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The dog as a patient rather than an experimental animal in cancer treatment: Implications for comparative oncology and translational medicine

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ABSTRACT

Comparative oncology leverages spontaneously occurring canine malignancies as robust bidirectional models to bridge the translational gap between preclinical laboratory discoveries and human clinical applications. Unlike conventional genetically uniform rodent models, which often fail to capture natural tumor dynamics, companion dogs develop cancers within an intact, co-evolved immune system and a shared anthropogenic environment. This comprehensive review examines the deep histopathological, genomic, and molecular homologies shared between canine and human neoplasms, with particular emphasis on aggressive entities such as osteosarcoma, malignant melanoma, mammary carcinoma, and non-Hodgkin lymphoma. High-throughput sequencing confirms mutual somatic driver mutations and identical signaling pathway aberrations (e.g., TP53, HER2, and PTEN), substantially increasing translational predictability. Furthermore, companion dogs act as important environmental sentinels for shared ecological carcinogens and provide an accelerated clinical timeline due to their compressed lifespans. Integrating veterinary clinical trials into drug development timelines enables the realistic evaluation of therapeutic efficacy, systemic toxicities, and immune-mediated resistances without compromising animal welfare. Recent advancements in experimental therapeutics, particularly Newcastle Disease Virus (NDV)-based oncolytic virotherapy using the ZG1999HDS strain, underscore the immense clinical and immunological potential of comparative frameworks. Although challenges regarding international trial standardization and cross-species regulatory frameworks persist, the companion canine model represents an irreplaceable, ethically sound foundation within the modern "One Health" paradigm, driving parallel medical breakthroughs that directly benefit both human and veterinary oncology.

Keywords: Comparative oncology, One Health, translational models, canine tumors, oncolytic virotherapy

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INTRODUCTION

Comparative oncology represents a critical interface between veterinary and human medicine, offering a robust bidirectional framework that aligns with the contemporary "One Health" paradigm (Khanna et al., 2006; Vail and Mac Ewen, 2000). Dogs (*Canis lupus familiaris*) living in close anthropogenic environments are naturally exposed to identical environmental risk factors, including chemical carcinogens, air pollutants, and dietary shifts, making them invaluable, highly sensitive biological sentinels for shared ecological carcinogenesis (Schiffman and Breene, 2015; Reif, 2011). Consequently, companion dogs develop spontaneous malignancies that closely parallel human cancers in their biological behavior, clinical presentation, histological appearance, and response to therapeutic interventions (Vail and Mac Ewen, 2000; Gardner et al., 2016). High-throughput genomic analyses have demonstrated a profound degree of sequence homology and evolutionary conservation between the canine and human genomes (Lindblad-Toh et al., 2005). These molecular studies have revealed shared somatic driver mutations, copy number variations, and identical aberrations in critical oncogenic signaling pathways, such as the PI3K/AKT/mTOR and MAPK pathways (Lindblad-Toh et al., 2005; Simpson et al., 2017). Notably, highly aggressive malignancies such as osteosarcoma, malignant melanoma, urothelial (bladder) carcinoma, and non-Hodgkin lymphoma in dogs exhibit striking molecular and clinical redundancies with their human counterparts, presenting ideal target-rich environments for translational oncological research (Gardner et al., 2016; Simpson et al., 2017; LeBlanc et al., 2021).

Traditional preclinical paradigms in drug development heavily rely on syngeneic, genetically engineered, or patient-derived xenograft (PDX) rodent models. However, these murine systems consistently fail to fully recapitulate macroscopic tumor heterogeneity, complex immune macroenvironments, clonal evolution, and natural disease dynamics over an extended timeline, contributing significantly to the high failure and attrition rates (>90%) of novel anticancer therapies during human phase I/II clinical trials (Hansen and Khanna, 2004; Mak et al., 2014). In contrast, tumors in companion dogs arise spontaneously within an intact, co-evolved immune system and a shared natural environment, providing a superior, highly predictive translational matrix (Vail and MacEwen, 2000; Somarelli et al., 2020). The canine immune apparatus shares profound structural and functional similarities with human immunology, particularly regarding tumor-infiltrating lymphocyte (TIL) architecture, myeloid-derived suppressor cell (MDSC) dynamics, and the expression profiles of immune checkpoint molecules such as PD-1 and PD-L1 (Somarelli et al., 2020; Maekawa et al., 2021). Utilizing the canine model facilitates the rigorous, ethical study of complex tumor-host interactions, the validation of novel small-molecule inhibitors and immunotherapies, and the optimization of multi-modal combination protocols (Khanna et al., 2006; LeBlanc et al., 2021). Crucially, these insights can be generated in a compressed timeframe driven by the naturally accelerated progression of canine diseases compared to humans, benefiting both veterinary and human oncology (Vail and Mac Ewen, 2000; Gordon et al., 2009).

Comparative Oncology and Translational Value

Spontaneously occurring canine tumors provide an invaluable translational model for human oncology due to deep histopathological, genetic, and clinical homologies. Unlike induced rodent models, canine malignancies develop naturally within an intact immune system, capturing the complex tumor heterogeneity and metastatic patterns seen in humans (Vail and Mac Ewen, 2000; Gardner et al., 2016). Comparative transcriptomics confirm shared driver mutations in key oncogenes and tumor suppressor genes such as TP53, RB1, PTEN, and HER2, which is particularly evident in osteosarcoma, lymphoma, melanoma, and mammary carcinoma (Gardner et al., 2016; Lindblad-Toh et al., 2005). Canine osteosarcoma exhibits identical skeletal localization, histological features, gene expression profiles, and a high propensity for early pulmonary metastasis, effectively mirroring human pediatric osteosarcoma (Simpson et al., 2017). Similarly, canine non-Hodgkin lymphoma shares clinical progression, pathophysiology, and therapeutic response to standard CHOP regimens with human counterparts (Somarelli et al., 2020). Furthermore, canine oral melanoma closely models rare and aggressive human mucosal melanoma, serving as an ideal platform for evaluating novel immunotherapies, while canine mammary tumors exhibit strong genetic and hormonal concordance with human breast cancer, including triple-negative breast cancer subtypes (Gardner et al., 2016; LeBlanc et al., 2021).

These tumors develop in complex biological conditions involving broad genetic diversity and environmental exposure (Reif, 2011; Rowell et al., 2011). While the canine species displays vast overall genetic diversity, individual breeds exhibit extreme genomic homogeneity due to selective breeding and founder effects (Lindblad-Toh et al., 2005). Specific breeds demonstrate high predispositions to distinct malignancies, such as lymphoma in Golden Retrievers or histiocytic sarcoma in Bernese Mountain Dogs (Rowell et al., 2011). This unique population architecture simplifies the mapping of heritable cancer-associated risk loci, thereby accelerating the discovery of oncogenic pathways relevant to both species. Furthermore, by sharing the human exposome, companion dogs act as effective sentinels for environmental carcinogens (Reif, 2011). They are exposed to identical household chemicals, passive smoke, pesticides, and air pollutants. The detection of matching bioaccumulated endocrine disruptors and organic pollutants in canine and human biospecimens underscores their utility as early warning systems for shared environmental oncogenic risks before clinical manifestation in humans. Finally, the shorter lifespan of dogs allows for accelerated clinical evaluation compared to human medicine (Vail and Mac Ewen, 2000; Gordon et al., 2009). Canine clinical trials offer condensed timelines to evaluate long-term efficacy, safety, resistance mechanisms, and pharmacokinetic profiles of novel therapies. These veterinary outcomes directly optimize human clinical trial designs, mitigate late-stage translational failures, and speed up the approval of innovative targeted molecules and immunotherapies.

Dogs in Drug Development

Spontaneously occurring canine tumors represent a vital translational bridge between conventional experimental rodent models and human clinical trials (Gordon et al., 2009). While traditional murine models often fail to predict human outcomes due to artificial tumor induction and immunodeficiency (Hansen and Khanna, 2004; Mak et al., 2014), pet dogs develop malignancies naturally within an intact, fully functional immune system (Somarelli et al., 2020). This allows for a rigorous and realistic evaluation of therapeutic efficacy, systemic toxicity, and the evolution of drug resistance pathways under real-world biological conditions. Integrating canine clinical trials into the early phases of drug discovery helps establish critical pharmacokinetic and pharmacodynamic profiles, enabling researchers to optimize drug dosing and schedules while identifying target toxicities that standard rodent assays frequently miss (LeBlanc and Mazcko, 2020).

Furthermore, the outbred nature and extensive genetic diversity of the companion dog population significantly enhance translational predictability compared to genetically homogenous laboratory strains (Mak et al., 2014). This genomic variation, combined with shared lifestyle and environmental exposures with human owners (Schiffman and Breene, 2015; Reif, 2011), closely mirrors the heterogeneous patient populations encountered in human medicine. Concurrently, enrolling client-owned dogs in veterinary clinical trials provides these patients with direct access to cutting-edge, novel anticancer interventions that would otherwise be unavailable. This parallel benefit supports a highly ethical research framework where veterinary patients receive advanced medical care, while the generated data directly mitigate the risk of late-stage failure in human clinical pipelines, advancing the core principles of the One Health initiative.

Experimental Therapeutics

Oncolytic Virotherapy

Oncolytic virotherapy has emerged as a compelling immunotherapy paradigm that utilizes either replication-competent, naturally occurring, or genetically engineered viruses to selectively target and destroy malignant populations while leaving healthy tissues undamaged. Oncolytic viruses preferentially replicate within neoplastic cells primarily due to the severe impairment of innate antiviral signaling pathways, such as the interferon-mediated antiviral response and translational suppression mechanisms, which are characteristically downregulated during tumor immunoediting and transformation (Russell et al., 2012; Kaufman et al., 2015). Upon entering the permissive intracellular milieu of a cancer cell, the virus hijacks the host metabolic machinery to undergo rapid replication, ultimately inducing direct tumor cell lysis through immunogenic cell death. This lytic event triggers a profound systemic immune activation by releasing a cascade of tumor-associated antigens, pathogen-associated molecular patterns, and danger-associated molecular patterns directly into the tumor microenvironment (Lichty et al., 2014). Consequently, this converts an immunologically "cold" tumor into a "hot" zone, recruiting innate effector cells and priming tumor-specific T lymphocytes to search and eliminate distal, non-infected metastatic deposits.

Newcastle Disease Virus (ZG1999HDS)

The Newcastle disease virus, an avian paramyxovirus, stands out as a highly promising agent within this therapeutic class, demonstrating intrinsic, selective replication capabilities in mammalian tumor cells while inducing robust, multi-faceted immune responses (Russell et al., 2012; Kaufman et al., 2015; Lichty et al., 2014). A particularly notable candidate is the specific ZG1999HDS strain, which has demonstrated pronounced, simultaneous cytolytic and immunomodulatory effects in preclinical models (Mazija et al., 2021). The oncolytic selectivity of the ZG1999HDS strain relies on its exploitation of defective interferon pathways inherent to malignant cells, allowing for unhindered viral transcription and syncytium formation that precipitates cell death, all while healthy host tissues easily restrict viral propagation. Crucially, this strain exhibits an exceptionally high safety profile with negligible off-target toxicity, making it a well-tolerated biological intervention in veterinary medicine. Recent clinical evaluations of the ZG1999HDS strain in canine cancer therapy have yielded highly promising results, demonstrating noticeable tumor regression, prolonged survival times, and an enhanced quality of life in veterinary patients diagnosed with advanced or chemoresistant malignancies (Ivanković et al., 2022).

Dogs vs Small Animal Models

Conventional rodent models, despite their utility in fundamental biological research, lack the physiological complexity and genetic diversity required to accurately predict human clinical outcomes (Hansen and Khanna, 2004; Mak et al., 2014). Induced or xenografted tumors in mice fail to replicate the sophisticated evolutionary pressure of an intact immune system, often leading to misleading data regarding therapeutic efficacy and systemic toxicity. Conversely, companion dogs develop malignancies spontaneously, better reflecting human physiology, functional immunity, and realistic tumor heterogeneity (Vail and MacEwen, 2000; Gardner et al., 2016). Canine cancers arise within a complex microenvironment that mimics human disease architecture, including intact stromal interactions, natural immune editing, and spontaneous metastatic cascades. Furthermore, the outbred nature of the canine population mirrors human genetic diversity far more accurately than syngeneic, inbred rodent strains, thereby enhancing the translational predictability of oncology pipelines (Lindblad-Toh et al., 2005; Somarelli et al., 2020).

Advanced *In Vitro* Systems

Modern *in vitro* platforms, including patient-derived organoids, microfluidic organs-on-a-chip, and multicellular three-dimensional cultures, have advanced pre-clinical drug screening while supporting the ethical 3Rs principles of replacement, reduction, and refinement in animal experimentation. These advanced systems excel at modeling early cell-to-cell signaling, specific metabolic pathways, and initial cytolytic responses in a controlled environment. However, they remain fundamentally limited by their inability to replicate systemic physiological complexity, such as functional macro-circulation, systemic immune-mediated toxicities, and multi-organ drug clearance mechanisms. Consequently, while high-throughput *in vitro* systems serve as excellent initial selection filters for therapeutic candidates, companion dogs provide an irreplaceable translational bridge between initial laboratory discovery and human clinical research (LeBlanc and Mazcko, 2020).

DISCUSSION AND CONCLUSION

The integration of companion dogs with spontaneously occurring tumors into preclinical research pipelines helps address a critical bottleneck in translational oncology. Dogs represent a highly relevant translational model due to their unique capability to mimic key clinical and biological features of human malignancies, including complex intratumor heterogeneity, dynamic immune system interactions, and natural, un-induced disease progression. By embedding these outbred animal patients into the therapeutic development timeline, researchers can successfully overcome the profound physiological and genomic limitations inherent to traditional, highly inbred experimental rodent models, thereby substantially improving the predictive value and safety margins of preclinical oncology research.

Furthermore, conducting clinical studies in companion dogs enables rigorous longitudinal monitoring of novel therapeutics under realistic, heterogeneous conditions. Unlike laboratory environments, the veterinary clinical setting naturally incorporates diverse environmental exposures, variable lifestyles, and age-related comorbidities that closely reflect the actual complexity of human oncology. This realistic backdrop allows for a far more accurate and stringent assessment of therapeutic efficacy, systemic toxicity, and the real-time emergence of cellular drug resistance mechanisms.

From an ethical standpoint, the modern paradigm shift toward treating companion animals as genuine patients—rather than mere experimental subjects—ensures the highest possible animal welfare standards while simultaneously providing veterinary patients with compassionate access to advanced, otherwise inaccessible anticancer therapies. This approach aligns seamlessly with contemporary biomedical ethics, fostering broader public and institutional acceptance of comparative oncology initiatives.

Within the broader "One Medicine" framework, canine oncology serves as a bidirectional catalyst that accelerates drug development pipelines and ultimately improves clinical outcomes in both human and veterinary medicine. The successful evaluation of novel therapeutic modalities, such as Newcastle Disease Virus (NDV)-based oncolytic virotherapy, underscores the immense value of integrating advanced immunological and translational perspectives into comparative protocols (LeBlanc and Mazcko, 2020; Ivanković et al., 2022). These biological interventions demonstrate that leveraging the dog's intact immune microenvironment can yield critical data regarding systemic anti-tumor immunity and bystander effects. Despite persistent operational challenges, including the standardization of veterinary clinical trial protocols and cross-species regulatory variability, companion canine models remain one of the most powerful, biologically accurate, and ethically sound approaches in modern translational oncology (Khanna et al., 2006).

In conclusion, companion dogs diagnosed with spontaneous tumors provide a highly relevant, biologically faithful, and ethically justified translational model that effectively bridges the gap between laboratory benches and human clinical trials. Their utilization enhances the clinical relevance of preclinical data, mitigates late-stage translational failures, and actively supports the development of innovative, multi-modal cancer therapies. Future progress in this field will fundamentally depend on strengthening interdisciplinary collaborations between human and veterinary oncologists, standardizing international comparative trial networks, and continuously integrating advanced therapeutic technologies to benefit both human and animal patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Pas kao pacijent, a ne eksperimentalna životinja u liječenju raka: Implikacije za komparativnu onkologiju i translacijsku medicinu

SAŽETAK

Komparativna onkologija koristi spontano nastale malignitete kod pasa kao pouzdane, dvosmjerne modele za premoštavanje translacijskog jaza između pretkliničkih laboratorijskih otkrića i humane kliničke primjene. Za razliku od konvencionalnih, genetski uniformnih modela glodara koji ne uspijevaju obuhvatiti prirodnu dinamiku tumora, psi kućni ljubimci razvijaju karcinome unutar netaknutog, koevoluiranog imunološkog sistema i zajedničkog antropogenog okruženja. Ovaj sveobuhvatni pregled istražuje duboke patohistološke, genomske i molekularne homologije koje dijele neoplazme pasa i ljudi, s posebnim naglaskom na agresivne entitete kao što su osteosarkom, maligni melanom, karcinom mliječne žlijezde i ne-Hodgkinov limfom. Visokopropusno sekvenciranje potvrđuje zajedničke somatske driver mutacije i identične aberacije signalnih puteva (npr. TP53, HER2 i PTEN), što značajno povećava translacijsku predvidljivost. Osim toga, psi kućni ljubimci djeluju kao ključne ekološke sentinelne vrste za zajedničke karcinogene iz okoliša i omogućavaju ubrzani klinički vremenski okvir zbog svog skraćenog životnog vijeka. Integracija veterinarskih kliničkih ispitivanja u vremenske okvire razvoja lijekova omogućava realnu procjenu terapijske efikasnosti, sistemske toksičnosti i imuno-posredovane rezistencije bez ugrožavanja dobrobiti životinja. Nedavni napredak u eksperimentalnoj terapeutici, posebno onkolitička viroterapija zasnovana na virusu Newcastle bolesti (NDV) uz korištenje soja ZG1999HDS, naglašava ogroman klinički i imunološki potencijal komparativnih protokola. Iako i dalje postoje izazovi u pogledu međunarodne standardizacije ispitivanja i međuvrsnih regulatornih okvira, model pasa kućnih ljubimaca predstavlja nezamjenjivu, etički utemeljenu osnovu unutar moderne paradigme "Jedno zdravlje" (One Health), podstičući paralelna medicinska otkrića koja direktno koriste humanoj i veterinarskoj onkologiji.

Ključne riječi: Jedno zdravlje, komparativna onkologija, onkolitička viroterapija, translacijski modeli, tumori pasa