation of pre-clinical studies to clinical trials in humans, actually with benefits for both species. Moreover, their unique genetic features of breeding and breed-related mutations have contributed to assess and optimize therapeutics in individuals with different genetic backgrounds. This review aims to outline four main immunotherapy approaches – cancer vaccines, adaptive T cell transfer, antibodies, and cytokines –, under research in veterinary medicine and how they can serve the clinical application crosstalk with humans.

Keywords

Pet dog, cancer model, comparative oncology, tumor antigens, immunotherapy

1. Introduction

In the USA, 63.4% of households owned nearly 89.7 million dogs [1]. In the European Union, the estimated number of owned dogs exceed 87.5 millions in 38% of all households [2]. Worldwide, Argentina, Mexico, and Brazil are the countries which have the highest percentage of pet owners, totaling more than 115 million dogs [3]. However, due to the lack of national census and a global and harmonized system of animals' registry, the real dimension of pet dog population in the world remains unknown, though it has been increasing for the last few decades. Additionally, the interaction between dogs and humans have changed. Once used to perform practical tasks (e.g., protection or hunting), dogs are kept today as pets independently the purpose to which they were originally bred. Shepherd dogs used in the past to herd the flocks, for example, are now kept indoor as companion animals. Moreover, dogs have earned the status of family members mainly in Western societies, but also in East Asian societies like Japan [4,5]. Dog owners are now demanding for more advanced veterinary

healthcare and to invest more resources in diagnosis' technologies and pioneer therapeutics like those applied to humans. At the same time, the food industry has created a wide range of nutritionally balanced diets, specially formulated to provide tailored nutrition to pet dogs of different body weight, breeds, and health conditions. Altogether, dog's health have improved substantially, leading to longer life expectancies [6,7], and consequently the development of cancers and other age-related diseases [8–13].

In the pet dog population, cancer represents one of the major causes of death, varying between 15% to 30% [6,14–19]. However, very few epidemiological studies have attempted to estimate population-based rates of cancer incidence in pet dogs, ranging from 142.8 in Venice and Vicenza provinces, Italy, to 852.0 cases per 100,000 dogs/year in Ontario, Canada (Table 1). This great variability is mainly due to dissimilar methodologies and base populations, which biases the estimated incidence [20–22]. Three studies used a national population-based registry, two of them an insurance database [23,24] and the other a national canine cancer registry [25]. The latest – the Swiss Canine Cancer Registry (SCCR) – is a reference database that compile retrospectively canine cancer cases across Switzerland, whose diagnosis were based on histopathological or cytological examination and coded according to the ICD-O-3 standards [25]. Meanwhile, improvement of statistical methods for a more powerful estimation of canine cancer incidence based on the SCCR have been recently developed [26,27]. In addition, some studies start focusing on the incidence of certain types of tumors (e.g., mammary tumors [28,29]).

Table 1 – Estimated incidence of cancer in pet dogs.

Year	Location	Scope	Population	Incidence#	References
1968	Alameda county, CA, USA	Regional	Canine cancer registry	381.2	[30]
1978	Tulsa county, OK, USA	Regional	Canine cancer registry	507.0	[31]
2000	Ontario, Canada	Regional	Practice clinical records	852.0	[32]
2002	UK	National	Insured dogs	747.9	[23]
2005	Sweden	National	Insured dogs	500.0	[24]
2008	Genoa municipality, Italy	Regional	Practice clinical records	169.2 males 312.0 females	[33]
2009	Venice and Vicenza	Regional	Telephone	142.8	[34]

	provinces, Italy		survey		
2015	Switzerland	National	Canine cancer registry	695.0	[25]
2017	Piedmont, Italy	Regional	Canine cancer registry	804.0	[35]

number of cases per 100,000 dogs/year.

Studies on the prevalence of tumors in pet dogs are also scarce and limited by the existence of few cancer registries (mainly in the USA and some European countries), inconsistency of the code used (hystiotype versus anatomical site), the type of base population (insurance databases, referral practice clinical records, primary care practice clinical records, cancer registries or questionnaire-based data collection), geographical and environmental features, and non-standardized inclusion/exclusion criteria [20,21]. The need for a computerized technology to the collection of veterinary data using a standard coded case record was acknowledged in the early 1980s [36], but a harmonized methodology allowing good quality epidemiological studies continuous to be a claim in nowadays. Considering these limitations, the SCCR seems to be a reliable source to extract useful information on the prevalence of tumors in the dog population due to its methodology and representativeness. Comprising 121,963 diagnostic records for the period 1955-2008, the multivariate analysis conducted by Grüntzig et al. [37] revealed the prevalence of malignant and non-malignant tumors (Table 2).

Table 2 – Prevalence of tumors (malignant and non-malignant) in pet dogs based on the Swiss Canine Cancer Registry [37].

Type of tumor	Frequency (%)
Adenoma, adenocarcinoma (ICD-O 8140)	18.09
Mast cell tumor (ICD-O 9740)	6.50
Lymphoma (ICD-O 9590, 9591, 9700)	4.35
Melanocytic tumor (ICD-O 8720, 8730)	3.63
Fibroma, fibrosarcoma (ICD-O 8810, 8812)	3.40
Squamous cell carcinoma (ICD-O 8070, 8071, 8078)	1.95
Osteoma/osteosarcoma (ICD-O 9180)	1.24

Adenoma/adenocarcinoma were the most frequent tumor, with 55.4% to be found in the mammary gland and 8.3% in the gastrointestinal tract [37]. Other studies have reported a similar prevalence [25,29,35]. The influence of age and neutering status on the rate of these tumors is well-established, prevailing in female dogs over 5 years of age and

entire females [31,37–39]. Interestingly, exceptional longevity in dogs seems to have a cancer-resistant phenotype just like in the oldest-old humans [40]. Overall, the risk of tumor increases with age, which was confirmed by Grüntzig et al. [37] for adenoma/adenocarcinoma, melanocytic tumors, and squamous cell carcinoma. The same authors have found a set of purebreds with an increased risk of developing adenoma/adenocarcinoma tumors in comparison with crossbreds and other purebreds. Similar findings were reported by other authors strongly suggesting a genetic predisposition for certain types of tumors [6,15,16,25,30,35,39,41,42]. Skin and female reproductive system seems to be the most common locations of cancer in pet dogs [39].

In this review, we will start addressing briefly the main features that make the pet dog a powerful translational model for human cancer research. Then we will focus on the challenges of comparative oncology, especially in terms of data integration, and how the research community is coping with these challenges through the creation of innovative methods and tools. Finally, considering that there are numerous reviews focusing the translational power of pet dog model in different types of cancer, it is described four immunotherapy approaches currently under clinical research in veterinary medicine – cancer vaccines, adaptive T cell transfer, antibodies, and cytokines –, and discussed to what extent they can serve the clinical application crosstalk with humans.

2. Pet dog as a powerful cancer model to humans

Rodent models have been extensively used for decades in biomedical research to understand the mechanisms and genetic pathways in cancer initiation, progression and metastasis, and to evaluate novel anticancer drugs [43–49]. Many characteristics have made it an interesting model, including resemblance of human carcinogenesis, ease to handle and maintain at a low cost, ease of implementation and manipulation, availability of well-characterized cell lines and immune-deficient lines, controlled cancer progression in selected organs, a genome that is easily manipulated, and an impressive volume of published data [44,50]. However, constrains in the representation of several important features that define human cancer (e.g., spontaneous development of cancer, immunocompetency, long period of latency, the biology of cancer, including metabolism, vascularization and inflammation, tumor microenvironment [51]) and

intrinsic limitations of the model (e.g., tolerance to higher drug concentrations than humans, a bone marrow less sensitive to cytotoxic agents, lower mutational burden of tumors [52,53]) reduces their translational power [47,54,55]. In fact, Mak et al. [56] estimated the average rate of successful translational from rodent models into the clinic to be less than 8%. These limitations have been addressed over the last few decades through the development of models resembling more closely the humans, namely the generation of humanized rodent models reconstructed with human immune systems [57–60]. These models are characterized by improved designs, functionalities and applications (e.g., the possibility of *in vivo* evaluation of cellular and antibody-based immunotherapies [61]) that may potentially contribute to boost human cancer research; however, some major limitations persist, namely their allogenicity in relation to the inoculated human tumors, the MHC incompatibility and lack of species-specific growth factors, cytokines and chemokines [57,61].

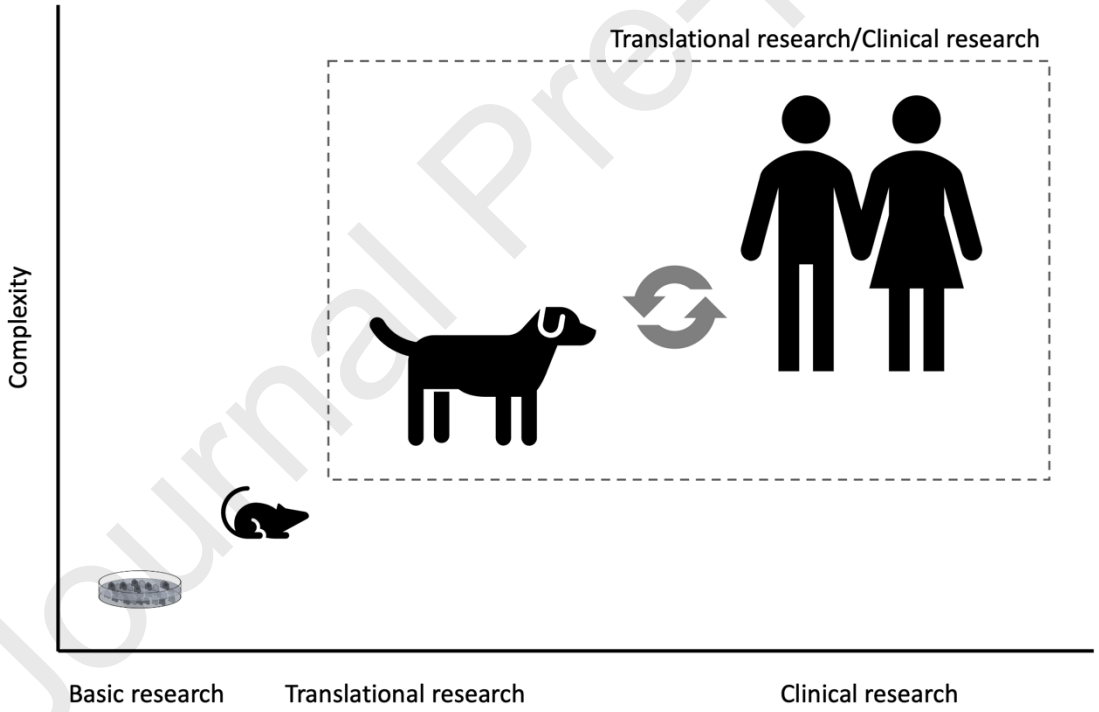

Figure 1 – Different models involved in the study of oncogenesis according their biological complexity and its relative position in the type of research (basic, clinical and translational). More than a translation model, pet dogs are involved in both translational and clinical research, which increase its value as a cancer model. (Adapted from [62].)

Pet dogs have been considered valuable additional models that may overpass some important limitations of rodent models. Numerous studies have highlighted in detail its relevance for cancer research and pointed out its translational power [8,48,56,62–88], but one major advantage of this model is their unique position in translational and clinical research which ultimately benefits both pet dogs and humans (Figure 1). There are clinical trials involving pet dogs to better understand not only the mechanism and pathways of oncogenesis in this species, but also to explore novel therapies. The outcomes of these trials can be useful for human cancer research, which means that pet dog is simultaneously involved in clinical veterinary studies and in preclinical human studies. Interestingly, clinical human studies are also informative to pet dog cancer research. In broad terms, humans may also be a "model" to pet dogs [81]. Table 3 summarize the relevant features of pet dogs as human cancer models comparing to rodent models.

Table 3 – Comparison of rodent and pet dog model characteristics and similarities with human tumors (adapted from Gordon & Khanna [70]).

	Rodent models	Pet dog models
Genetic variability	Inbred	Outbred
Tumor occurrence	Induced	Spontaneous
Histopathologic similarities	Variable	Yes
Physiologic and systemic effects	No	Yes
Tumor progression	Rarely	Yes
Tumor molecular profile	Homogeneous	Heterogenous
Tumor microenvironment	Variable	Yes
Genes and pathways involved in cancer initiation, progression, and metastasis	Variable	Frequently
Environmental factors	Highly controlled but doesn't resemble the human environment	Less controlled but are exposed to the same environment as humans
Response of corresponding human tumors to therapies	Variable	Frequently
Assessment of the influence of germline genetic variation on tumor response to drug	No	Yes
Approach	Experimental	Clinical

Rather than being chemically or genetically induced, pet dogs develop cancer spontaneously. They are immunocompetent hosts, immunological outbred and show a reasonable cellular, molecular and genetic homology with humans, including

phenotype, anatomical location, biological behavior, histology, mutational signatures, signaling pathways, immunological reaction and the influence of tumor microenvironment in the cancer progression [75,89,90]. Age, diet, sex, hormonal status, and environment are common factors that influence cancer development both in humans and pet dogs [9,37,91–96]. More recently, special attention has been given to the epigenetic mechanisms involved in pet dog cancer initiation and progression and its potential to elucidate human cancer and eventually therapeutical targets [97,98]. Genome mapping of boxer dog with the shotgun sequencing technique revealed the existence of approximately 19,300 genes and a high level of homology to those in human known genomes [99,100]. This homology seems to be associated to a positive selection during domestication, which overlaps extensively with the corresponding positively selected genes in humans, in particular those related with digestion and metabolism, neurological process and cancer [101]. In fact, pet dogs are phylogenomically closer to humans than the mouse or other rodents [102]. They share about 650Mb of common ancestral sequences, compared with the 380Mb observed in the mouse [103]. Overall there is an estimated orthology of 70 to 80% between mouse/dog/human, with 80% and 75% of all human transcripts and genes in common [103]. Perhaps one unique feature of pet dogs is its intraspecific variation. Breeding have changed the canine genome structure, affecting linkage disequilibrium, haplotype structure, heterozygosity, and eventually the rates of mutation [104]. Notably, a short-range linkage disequilibrium was found within breeds and a long-range linkage disequilibrium across breeds, corresponding to the effect of an ancient bottleneck created by early domestication and to recent breed creation, respectively [99]. This is very important because certain pure dog breeds have shown a predisposition to develop specific cancers (e.g., squamous cell carcinoma of the digit in poodles with KIT Ligand locus mutation in poodles [105] or histiocytic sarcoma risk with mutations of PTPN11 mutations in Burmese mountain dogs [106–108]), which allows to understand the genetic basis of different types of cancer [6,109]. Huskey et al. [110] have recently conducted a whole genome sequencing analysis in four different purebred dogs to investigate orthologs of human breast cancer susceptibility genes, *BRCA1*, *BRCA2*, *CDH1*, *PTEN*, *STK11*, and *TP53*, revealing that variants in *BRCA2* and *STK11* are potentially associated with risk in purebred dogs.

Homologies between dogs and human cancers have been explored to study different types of tumors affecting both pet dogs and humans aiming to shed light to the mechanisms of cancer, including the mammary gland, prostate and bladder tumors, osteosarcoma, lymphoma, malignant melanoma and squamous cell carcinomas [62,88,111–114]. The recent characterization of the genomic landscape of osteosarcoma in pet dogs revealed a similar mutation burden and complex spectrum of structural aberrations to that recognized in pediatric human osteosarcoma. Several oncogenes have been amplified in both humans and pet dogs, including *MET*, *FOS*, *IGF1R*, *PVT1*/*MYC*, *RUNX2*, and *HER2* [115]. However, unique features of osteosarcoma in pet dogs, such as mutations in the epigenetic regulator, SETD2, and deletions in *DMD*, the gene encoding dystrophin, may help explain the more aggressive disease biology recognized in canine osteosarcoma [116–118]. These canine-specific molecular alterations may inform on the biology of aggressive disease or pinpoint a unique molecular subtype of aggressive human osteosarcoma. Canine cancers with shared disease biology in humans include diffuse large B-cell lymphoma and leukemias, urothelial carcinomas, and soft tissue sarcomas, among others. Another example is the assessment of genomic landscape of canine hemangiosarcoma through whole-exome sequencing and RNA-sequencing of golden retrievers revealed similar tumor suppressor TP53, PI3K pathway and oncogene *PIK3CA* to that found in human angiosarcoma [119].

Like in humans, the same similar signaling pathways were found to be altered in pet dog's cancer. Whole genome sequencing performed in a group of canine cancer cells from different histotypes was able to identify frequently mutated gene drivers, which were then cross-referred with a list of somatic mutations from the Cancer Gene Census (COSMIC). Sixty-one driver mutations were registered from four functional categories, chromatin organization, regulation kinase activity, GTPase binding and activity and RNA binding. As consistently found in humans, the most important signaling pathways identified in canine cancers where phosphoinositide-3-kinase (PI3K), Receptor Tyrosine Kinase (RTK)/Ras GTPase/MAP kinase (MAPK) (RTK/RAS/MAPK), β-catenin and Wnt ligand (WNT/β-catenin) or cell cycle signaling, the most predominantly therapeutic targets [107,120,121]. As expected, *TP53* is the most frequently mutated gene among canine tumors [121]. Canine oral melanoma shares over 80% significant oncogenes with human melanoma [122]; BRAF mutation is homologous in both species in bladder transitional cell carcinoma [123]; BCR-Abl translocations in chronic

myelogenous leukemia [124,125]; c-KIT mutations in gastrointestinal stromal tumors [126]. Although the list is continuously increasing, a selection of the common driver mutations and the corresponding signaling pathways between humans and pet dogs are summarized in Table 4.

Table 4 – Common mutated genes and target pathways between pet dogs and humans in frequent cancer types using comparative genomic hybridization, exome sequencing, or RNA sequencing.

Tumor type	Common mutated genes	Signaling pathways	References
Melanoma	*P53, NRAS*, *KRAS*, *PTEN, NF1, BRAF, CDKN2A, CDK4, MDM2, PTPRJ, FAT4, BUB1B, SPRED1*	RTK/RAS/MAPK PI3K p53 Cell cycle Hippo	[121,122,127–132]
Histiocytic sarcoma	*PTPN11, NF1, KRAS*	RTK/RAS/MAPK	[121,133,134]
Transitional cell carcinoma of the bladder	*CDKN2A, KRAS, ARID1A, BRAF, S100A8/9, LRP1B EGFR, ERBB2*	RTK/RAS/MAPK P53 Cell cycle PI3K	[121,123,135–143]
Hemangiosarcoma	*P53, PLCG1, PIK3, ERK, PTEN, NRAS*	PI3K RTK/RAS/MAPK	[119,144,145]
B cell lymphoma	*NF-κB, BCL2, MYC TRAF3, POT1 MAP3K14, TP53*	PI3K MYC MAPK	[146–151]
Mammary	*P53, PIK3CA,* AKT1, *PTEN*, *KRAS, ERBB1, BRCA2, STK11, WNT/β-catenin*	PI3K RTK/RAS/MAPK WNT/β-catenin	[110,112,152–158]
Osteosarcoma	*P53, PTEN, SETD2, DMD, DLG2, RB1, MYC, CDKN2A/B, AKT2, BCL2*	PI3K RTK/RAS/MAPK	[117,118,121,159–162]

Beyond the biological similarities, pet dogs are by definition owned, which means that there is an inherent will to keep the animal healthy and alive as long as possible. The quality of veterinary care provided at different levels (primary, secondary and tertiary) have resulted in a longer life expectancy, though shorter compared with humans [50]. Exposed to the same environment and therefore to similar environmental risk factors as humans, including carcinogens, cancer in pet dogs allow a more control over confounding variables related to lifestyle, diet and hormonal status. Associated to the

fact that dogs develop cancer spontaneously, although the period of latency is quite similar to that in humans, when it occurs is rapidly diagnosed and treated, which allows to follow the progression of the disease and the response to therapy over time. Cancer diagnosis and treatment in pet dogs are now common procedures within the veterinary clinical practice, including the use of similar imaging technologies as in human clinical practice (ultrasound, CT and MRI) [163] and tumor staging according to defined classifications such as the TNM classification of malignant tumors in domestic animals [164]. In terms of treatment, pet dogs are submitted to similar radiation and chemotherapy agents and protocols, as well as oncological surgery, resulting in an overall improvement of the prognosis. The overview of treatment response is also well defined in pet dogs, and methods are standardized for both adverse effects [165–167] and tumor response, including the Response Evaluation Criteria in Solid Tumors [168] and the Lymphoma Response Evaluation Criteria [169]. Clinical case management and data are of high quality with a relative lower cost compared with similar human clinical cases [151]. In the advent of cancer, pet dogs can live for longer and longer periods of time with tumor and metastasis. This means that pet dog (and cat) is perhaps the unique non-human animal to experience cancer as a chronic disease. The similarities to humans in disease presentation, response to treatment, and the development of drug-resistance and metastasis provide an opportunity to interrogate points of therapeutic intervention and generate a thorough preclinical assessment of novel treatments. Notably, while many canine cancers exhibit a similar genomic landscape to their human counterparts, novel features of the disease in pet dogs may also help to explain some of the differences in behavior of these diseases between species.

Pet dogs have allowed preclinical evaluation in several cancer treatment categories such as local therapy, including surgery, radiotherapy, target inhibition, minimal residual disease treatments, immunotherapy and personalized medicine [151,170,171]. Regarding onco-immunotherapy, new molecules and combinations are emerging fast. Tolerability and potential efficacy of onco-immunotherapies and their combinations can be done in pet dogs predicting ultimate effectiveness against tumors and metastatic disease, with valuable translational information that overcomes what is provided in common rodent models [75,151,172].

The ethical implications of using pet dogs as cancer models is a matter of concern. In fact, being owned dogs that were not designed to intentionally develop diseases, in opposition to laboratory animal (including lab dogs), and also considering that they can benefit of the knowledge produced, their use could be viewed in accordance with the principles of 3Rs. Yet, it may raise ethical issues on the informed consent concerning the inclusion of pet dogs in preclinical/clinical trials, which needs to be considered.

3. Human oncology meets veterinary oncology

Humans and pet dogs share not only similarities in the initiation and progression of cancer, and the way they respond to therapies, but also the burden of its epidemiological impact. In the USA, for example, more than 1.66 million humans and more than 4.2 million pet dogs are diagnosed with cancer annually [83]. This raises great challenges to both human oncology and veterinary oncology, which can be tackled in a more effective way through a comparative framework. Therefore, comparative oncology emerged precisely to bridge human and veterinary cancer research and to explore and understand cancer risk and tumor biology across different species.

There are numerous studies using pet dog as a model to human cancer, including the development of nanomedicine compounds [173], and the exploration of novel immunotherapies that could enhance human cancer research [75,151]. Other studies are exploring the translation of novel cancer therapies [85], e.g., the development of cancer immunotherapy targeting pet dog dendritic cells [174], age-related diseases [10,175], Zirconia dental implants [176], anti-fibrotic and antioxidant therapies for chronic inflammatory liver disease [177] or antiepileptic drug testing in canine epilepsy [178]. The development of targeted nanoparticles to deliver therapeutic agents to disease sites is also an interesting topic under research [179–181].

One of the assumptions of comparative oncology is the existence of a synergic cooperation between human oncology and veterinary oncology. Despite the efforts that have been made over the last two decades, there is still great challenges in methods' harmonization and data integration. To address these challenges, the National Cancer Institute, through its Division of Cancer Treatment and Diagnosis, have launched in 2019 the Integrated Canine Data Commons (ICDC)

(https://caninecommons.cancer.gov/#/home), a cloud-based repository aiming to foster research on human cancer by enabling comparative analysis with pet dog cancer. One interesting feature of this platform is that offers the possibility to search the cases within ICDC and to build cohorts, though its power will depend greatly on the openness and intensity of submission data by the research community. So far ICDC houses three studies, corresponding to 225 cases, 509 samples and 765 files. Another initiative tackling the same challenges is the Clinical and Translational Science Award One Health Alliance, comprising a multidisciplinary platform aiming to advance the understanding of diseases shared by humans and pet dogs. One of the key areas developed within this alliance is clinical research on naturally occurring animal models of human disease, providing valuable resources and training for veterinary clinical trials. It also provides a searchable database of clinical trials being developed in different USA veterinary schools.

Table 5 – Some active digital platforms gathering oncological trials involving pet dogs with a potential of translation to humans.

Comparative Oncology Trials Consortium	https://ccr.cancer.gov/comparative-oncology-program/consortium
Canine Comparative Oncology & Genomics Consortium [72]	https://ccogc.net/
AVMA Animal Health Studies Database	https://ebusiness.avma.org/aahsd/study_search.aspx
Pre-medical Cancer Immunotherapy Network Canine Trials	https://www.precinctnetwork.org/
Comparative Brain Tumor Consortium	https://ccr.cancer.gov/comparative-oncology-program/cbtc
Integrated Canine Data Commons	https://caninecommons.cancer.gov/#/
Purdue Comparative Oncology Program	https://vet.purdue.edu/pcop/index.php
Clinical and Translational Science Award One Health Alliance	https://www.ctsaonehealthalliance.org

Parallel to the need of data sharing and integration, and harmonization of methods, it was developed collaborative consortia to perform multicenter clinical trials and databases devoted to the registry of clinical trials (Table 5). The objective of these consortia is to conduct clinical trials using spontaneously occurring cancers in the pet dog to study pharmacokinetics and pharmacodynamics end points, correlate drug exposure in modulation of tumoral markers, informing the cancer drug development

pathway [69,84,182], and ultimately to gather canine patient specimens in a biobank. Meanwhile, other initiatives were developed focusing specific tumors, like the Comparative Brain Tumor Consortium [183] promoted by the National Cancer Institute. More recently, the American Veterinary Medical Association (AVMA) launched the AVMA Animal Health Studies Database, which intends to be a central registry for clinical trials involving different animal species. Currently, this database has the registry of 42 pet dog oncology clinical trials that are studying a wide range of tumors (e.g., melanoma, soft tissue sarcoma, osteosarcoma, lymphoma) and innovative therapeutics (e.g., gene therapy, chemotherapy, electrochemotherapy, immunotherapy). Seven out of 42 are testing vaccines and immunotherapies (Table 6).

Table 6 – Oncology clinical trials of vaccines and immunotherapies registered at the AVMA Animal Health Studies Database (https://ebusiness.avma.org/aahsd/study_search.aspx).

Type of cancer	**Location**	**Purpose**
Melanoma	–	To test a ganglioside targeted cancer vaccine in dogs with malignant melanoma.
Osteosarcoma	Bone	To test a HER2/neu targeted cancer vaccine for the stimulation of anti-tumor immunity.
	Appendicular	To assess the effectiveness of cryoablation and an investigational immunotherapy (STING agonist).
	Appendicular	To evaluate the effectiveness and safety of an autologous prescription product that combines cancer vaccination pretreatment and activated killer T cell immunotherapy.
Tumor	Brain	To evaluate the tumor response to a vaccine that targets cancer stem cells.
Transitional cell carcinoma	Bladder or prostate	To test a HeR2/neu targeted cancer vaccine for the stimulation of anti-tumor immunity.
Various	–	To test a DNA telomerase targeted vaccine for the stimulation of anti-tumor immunity.

Since 2003, when it was established the Comparative Oncology Program promoted by the National Cancer Institute, pet dog genomic data is now available through public platforms and databases, such as the Sequence Read Archive (SRA), the Genome from the National Center for Biotechnology Information (NCBI) and the ICDC. Other private organizations are also pursuing the same objective, such as the Dog Disease Mapping Project (DogDNA) from the Broad Institute. All these initiatives provide valuable data allowing the map of the most common pet dog tumors using reliable data provided by

the latest generation of omics technologies (genomics, transcriptomics, proteomics and metabolomics). This knowledge altogether improves the selection of the model disease for preclinical trials in pet dogs as the results may be directly applicable to human clinical trial design, enhancing to great extent the ability to compare cancer genomics and transcriptomics in a meaningful way [74,184].

The Comparative Oncology Trials Consortium – part of the NIH's Comparative Oncology Program – is currently conducting two clinical trials using spontaneously occurring cancers in pet dog to study pharmacokinetics and pharmacodynamic end points, correlating drug exposure to modulation of tumoral markers, and informing the cancer drug development pathway [69,84]. The Pre-medical Cancer Immunotherapy Network Canine Trials (PRECINCT) (https://www.precinctnetwork.org) is conducting two multicenter trials on chimeric human HERs/neu protein for dogs with osteosarcoma and another on the assessment of a p97 inhibitor in various tumors. The Comparative Brain Tumor Consortium is conducting two trials, one on the molecular targeted cytotoxins for canine primary brain tumors and the other to evaluate procaspase-3 combined with hydroxyurea in canine meningiomas [184].

4. Immunological links and break downs between pet dogs and humans

Although the relative concentration of immune cells differ, as would be expected, there are more similarities than differences in their dynamic interaction with antigens [185]. During the progress of cancer disease, interactions of the immune system with the cancer changes, especially in more advanced stages. This interaction, as stated before, is difficult to reproduce in laboratory models.

The relative number of T cells in both pet dogs and humans is notably similar, e.g., the CD4:CD8 proportion is approximately 2:1. Neutrophils, monocytes and regulatory T lymphocytes are also well characterized during health and disease. It was reported that regulatory T cells changes in pet dogs with cancer [186,187] and it was identified an association between a decreased ratio of CD8+ and decreased survival in dogs with osteosarcoma [188]. Humoral immunity, immunoglobulin functional subclasses are functional and suturally similar. Antigen presenting cells, stimulation and inhibition molecules are also the same. Interactions between TLR ligands and the productions of

pro and anti-inflammatory cytokines are also very similar [75]. Homology of cytokines amino acid sequences is remarkably higher between both species, existing high cross reactivity of canine cytokines with anti-human monoclonal antibodies [189,190].

Natural Killer (NK) cells are still being studied and characterized, since are not so well described in pet dog. Nevertheless, it has been encountered homologies with human NK cells in terms of origin, development and differentiation, and some phenotypic surface markers, such as CD3, CD16, CD94, NKG2D [191].

Major differences are related to mast cell neoplasms occurring in pet dogs, which are more frequently than in humans, especially arising in mucosal sites and skin as primary tumors [192–194]. Malignancies of dendritic cells or macrophage lineage such as histiocytic sarcoma also occur more frequently in pet dogs, where there is a known genetic susceptibility already described [195–197].

5. ImmunoOncotargets: crosstalk between pet dogs and humans

Three categories of antigens can be found in tumors: tumor-specific antigens (TSA), tumor-associated antigens (TAA) and cancer-germline antigens (CGA). TAA and CGA are present in both tumor and normal cells, although highly expressed in abnormal cells secondary to genetic amplification or post translational modifications. TSA can only be found in cancer cells and not in healthy cells. They are the truly foreign proteins, novel peptide sequences, also known as neoantigens. Neoantigens result from a variety of genetic alterations, single nucleotide variants, insertions and deletions, gene fusions, frameshift mutations and structural variations. Some can be viral induced, such as tumors resulting from papilloma or herpesvirus infections. Alternative source of neoantigens can result from transcriptome level modifications, such as errors in RNA transcription, alternative or mis-splicing [198–200].

Neoantigens, TAA and GSA have been the path followed for the development of immunotherapy drugs, with some discoveries proven to be clinically very effective. Transtuzumab is an example of a currently used and approved substance for humans that can potentially be translated to veterinary medicine [112,201]. From a theoretical perspective neoantigens are the ideal immunotherapy target. These neoepitopes can

trigger immunogenic responses, recognized by major histocompatibility complex molecules (MHC) and by T-cell receptors, leading to their selection. Since they are specifically recognized by T cell receptors as non-self they are less likely to trigger autoimmunity.

Methods for the identification of neoepitopes are based in gene and exome sequencing and bioinformatic machine algorithms that are able to predict immunogenicity and the probability to identify clinically relevant neoepitopes and define the genomic landscape of cancer [117,121,202]. However, less than 3% of the neoepitopes identified are able to elicit T cell response [203]. The reason is related with their role in immunoediting, escape mechanisms and interactions with checkpoint inhibitors [171,204]. These mechanisms have to be acknowledged in the production of anti-tumor agents, since the discovery of a neoantigen is not enough to result as a druggable target. Cancers are able to use the immune system to constrain and promote their own development and this process is one of the major challenges in immunotherapy since these processes comprise the main form of immunotherapy resistance. Again, the canine model can provide an opportunity in the identification of new treatments and the evaluation of its efficiency, especially understanding the interrelationships between the molecular/genomic landscape, from the *in vitro* to the *in vivo* treatment response in a dog [171].

In the proliferative field of immunotherapy there are four main immunotherapy approaches: *a) Cancer vaccines*, *b) Adaptive T cell transfer*, *c) Antibodies* and d) *Cytokines* [204].

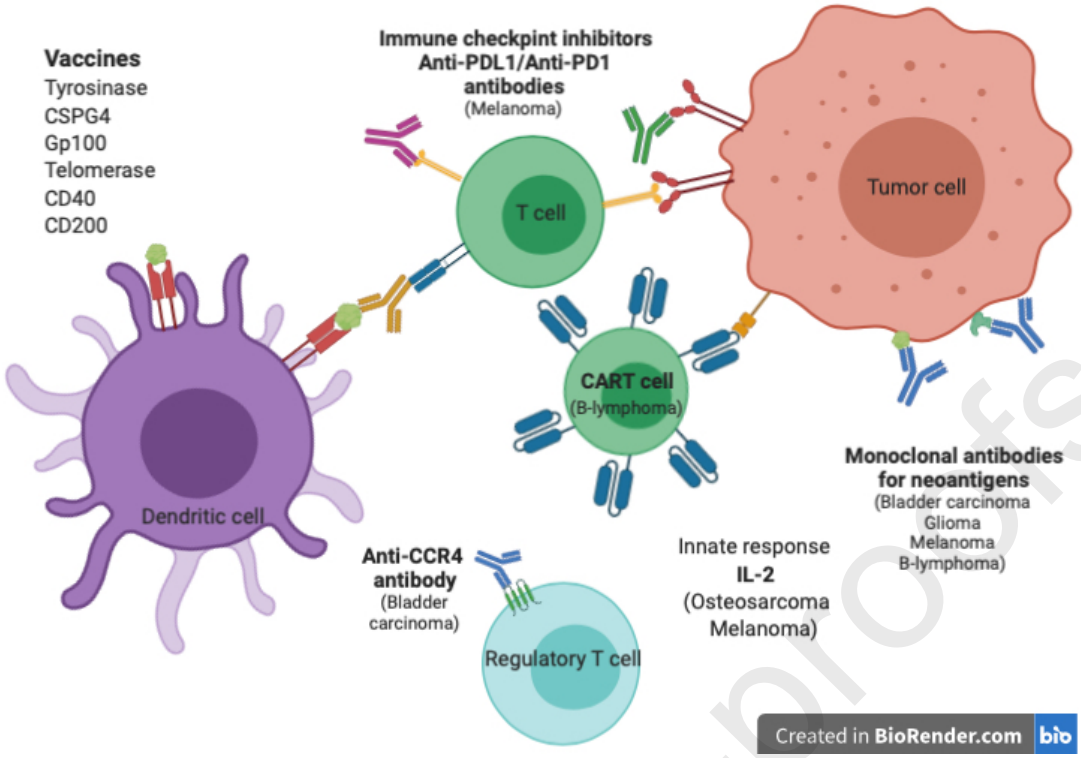

Figure 2 – Summary of the immunotherapy agents used in pet dogs with spontaneous cancers. CART Cell (T lymphocyte with chimeric receptors to target tumor associated antigens (TAA). Tumor vaccines represent the most frequent immunotherapy approached applied in the veterinary clinical setting, one is licensed for the treatment of canine melanoma.

5.1 Cancer vaccines

Currently there are DNA, RNA, synthetic long peptides, and dendritic cell vaccines. Their production can be personalized and very flexible, allowing easily the incorporation of multiple genes for tumor antigens, immunostimulatory molecules and other immunotherapy approaches including nanoparticles [204–206]. In the case of nanoparticles, clinical trials involving dogs allow longer term follow-up of treated animals and provide the unique opportunity to assess for the effects of nanoparticle persistence in tissues [173]. There is high volume of research revealing an increased efficacy of the combination of cancer vaccines with other immunotherapy approaches [207]. The production process involves the collection of tumor and normal samples, identification of neoantigens and formulation of the vaccine itself [204]. However, an effective neoantigen prediction is still a complex and expensive process which includes

the identification of DNA mutations, its expression from RNA sequencing and MHC binding prediction to the antigen [208]. The canine model is a valuable alternative to test and optimize neoantigen cancer vaccines, by prediction CD8 and DC4 recognizable antigens [208].

The most used pet dog model of spontaneous cancer is oral melanoma. Melanoma represents 7% of all malignant tumors in dogs [209], appearing most frequently in the oral cavity, mimics human mucosal melanomas [210]. Thus, due its homologies dog constitutes a relevant translational model for human malignant melanoma. There are several publications related to the use of tumor vaccines as a very important hallmark of treatment combined with surgery and adjuvant treatments [207,208]. With regards to vaccination there is a currently a commercially available xenogeneic vaccine targeted against human tyrosinase antigen, licensed for stage II and III oral malignant melanoma after loco-regional control [211,212]. Other research groups have developed other vaccine strategies, namely electrovaccination targeting chondroitin sulfate proteoglycan-4 (CSPG4), allogeneic vaccine carrying human interleukin -2 (IL-2) and human granulocyte macrophage colony-stimulating factor (hGM-CSF) genes [213] or dendritic cell vaccines targeting the human melanoma antigen gp100 [214]. Some of these vaccines can also be classified as gene therapy since there is DNA transfer using viral vectors resulting in the delivery of cytokines, suicide genes or tumor antigens.

Another relevant model is lymphoma, which includes a large heterogenous group of lymphoid tumors with remarkable similarities with human Non-Hodgkin lymphomas, of which 80% are mature B-cell tumors [215]. The telomerase reverse transcriptase (TERT) is a TAA largely confined in tumor tissues. TERT is processed and presented by MHCI cells, which can be recognized by T lymphocytes. Like human TERT vaccines are being tested in phase I trials, the same is being done in dogs [206][216]. A virus vector based (adenovirus) genetic vaccine targeting canine telomerase (dTERT) demonstrated efficacy for the treatment of canine lymphoma, associated with chemotherapy [216].

Vaccines for brain tumors and several sarcomas were also studied as relevant models [217–221] in phase I or II studies (Table 7). Vaccine development was based in autologous tumor lysates associated or not with immunological adjuvants. Glioma and

meningioma in dogs have been contributing with important clinical and translational information for similar human cancers. In pet dogs with high-grade glioma and glioblastomas, the local intradermal injection of the canine immune checkpoint inhibitor CD200AR-L prior to the administration of an autologous tumor lysate significantly enhanced its efficacy[220,221], previously developed by the same group for the treatment of meningiomas [222]. In this later study tumor lysate vaccine was combined with toll-like receptor ligands [222].

Considering sarcomas, the autologous dendric cell vaccine of autologous tumor lysate associated with TNF alpha have not shown very promising effects in the 14 dogs with osteosarcoma [218]. On the contrary, the efficacy of ADXS31-164 recombinant *Listeria monocytogenes* expressing chimeric human HER2/neu construct was tested in 18 dogs showing improved outcomes [217,219]. However, due to the zoonotic risk associated with *Listeria* infection this vaccine was removed from the market.

Table 7 – Tumor vaccines under research using pet dogs with spontaneous tumors as translational research models.

Cancer type	Antigens	Comments	References
Melanoma	Tyrosinase	Bacterial plasmid DNA vaccine	[211,212]
	CSPG4	Xenogeneic DNA electroporation performed after vaccine delivery	[223–226]
	Gp100	Dendritic cell vaccination	[214]
	Allogenic tumor	Allogeneic formolized tumor extracts and lipoplexes carrying human IL-2, and hGM- CSF genes.	[213]
	Autologous tumor	Autologous tumor lysate vaccine combined with an immune adjuvant protein from the small intestine submucosa	[227]
Lymphoma	-	CD40-activated B cell cancer vaccine associated with chemotherapy	[228]
	TERT	Tel-e-vax pDUV5	[206,216]
Osteosarcoma	HER2/neu	Listeria vector live chimeric human HER2/neu	[217,219]
	Autologous tumor	Autologous vaccine Combined with IL-2 and adoptive T cell transfer	[229]
High grade glioma, glioblastoma and meningioma	HSP60 and others not specified	Lysate-based vaccine combined with the immune checkpoint reversal CD200AR-L or toll-like receptor ligands	[220–222]
Hemangiosarcoma	Autologous	Tumor cell lysate associated	[230]

	tumor	combined with alpha interferon and doxorubicin	
		Autologous tumor lysate associated with an immune adjuvant protein from the small intestine submucosa	[231]

Under the scope of cancer prevention, it is worth noting the current trial VACCS: Vaccination Against Canine Cancer Study, which is hopping to include 800 healthy, middle-aged pet dogs to test the effectiveness of the new vaccine targeting approximately 30 neoantigens, resulting from frame-shift mutations (https://www.csuanimalcancercenter.org/vaccination-against-canine-cancer-study/). In humans, preventive vaccination against papillomavirus or hepatitis B to prevent cervical or liver cancer in humans is well known, however, vaccination for nonviral antigens are also being studied in phase I and II clinical trials [56][207]. Humans trials for such approach is very limited to healthy individuals who were at risk of cancer recurrence [207]. A study like this in veterinary patients might contribute to valuable information in long term cancer prevention.

5.2 Adaptive T cell transfer

Adaptive T cell immunotherapy is based on the transfer of immune cells expressing chimeric antigen receptors (CAR). These CAR are engineered proteins that combined the specificity of a monoclonal antibody with the effector function of the immune cell directed towards a tumor [232]. Is based on two methods isolation of T lymphocytes from primary tumor sites or gene modification of these cells. A first report suggested that adoptive T-cell therapy after chemotherapy improved tumor free survival in a group of dogs with B cell lymphoma where chemotherapy itself was used as an immune modulating agent [233].

Genetic modification can be accomplished with the expansion of predetermined specific monoclonal T cells or by receptor gene transfer [234]. Genetically engineered T lymphocytes with chimeric receptors to target TSA or TAA (CART Cells) was applied in pet dogs bearing B cell lymphoma in relapse. In this a proof of concept study, the expansion methods for canine normal and abnormal T cells were developed and optimized, followed by mRNA electroporation to produce specific CD20-specific CART cells [235]. Results were transient but promising. Due to the high associated

costs and some technical drawbacks this approach targeting tumor antigens is still at is beginning. Recently, using a virus-transfection, CART cells CD20-specific generated were effective in vitro against canine B cell lymphoma [236]. Side effects cytokine release syndrome and neurotoxicity observed in humans were not observed in the small number of studies using the dog's spontaneous model

5.3 Antibodies

Monoclonal antibodies are used now currently as part of many oncotherapies in humans. They can be very specific (antiidiotype antibodies, when targeted to a specific antigen of a specific tumor), conjugated with other components (such as nanoparticles, toxins, etc.) or engineered [237]. Engineered antibodies can be bispecific, binding to two targets at the same time, act as artificial T cell receptors and/or as dual modulators. Some examples are cytotoxic effector cell redirectors, which can engage the neoantigen and the T cell receptor (CD3), tumor targeted immunomodulators, binding to CD40 and the neoantigen and dual immunomodulators, e.g., with mutual blockage of PD1 and CTLA-4.

TAA between dogs and humans are comparable at a biological and molecular level. This fact has been proved in some studies. There was a 91% and 92% amino acid homology, respectively, of canine Erb-1 and -2, which were recognized by human monoclonal antibodies cetuximab and transtuzumab, at identical binding sites [112]. The same humanized antibodies were also able to induce antibody-dependent cellular cytotoxicity in NK lymphocytes [238]. On the contrary, rituximab, a chimeric anti-CD20 monoclonal antibody although improved significantly the outcome of patients bearing B-cell tumors it showed lack of cross reactivity with canine B-lymphocytes [239].

Another example is the monoclonal antibody targeting the cell surface receptor CCR4 (C-C motif chemokine receptor 4) found mostly on immunosuppressive regulatory T cells (Tregs). The humanized monoclonal antibody mogamulizumab, provides CCR4 blockage in dogs, resulting into depletion of Tregs [240]. A study showed that tumor infiltrating Tregs were associated with a poor prognosis in dogs with spontaneous bladder cancer and that their administration was associated with tumor regression and

improved survival [240]. In half of the cases, it was reported an adverse event after administration of mogamulizumab, but mostly were mild and transient.

The chimeric antibody 1E4-7-B targeting CD-20 is a new potential antibody that holds promise, showing a high cytopathic effect on a $CD20^+$ canine cell line. Although the study was mostly in vitro an in a SCID mouse model, it was demonstrated to cause B-cell depletion in an experimental group of beagle dogs [241] and clinical trials are being prepared by this research group.

Podoplanin (PDPN) is a transmembrane mucin-like glycoprotein TAA, overexpressed similarly in both human and canine various tissues and tumor types [242,243]. After being first experimented the anti-human PDPN antibody in a pleural mesothelioma orthoptic xenograft model, phase I and II clinical trials were attempted in in dogs [242,244]. The anti-PDPN was first stabilized to recognize only the aberrant glycosylation of the PDPN (dPDPN) and become tumor specific and induce antibody-dependent cellular toxicity. In this first trial in a healthy dog and three PDPN-positive cancer bearing dogs showed that the chimeric mouse-canine anti-dPDPN, P38Bf, was, at least safe [242]. This antibody was administered intravenously every 2 weeks in three dogs with malignant melanoma without major adverse effects. Although P38Bf induced a significant *in vitro* antitumor activity, it's *in vivo* efficacy, still needs evaluated using a larger number of dogs bearing PDPN positive cancers.

Monoclonal antibodies targeting immune checkpoint inhibitors were also applied in clinical research studies in dogs with spontaneous tumors, namely melanoma. Anti-PD-L1 monoclonal antibody (c4G12), was tested in a pilot clinical study in 7 dogs with oral malignant melanoma and two with undifferentiated sarcoma, showing safety albeit efficacy results were limited [245]. Canine anti-PD-1 antibody (4F12-E6) was used in dogs with advance stage melanoma as well as other tumors, and reported as a safe and of potential clinical benefit [246].

Table 8 – Tumor antibodies under research in canine spontaneous tumors

Type of cancer	**Antigen**	**Comments**	**References**
B cell lymphoma	CD20	Chimeric (4E1-7-B)	[241]
Transitional cell	CCR4	Mogamulizumab	[240]

carcinoma of the bladder			
Melanoma and other tumors	PD-1	4F12-E6	[246]
Melanoma	PDPN	Chimeric (P38Bf)	[242]
	PD-L1	Chimeric (c4G12)	[245]

5.4 Cytokines

There are several cytokines that can be used ether associated or as monotherapy and limit tumor growth by a direct anti-proliferative/pro-apoptotic activity or stimulate the cytotoxic activity of immune cells against tumors. There are only 2 FDA approved cytokines for the treatment of human tumors are IL-2 and interferon alpha (IFN- α). IL-2 for use in veterinary medicine is EMA approved for subcutaneous sarcoma. The recombinant canarypoxvirus (vCP1338) expressing feline interleukin-2 (IL-2) is applied at the surgical site after tumor excision. There is no similar product approved for dogs as a monotherapy, although IL-2 has been reported as an immunological adjuvant leading to the augmentation of specific T-cell-mediated anti-tumor immunity and the activation of non-specific cytolytic effector cells. Direct injection of the recombinant protein in one of the possibilities to increase IL-2 in the tumor microenvironment. Another option is systemic or intratumoral gene therapy vectors that encode IL-2.

Orally administered *Salmonella* vector live encoding IL-2 was used as adjuvant in osteosarcoma, combined with surgery and doxorubicin [247]. The combination improved survival compared with the doxorubicin and surgery controls, however not significantly superior to the chemotherapy combination doxorubicin and carboplatin. Regardless, the administration was safe and potentially interesting. Also in osteosarcoma, another group reported IL-2 also as an adjuvant, in a combined approach with vaccine and activated T-cells [229]. The study reported this treatment to be safe, tolerable and effective compared with historical controls treated with surgery alone.

Human IL-2, along with human GM-CSF was part of a multimodal approach surgical site injection of gene therapy co-delivering cIFN β gene and bleomycin followed by subcutaneous administration of an allogenic whole tumor cell vaccine, in a clinical trial using 364 canine melanoma patients [213]. This study reported an increased 6.5-fold on

the median survival of treated group of patients compared with a complete surgery control.

6. Discussion

Opportunities for cancer research are emerging from pet dogs. This species provides valuable opportunities to test theories for cancer treatment that ultimately benefit both species. On the one hand, pet owners seek the possibility to provide the latest and ultimate treatment option that science can offer, when standard approaches have failed; on the other hand, the opportunity to test novel treatments for the first time in a subject that has a shorter life span can bring forth results that would not be obtained using human volunteer subjects. At the same time, pet dogs' intrinsic advantages bring together what is good in laboratory subjects and adds natural exposure, spontaneous tumor development and genetic unique backgrounds related with breed.

One of the most advocated advantages of pet dog cancer models rely on the argument they serve as sentinels for environmental risk factors to which humans are also exposed, but cancer incidence and geographical distribution in dogs remains unclear. It is now well known that pet dog have a similar global distribution as humans [248,249] and they tend to have similar cancer types [25]. However, there is a lack of a coordinated and worldwide cancer registry of veterinary patients [26], and the incidence and prevalence of pet dog cancer is only estimated from narrowed sample collections [25,35].

It is now well recognized that pet dog is a valuable model in human cancer research and the clinical veterinary setting provides unique emerging translational opportunities for comparative oncology. But pet dogs are not laboratory animals. This condition may be seen simultaneously as a strength and a weakness of the model. In fact, they are patients with caregivers and access to healthcare. Therefore, there is the need to consider some natural bias, most associated with access to veterinary care. Economic factors can be a major limitation, since only those pet dogs with access to at least a diagnosis will have the chance to be conducted to a possible treatment plan. Consequently, there is a limited pet dog population who will take part of a clinical trial. Still within this scope, funds to veterinary clinical research is very limited especially compared with the overall

veterinary professional coverage. Food safety and zoonotic diseases hijack the bulk of overall research funding for veterinary sciences. Although there is a growing support for the advancement of veterinary oncology treatments and an increase in oncology research, large scale studies are still very difficult to implement. The ongoing veterinary clinical trials are still sparse around the world and limited to a small group of academic institutions. Finally, new ethical challenges related with veterinary clinical trials are emerging and new concerns have been raised. In general, there is a formal need to harmonize the informed consent process and improve the clinical trials registry.

Regarding veterinary clinical oncology and immune-oncotherapy research, very significant advances have provided the pillars to start seeking for druggable targets in pet dogs with spontaneous cancers. However, there are important gaps that should be addressed shortly, e.g., there is still no cancer gene census available similar to the COSMIC cancer gene census for humans. It would be very fruitful to have a comparative cancer gene census for pet dog in order to identify all genes with mutation drivers for cancer supported by integrative oncogenomic tools as proposed for humans [250].

With the available computational algorithms, it is possible to predict neoantigens from various genome sequences. This computational machinery can identify and/or prioritizing neopeptides that are most likely to elicit T-cell response, by determining the neoantigen's "quality" from a set of biophysical, chemical, and computationally inferred properties. Based on these properties is it possible to predict affinity of a neoantigen to MHC, avidity neopeptide-MHC complex to T cell receptor, type of T cells that respond to the neoantigen and sequence similarity to other known highly immunogenic epitopes [251]. The neoantigen pipeline includes the several steps that demand a deep knowledge from the mutated gene driver to the protein 3D structure, calling upon currently available toolkits for the identification, selection, prioritization and visualization of neoantigens, such as pVACtools that provide an interactive display of predicted neoantigens for review by the end user [252]. In the comparative oncology perspective, at least for now, pet dogs are receiving more from this alliance, especially due to a gateway access to the most advanced technologies which would not be possible to achieve otherwise. Veterinary researchers are integrating multidisciplinary teams, prospecting cancer antigens, and finding immunologic triggers to fight cancer. At this

point, optimization of procedures is critic to fill the many gaps related with the knowledge of comparative immune response between pet dogs and humans, especially regarding species-specific antibodies for the recognition of canine immune cells to be ultimately included in these computational tools.

7. Future perspectives

The absence of a representative, collaborative, and standardized network of animal cancer registries is a major constraint to the advance of veterinary cancer research and surveillance and therefore to its translational power [22]. Despite its vivacity in the 1960s and 1970s in the USA [30,253–256], only in the later 1990s and early 2000s were established the first cancer registries in Europe (Italy [33], Norway [29], Denmark [39] and Switzerland [25,37]). In 2010 the Norwegian School of Veterinary Science in Oslo hosted an international workshop to discuss the key challenges of veterinary cancer registration and foster international collaborations [20]. Separately, in 2019 it was established the Global Initiative for Veterinary Cancer Surveillance (https://www.givcs.org) which aims to join animal cancer registries of different countries and to harmonize methods. However, it is crucial to develop a strategy to accelerate the implementation in firsthand of effective national animal cancer registries following international consensual standards and good practices. This strategy inevitably involves the need for census of the pet population globally.

In perspective the tendency is for immunotherapy to pass from trials to be included in treatment protocols in veterinary medicine as it is happening now in humans. During this time, pet dogs can and should be considered as valuable models of cancer research, bridging the gap between laboratory models and humans. They can contribute with robust data in a realistic way, some related with the long-term metastatic control provided by immunotherapies, safety and efficiency trials of therapeutic combinations involving checkpoint inhibitors, microenvironment targeting, effects of immunotherapies in the selection of genetic variants that lead to tumor relapse, among others.

Since immunotherapies tend to become more complex, vectored, and personalized, bioinformatic methods will become the state of the art in the identification of

neoantigens from mutational cancer gene compendiums of public access, only available for human research. By integrating information from large- and small-scale sequencing efforts it will be produced canine gene compendiums as well, and consequently common mechanisms of tumorigenesis between canine and human cancers will be further uncovered.

All these developments will obviously increase treatment costs which by itself can be a major limitation of its application in the context of veterinary clinical practice. Therefore, cancer research should simultaneously continue to point to the discovery of monotherapies for individuals at risk of cancer and to increase the immunosurveillance to prevent disease.

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Graphical abstract