Using the canine microbiome to bridge translation of cancer immunotherapy from pre-clinical murine models to human clinical trials

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The microbiome has clearly been established as a cutting-edge field in tumor immunology and immunotherapy. Growing evidence supports the role of the microbiome in immune surveillance, self-tolerance, and response to immune checkpoint inhibitors such as anti PD-L1 and CTLA-4 blockade (1–6). Moreover, recent studies including those using fecal microbial transplantation (FMT) have demonstrated that response to checkpoint immunotherapies may be conferred or eliminated through gut microbiome modulation (7, 8). Consequently, studies evaluating microbiota-host immune and metabolic interactions remain an area of high impact research. While observations in murine models have highlighted the importance of the microbiome in response to therapy, we lack sufficient understanding of the exact mechanisms underlying these interactions. Furthermore, mouse and human gut microbiome composition may be too dissimilar for discovery of all relevant gut microbial biomarkers. Multiple cancers in dogs, including lymphoma, high grade gliomas, melanomas and osteosarcoma (OSA) closely resemble their human analogues, particularly in regard to metastasis, disease recurrence and response to treatment. Importantly, dogs with these spontaneous cancers also have intact immune systems, suggesting that microbiome analyses in these subjects may provide high yield information, especially in the setting of novel immunotherapy regimens which are currently expanding rapidly in canine comparative oncology (9, 10). Additionally, as onco-microbiotic therapies are developed to modify gut microbiomes for maximal responsiveness, large animal models with intact immune systems will be useful for trialing interventions and monitoring...
adverse events. Together, pre-clinical mechanistic studies and large animal trials can help fully unlock the potential of the microbiome as a diagnostic and therapeutic target in cancer.

**KEYWORDS**

microbiome, immunotherapy, cancer, comparative oncology, canines

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**Success and limitations of the murine model**

Murine models represent the most used model for studying host-microbiome physiology at both functional and mechanistic levels. Due to genetic homogeneity and laboratory environments, mouse models allow for high levels of control and improved experimental reproducibility (11). In cancers with representative murine models, mice have uncovered cancer promoting microbiota, and microbiota associated with improved response to treatment. Murine colon cancer models, for example, have contributed to understanding the influence of the gut microbiome on colorectal tumorigenesis via modulation of inflammation. In these models, transfer of the microbiome from tumor-bearing mice to germ free mice accelerated tumor growth, demonstrating causality (12, 13). Similarly, TLR4 knockout mice have been critical in understanding the oncogenic effect of gut microbiota in liver cancer (14). Sivan et al. (15) demonstrated key differences in tumor kinetics and responses to immunotherapy between genetically similar mice bred in two different environments. One cohort showed anti-tumor effects following anti-PD1 checkpoint inhibitor therapy, while the other cohort showed no benefit. However, co-housing the mice together reversed the differences in anti-tumor responses, which were then restored by the administration of oral Bifidobacterium spp (15). Similar observations were made for mice receiving anti-CTLA checkpoint inhibitors with effects modulated by Bacteroides species, (specifically *B. fragilis* and/or *B. thetaiotaomicron*) (16).

Despite the strength of these mechanistic murine studies, there are limitations to mouse models, particularly when considering the complex interactions between microbiome, immune response, and cancer. Laboratory mice demonstrate different microbial compositions to their wild counterparts. Attempts to convert lab-type to wild type mice have successfully altered, but not completely recapitulated, natural microbiome profiles (17). Moreover, animal facilities themselves significantly impact microbiome composition. For example, key differences in dominant taxa have been observed between identical mouse lines from different animal locations (18). Similarly, the use of germ-free mice is both a strength and a weakness of mouse models (19). These sterile conditions allow mice to be born without microbial colonization prior to the introduction of species of interest. However, this germ-free environment also leads to significant impairment of immune system development and responses. For example, mice raised in sterile conditions develop higher levels of IgE and fail to induce the same levels of immune reactivity seen during the “weaning period” of wild-type mice (20–23). This results in susceptibility to certain bacteria and increased risk of immunopathologies, complications which are not resolved with instillation of an “adult” or “wild-type” microbiome (21, 22, 24). Additionally, mouse studies of the microbiome show a large genetic influence which is distinct from humans where <10% of taxa are thought to be heritable (24–28). The high level of genetic homogeneity present in most murine models raises questions of generalizability to the human situation where genetic backgrounds and environmental exposures are vastly more diverse. This concern is reinforced by studies which have demonstrated the impact of environmental influences especially diet and drugs, as the most prominent factors influencing the microbiome in humans (29–31).

Additionally, as laboratory animals, mice do not receive the multi-faceted cancer care that is provided to humans and companion animals such as dogs. While pre-clinical murine models of checkpoint blockade immunotherapy have demonstrated impressive ability to prevent disease progression in various cancer cell lines, translation to human medicine has shown mixed results (32). Clinically meaningful survival benefits of PD-1 & CTLA-4 checkpoint inhibitor therapy have been demonstrated in some cancers, such as melanoma and non-small cell lung cancer, but only in a subset of patients (31–34). While observations from murine studies have demonstrated microbiome-associated factors for responsiveness to treatment, another limitation of murine models is their tendency to be reductionistic in their capacity to explore all potential intersecting variables which influence the cancer-immunity cycle (3–8, 15, 35, 36).

Similarly, murine models are able to strictly control diet and environment, both of which are key drivers of microbiome plasticity and composition, but as with germ-free studies, this can be both a strength and a weakness. For example, Matson et al. and Gopalakrishnan et al. (5, 6) used FMT to study whether human commensal microbes would potentiate anti-tumor T cell
responses in germ-free mice in two separate studies. Matson et al. demonstrated slower tumor growth in some mice after transferring microbiota from human responders. Gopalakrishnan et al. (6) showed changes in tumor infiltrating cells and upregulation of PD-1 in the tumor microenvironment after FMT. Although these mouse experiments demonstrated significant proof-of-concept results, it is not clear why effects were seen in some, but not all, mice. Given that the mice were evaluated to be highly homogenous and genetically inbred, the mice are expected to respond similarly. It is unclear whether the effects on the treatment would persist when using models with more heterogeneous genetic backgrounds and environmental exposures. Additionally, the fact that similar mechanisms were identified in these studies but the precise microorganisms were different highlights potential concerns regarding generalizability and extrapolation as noted above.

Microbiome studies in dogs with spontaneous cancers receiving immunotherapy offer an additional avenue for exploration. As the development of canine immunotherapy advances, including the development of novel caninized anti-PD1, anti-CTLA-4 and anti-PD-L1 monoclonal antibodies, microbiome correlative studies and attempted therapeutic intervention in canines with intact immune systems and a lifetime of commensal gut microbiome symbionts may yield useful observations for human applications (37–39). Human clinical immunotherapy trials are impacted by immune-related adverse effects such as colitis and myocarditis (32, 33, 39, 40). While murine models have been developed to help study these immune-related events, these models are prone to develop autoimmune responses which may limit translational potential (41).

Canine models represent an opportunity to bridge mechanistic studies in mice with descriptive studies in humans, and microbiome studies in companion animal dogs can help advance our understanding of how the gut microbiome shapes immunotherapy responses as well as toxicity and adverse events.

**Human vs canine microbiome**

As in humans, studies of the canine microbiome have evaluated the relationship of the microbiome with inflammatory disease states, development of malignancies, and more recently, response to oncologic therapies (42–47). The “normal” adult microbiota comprises thousands of bacterial species across mucosal and skin surfaces and is determined by environmental and genetic factors. The colonization of both the human and canine gut microbiome, one of the densest bacterial environments on earth, increases in alpha diversity and decreases in beta diversity during the weaning period before stabilizing (0-3 years in humans, 0-9 weeks in canines) (45, 48–50). Exposure to microbes during delivery, early diet, and antibiotic exposure have all been shown to impact gut microbial development (22, 51, 52). Early influences have clinical impact – colonization with *C. difficile* during the first months of life is associated with increased risk of atopic disorders such as asthma and eczema in children (53). Microbiome compositions in pre-weened puppies display instability of prominent taxa. Puppies that displayed these “immature” microbiome profiles are more susceptible to diarrheal illness compared to those who have developed stable more “adult” compositions (54). Environmental factors such as diet, drugs, and living conditions also exert key influences on subsequent adult microbiota composition (29, 30). Microbiomes of genetically unrelated co-habitants are consistently demonstrated to be more similar than those of relatives who do not cohabitate, and genetic ancestry does not predict compositional similarities (29, 55). While environment is the primary influencer of composition, there appears to be heritability in human and canine gut microbiomes as well. A study of 400 human twin pairs raised in the same household compared monozygotic vs dizygotic siblings. Interestingly, monozygotic twins demonstrated more similar gut microbiota compared to their dizygotic counterparts (56). Canine comparisons of dog breeds show similar findings, although studies of breed variation indicate that breed does not cause major shifts in microbiome composition or diversity but may influence abundance of specific taxa (46). Although not to the extent of humans or mice, the canine gut microbiota has been surveyed in some detail (50, 57–59). Most large studies agree on the five most prominent phyla in dogs: *Firmicutes, Fusobacteria, Bacteroides, Proteobacteria and Actinobacteria*, the composition of which is more similar to humans than other commonly studied mammalian species. Coelho et al. (57) compared 129 stool samples from 64 dogs against previously published gut microbial gene catalogs based on similar sequencing methods. The phylum level distribution of genes in the dog was more like the published human data than that of a mouse or pig. When genes were clustered by each species pool, the dog gut gene pool overlapped most with the human gut microbiome (23%) compared to only 4.9% for the murine gene catalog. As in prior human data, the majority of the composition appeared to be influenced by environmental exposures, diet, and disease states. Importantly, certain bacterial species have been found to exert similar effect across species. Obesity, which is a growing problem in both humans and canines, is correlated with a change in *Firmicutes/Bacteroides* ratios in both humans and canines (60–62). Canine and human inflammatory bowel disorders are associated with a reduction in microbial community diversity and structure characterized by loss of key species or overgrowth of species with genotoxic potential such as *Bacteroides fragilis* and *E. coli* (45, 63). In humans, these microbiome shifts have been associated with colorectal cancer (12, 64, 65). While colorectal cancer is less common in dogs, increased *E.coli* is associated with canine intestinal lymphoma (42). Importantly, human and dog differences in microbiome interactions are also informative. Fusobacterium, for instance,
plays a role in energy utilization in the gut as a fermenting species. In humans, F. nucleatum is associated with colorectal cancer and thought to trigger inhibitory T cell receptors that suppress anti-cancer immune response (66, 67). In dogs, however, fusobacteria are associated with maintaining gut health (67).

While similarities in the development and composition of the gut microbiome present one advantage of the canine model, perhaps the most important is that of a shared environment with humans. As companion animals, dogs inhabit the same environment as humans. Therefore, shifts in composition caused by disease states or therapeutics must be robust enough to compete with the myriad of “real life” influences that patients encounter. Shared environments may also lead to shared taxonomy; canine housemates show similar microbiome profiles, similar to what is observed between human cohabiting with a spouse or partner (68). Interestingly, co-living between species influences microbiome profile as well (69). Companion dogs share more skin flora with their owners than with other dogs and oral microbiomes, which may show relevance in oral melanoma, as there is evidence of oral spread of symbionts and oral microbiomes, which may show relevance in oral health (67).

Shared environments may also lead to shared communities in other compartments have clinical implications as disease-free interval and time to progression which are highly relevant to the human situation.

Microbiome in canine therapeutics

Attenuation of immune surveillance and development of immunological tolerance to tumor-derived antigens contribute to cancer development and progression. Novel immunotherapies target one of these two mechanisms to stimulate the subject's immune system to recognize and target cancer as non-self. Overcoming both intrinsic and acquired resistance to these treatments are critical areas of study, and although several species of interest have been identified, no universal “responder signature” has been identified. Canine analysis that identifies similar bacterial enrichment as in human studies would greatly enhance the chances of replicable and generalizable effects.

Microbiome modulation has demonstrated exciting promise in increasing the number of human patients who may respond to PD-1/PD-L1 checkpoint inhibitor immunotherapy (4–6). Demonstrated first by Gopalakrishnan & Matson et al. (5, 6) in a murine model, and recently by Baruch et al. (7) in a human clinical trial, FMT from a drug-responsive subject to a nonresponsive subject was able to convert a subset of prior non-responders, allowing them to benefit from treatment. Importantly, when considering the human trial of FMT, extensive pre-and post-treatment analysis regarding microbiome composition, local metabolism, and expression of immune-related genes failed to show significant differences between those who became responsive to treatment and those who did not (7). Thus, while successful in proving the concept of FMT to be safe and potentially beneficial, the effects remain correlative. These types of immune-microbiome relationships could benefit from additional studies in dogs with spontaneous cancers in the setting of an intact immune system. FMT is accepted in community veterinary practice making high-powered studies possible once commercially available caninized ICI’s are readily available (59). Repeating FMT trials with canine immunotherapy provides an opportunity to integrate observations of gut microbial alterations with longitudinal changes in metabolism and immune surveillance. Dogs, unlike mice, allow for multiple collections of adequate blood samples that can detect metabolites of short chain fatty acids that can act as ligands for G-protein coupled receptors. Iosine and hypoxanthine have recently been associated with bacteria of interest, for example (71, 72).

While veterinary medicine is waiting for the widespread commercial availability of canine specific PD-1/PD-L1/CTLA-4 mAbs to usher the area of immunotherapy in dogs, other immunotherapy approaches are in use, and comparison of microbiome profiles between responder status in other immune-based therapies should be considered (73, 74). Longitudinal stool and blood sampling of these canine patients for microbiome and metabolic investigation presents a rich area of investigation. Standard treatments for dog cancers include chemotherapy and radiation, which may allow for evaluation of the impacts that traditional therapies have on the microbiome alone or in combination with immunotherapy. Canine lifecycles are also inherently shorter, so rapidly progressing canine cancers allow for collection of samples linked to critical end points such as disease-free interval and time to progression which are highly relevant to the human situation.

Microbiome in the tumor microenvironment

The gut microbiome represents the most extensively classified community in humans and animal models, yet increasing studies have demonstrated that microbial communities in other compartments have clinical implications (74–76). Tumor-associated microbiomes have been identified in multiple human cancers including breast, lung, pancreas, and melanoma tumors (74–79). While tumor infiltrating lymphocytes (TILs) have emerged as a key feature of the immune tumor microenvironment (TME), a deeper molecular and cellular signals responsible for immune-tumor-microbiome communication are not yet understood. While some studies demonstrate a higher number of tumor infiltrating lymphocytes (TILs) in the TME project more positive patient outcomes, others suggest that the upregulation of regulatory T cells in the TME is associated with a more negative outcome (80–82).
Although mouse models can provide key insights into the immune-tumor interactions in the TME and are important for mechanistic studies, these models have limitations given the nature of transplanted highly retroviral tumors. Known differences in tumor initiation and promotion are likely to impact the fidelity of the model for microbiome studies (83, 84).

Therefore, dogs represent an important translational opportunity for studies of the cancer-immunity cycle, including microbiome studies. Canine immunotherapy, including evaluation of novel therapies in the context of clinical trials, has received significant attention from researchers and funding agencies, including the Cancer Moonshot, and examples of ongoing canine immunotherapy trials can be seen in Table 1 (9, 10). Dogs are diagnosed with naturally occurring cancers which are highly similar to humans, and genetic studies have demonstrated notable overlap in the tumor genetic makeup of human and dog OSA, melanoma, mammary tumors, gliomas and lymphomas (84–90). Canine OSA recapitulates several feature of human OSA including frequent TP53, PI3K, and MAPK pathway mutations with low expression of immuno-associated genes and a trend toward higher mutation burden in metastatic disease (88). Canine mammary tumors and lymphomas share major gene alterations with their human counterparts in addition to having similar tumor mutation burdens (91). Gliomas have been shown to share specific alterations in receptor tyrosine kinases such as TP53 and cell cycle pathways with human pediatric gliomas (89). Overall, the incidence of these canine cancers is believed to be as high or higher than their human counterparts, although precise case numbers are not known since no national database exists for dogs. For example, soft tissue sarcomas make up 10-15% of malignant tumors in dogs with estimates of approximately 7700-31,800 new canine cases per year in the United States compared to soft tissue sarcoma in humans which represents approximately 1% of cancer cases and 10,000 – 12,000 new cases per year in the US (91).

### TABLE 1 Ongoing Clinical Trials in Dogs.

| Institution                      | Clinical Trial                                                                 | Cancer Type       |
|----------------------------------|-------------------------------------------------------------------------------|-------------------|
| University of California Davis   | Enhancing Natural Killer Immunotherapy with First in Dog Trials of Inhaled Recombinant IL-15 and Super agonist IL-15 in Naturally Occurring Canine Cancers | Osteosarcoma      |
| University of Alabama at Birmingham | Canine Immuno-Neurotherapeutics (Combination immunotherapies for canine brain tumors)  | Melanoma          |
| Colorado State University       | Optimizing Novel Immunotherapy Combination Targeting the Tumor Microenvironment in Canine Spontaneous Osteosarcoma | Glioma            |
| Tufts University                | Enhancing the Efficacy of Immunotherapy in DLBCL Using Rational Combination Approaches | Osteosarcoma      |
| University of Minnesota         | Novel Combined Immunotherapeutic Strategies for Glioma: Using Pet Dogs as a Large Animal Spontaneous Model | Lymphoma          |

**FIGURE 1**

Venn diagram comparing relevant aspects of canine model to humans. Important mouse model differences highlighted below.
canine OSA is estimated at approximately 25,000 – 50,000 cases per year, whereas the number of human OSA is approximately 3000 per year in the US (92–94). Data such as these highlight the value of the canine model as an important asset in tumor immunology and immunotherapy studies, especially where an intact immune system is critical for understanding tumor and host biology.

Conclusion

Murine models will always have utility as pre-clinical models, including for microbiome studies. However, due to the complex interactions between the immune system, the TME, and metabolism, utilization of canines for microbiome research is a promising strategy to yield additional data that can bridge our understanding from “proof of concept” to “proof of mechanism”. Further classification of the canine microbiome in cancer, changes in the canine microbiome in response to immunotherapy, and characterization of microbiomes outside the gut will all be important in deriving the most from canine models. This is particularly important now as veterinary medicine has made advances in canine specific immunotherapy agents that mirror human ICI. Canine clinical trials should consider collection of stool samples for microbiome biomarkers, as well as tissue and blood samples as well to correlate microbiome changes with immune infiltration and metabolic changes. As we increase our understanding of the interplay between specific commensal bacteria and the targets of immune therapy, the next step is therapeutic application. Through diet, antibiotics, fecal transfer, or other methods, reliably tailoring gut microbiomes to create maximal responsiveness with minimal side effects is the future of immuno-oncology. Dogs present a step-in bench to bedside science where their developing interventions can be tested on immune intact models exposed to complex environmental influences to ensure they demonstrate durability and utility.

References

1. Frank DN, St Amand AL, Feldman RA, Boedecker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA (2007) 104 (34):13780–5. doi: 10.1073/pnas.0706625104

2. Rodrigues Hoffmann A. The cutaneous ecosystem: the roles of the skin microbiome in health and disease. Vet Dermatol (2017) 28(1):60–e15. doi: 10.1111/vde.12408

3. Ni J, Shen T, Chen EZ, Bittinger K, Bailey A, Roggiani M, et al. A role for bacterial urease in gut dysbiosis and crohn’s disease. Sci Transl Med (2017) 9 (416):1–11. doi: 10.1126/scitranslmed.aah6688

4. Roux B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Duillère R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science (2018) 359(6371):91–7. doi: 10.1126/science.aan3706

5. Matson V, Feusler J, Rao R, Chongsuwat T, Zha Y, Alegre M-L, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science (2018) 359.

6. Gopalakrishnan V, Spencer CN, Neri L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science (2018) 359(6371):97–103. doi: 10.1126/science.aao4236

7. Baruch EN, Youngster I, Ben-Betzalel G, Ortenberg R, Lahat A, Katz L, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science (2021) 370(6529):602–9. doi: 10.1126/science.abf3363

Author contributions

KK and RC conceptualized the manuscript. KK, KI, LP, SC, and AR reviewed current literature. KK and KI wrote the manuscript and generated the associate figure. WC, MK, JE, and RR edited the manuscript and provided context for veterinary literature. RC edited the final paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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immunopathologies in the adult. Immunology (2015) 350(6264):1079

Kleber et al. Commensal biota: Environmental and genetic factors shaping the human gut microbiome. MBio (2014) 505(7484):559

Park JS, Withers SS, Medrache I, et al. Urine and fecal microbiota in a canine model of bladder cancer. J Clin Med (2020) 9:1598. doi:10.3390/jcm.915.1598

Bayer F, Ascher S, Pontarollo G, Reinhardt C. Antibiotic treatment protocols and germ-free mouse models in vascular research. Front Immunol (2019) 10:2174. doi:10.3389/fimmu.2019.02174

Labuda JC, Fong KD, McSorley SJ. Cohousing with dirty mice increases the frequency of memory T cells and has variable effects on intracellular bacterial infection. Appl Environ Microbiol (2013) 79(12):4559-70. doi:10.1128/AEM.01086-13

Korach-Rechtman H, Freilich S, Gerassiz-Vainberg S, Buhnik-Rosenblau K, Danin-Poleg Y, Bar H, et al. Murine genetic background has a stronger impact on the composition of the gut microbiota than maternal inoculation or exposure to unlike exogenous microbiota. Appl Environ Microbiol (2019) 85(18). doi:10.1128/AEM.00286-19

Bubja J, Cherel EJ, Weinstock GM. Host genetic control of gut microbiome composition. Mamm Genome (2021) 32(4):283-81. doi:10.1007/s00335-021-09884-2

Campbell JH, Foster CM, Vishnevskaya T, Campbell AG, Yang ZK, Wymore A, et al. Host genetic and environmental effects on mouse intestinal microbiome. ISME J (2012) 6(11):2033-44. doi:10.1038/ismej.2012.54

Org E, Parks BW, Joo JW, Emerit B, Schwartzman W, Kang EY, et al. Genetic and environmental control of host-gut microbiota interactions. Genome Res (2015) 25(10):1558-69. doi:10.1101/gr.194118.114

Gacesa R, Kurilshikov A, Vich Vila A, Sinha T, Klaassen MAY, Bolte LA, et al. Environment dominates over host genetics in shaping human gut microbiota. Genome Biol (2018) 19:28. doi:10.1186/s13059-018-1465-3

Machado J, Bader M, Palleratal L, Blumberg J, Chin WY, et al. Antibiotics rapidly and reproducibly alter the human gut microbiome. Nature (2014) 505(7484):559-63. doi:10.1038/nature13280

Simeos CD, Maksakon J, Kaprio J, Rissanen A, Pietilainen KH, Saarela M. Habitual dietary intake is associated with stool microbiota composition in monozygotic twins. J Nutr (2013) 143(4):417-23. doi:10.3945/jn.112.166322

Chae YK, Arya A, Iams W, Crut MB, Chandra S, Choi J, et al. Current landscape and future of dual anti- CTLA4 and PD-1/PD-L1 blockade in cancer; lessons learned from clinical trials with melanoma and non-small cell lung cancer (NSCLC). J Immunother Cancer (2018) 6(1):39. doi:10.1186/s40425-018-0349-3

Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage III/IV non-Small-Cell lung cancer: Results from a randomized, double-blind, multicenter phase II study. J Clin Oncol (2012) 30(17):2046-54. doi:10.1200/JCO.2011.38.4023

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med (2010) 363(8):711-23. doi:10.1056/NEJMoa1003466

Haslam A, Gill J, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for immune checkpoint inhibitor drugs. JAMA Netw Open (2020) 3(3):e200243. doi:10.1001/jamanetworkopen.2020.0423

Choi JW, Withers SS, Chang H, Spanier JA, de la Trinidad VL, Panesar H, et al. Development of canine PD-1/PD-L1 specific monoclonal antibodies and amplification of canine T cell function. Plos One (2020) 15(7):e0235518. doi:10.1371/journal.pone.0235518

Rothschild D, Weiszbor O, Barkun E, Kurilshikov A, Koem T, Zeevi D, et al. Environment dominates over host genetics in shaping human gut microbiota. Nature (2018) 555(7695):210-5. doi:10.1038/nature25973

Mason NJ, Chester N, Xiong A, Rotolo A, Wu Y, Yoshimoto S, et al. Development of a fully canine anti-cancer CTLA4 monoclonal antibody for comparative translational research in dogs with spontaneous tumors. MAbs (2021) 13(1):2004638. doi:10.1080/19420862.2021.2004638–9. doi:10.1080/19420862.2021.2004638

Marbach J, Ruiz D, Jaiswal AK, Bhattacharya R, Pantazes R, Agarwal P, et al. Nanobody-based CTLA4 inhibitors for immune checkpoint blockade therapy of canine cancer patients. Sci Rep (2021) 11(1):20763. doi:10.1038/s41598-021-03028-y

Yang JC, Beck KE, Blanfied JA, Trax KQ, Lowry I, Rosenberg SA. Tumor regression in patients with metastatic renal cancer treated with a monoclonal antibody to CTLA4 (MDX-010). J Clin Oncol (2005) 23(suppl):2501-6. doi:10.1200/jco.2005.23.16_suppl.2501

Uysk M, Pandey A, Hayes RB, Moran U, Pavlick A, Osman I, et al. Bacteroides vulgatus and bacteroides dorei predict immune-related adverse events in immune checkpoint blockade treatment of metastatic melanoma. Genome Med (2021) 13(1):160. doi:10.1186/s13073-021-01097-x

Omont M, Maeda S, Igarashi H, Ohno K, Sakai K, Yonezawa T, et al. Fecal microbiome in dogs with inflammatory bowel disease and intestinal lymphoma. J Vet Med Sci (2017) 79(11):1840-7. doi:10.1292/jvms.17-0229

Mordrich R, Padman C, Evans MV, Kisseberth WC, Dhawan D, Knapp DW, et al. Urine and fecal microbiota in a canine model of bladder cancer. Front Immunol (2021) 12:635. doi:10.3389/fimmu.2021.635

Billa R, Suchodolski JS. The role of the canine gut microbiome and metabolome in health and gastrointestinal disease. Vet Comp Oncol (2018) 16(1):169-75. doi:10.1111/vco.12367

Gavazza A, Rossi G, Lobas G, Cerquetella M, Minamoto Y, Suchodolski JS. Faecal microbiota in dogs with multicentric lymphoma. Vet J (2017) 218:222-7. doi:10.1016/j.tvjl.2017.06.026

Connor E, Ericsson AC, Franklin CL. Evaluation of fecal microbiome composition and its impact on the development of allergic diseases. Front Immunol (2020) 11:700. doi:10.3389/fimmu.2020.00700

Costa S, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their impact on the development of allergic diseases. JAMA Netw Open (2020) 3:2021-32. doi:10.1001/jamanetworkopen.2020.3170

Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Genetic and environmental control of host-gut microbiota interactions. Nature (2015) 520(7549):1558-69. doi:10.1038/nature14118

Usyk M, Pandey A, Hayes RB, Moran U, Pavlick A, Osman I, et al. Bacteroides vulgatus and bacteroides dorei predict immune-related adverse events in immune checkpoint blockade treatment of metastatic melanoma. Genome Med (2021) 13(1):160. doi:10.1186/s13073-021-01097-x

Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. Immune-stimulatory functions of gut microbiota. Science (2010) 327(5966):66-70. doi:10.1126/science.1184235

Giles RS, Armour R, Wilkes L, Pullen J, Alvarado E, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature (2012) 492(7427):54-8. doi:10.1038/nature11416

Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Antibody combination with ipilimumab and vemurafenib in patients with advanced melanoma. J Clin Oncol (2012) 30(17):2046-54. doi:10.1200/JCO.2011.38.4023

Kirkhorn M, et al. Mode and place of delivery, gastrointestinal microbiota, and their impact on the development of allergic diseases. JAMA Netw Open (2020) 3(2):e200243. doi:10.1001/jamanetworkopen.2020.0423
In mice, prebiotics are shown to decrease tumor growth and enhance the antitumor effects of radioimmunotherapy. These effects are thought to be mediated by the activity of the immune system, specifically the natural killer cells, which are activated by prebiotics and localized in the tumor microenvironment. The combination of radiotherapy and natural killer cell activation provides a promising approach for improving cancer treatment outcomes.

The role of the oral microbiome in cancer prevention and progression is also of interest. A study by Tzeng et al. (2013) showed that the oral microbiomes of canines and their owners are highly similar, suggesting a potential link between the oral microbiome and the risk of colorectal cancer. Another study by Rooks and Garrett (2016) demonstrated that the gut microbiota is involved in the development of canine osteosarcoma, with mutations in DMD and the histone methyltransferase gene SETD2.

In conclusion, the role of the microbiome in cancer prevention and progression is complex and multifaceted. Further research is needed to fully understand the mechanisms by which the microbiome influences cancer development and to develop strategies to harness these influences for the benefit of patients.