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Review Article

Harnessing the Gut Microbiota: Fecal Microbiota Transplantation as a Novel Strategy in Cancer Immunotherapy

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Abstract

Cancer immunotherapy, particularly immune checkpoint inhibitors (ICIs), faces challenges of resistance and toxicity. The gut microbiota critically influences anti-tumor immunity and ICI efficacy, with dysbiosis linked to carcinogenesis and immunosuppression. Fecal microbiota transplantation (FMT) restores microbial balance, overcoming resistance by enriching immunostimulatory species (e.g., *Akkermansia muciniphila* and *Bifidobacterium* etc.) and enhancing $CD8^+$ T cell infiltration and dendritic cell activation in melanoma, colorectal, and renal cancers etc. This review, we briefly discuss the potential of FMT in enhancing cancer immunotherapy, providing insights into current research and future directions.

Keywords: Fecal Microbiota Transplantation (FMT); Cancer Immunotherapy; Gut Microbiome; Immune Checkpoint Inhibitors (ICIs)

Introduction

Cancer remains one of the most significant global public health challenges, imposing a heavy and growing socioeconomic burden worldwide [1]. Over the past few decades, significant progress has been made in understanding the mechanisms underlying tumour development, progression, and metastasis [2]. These mechanisms form a complex network involving the host's immune status and external environmental factors. Among the most promising advances in cancer treatment is immunotherapy, particularly the use of immune checkpoint inhibitors (ICIs), which target co-inhibitory signals in T cell activation and immune evasion pathways. ICIs, such as monoclonal antibodies against programmed death receptor 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4), have revolutionised the clinical management of advanced malignancies [3]. However, despite their success, a significant proportion of patients experience primary or secondary resistance to ICIs, and immune-related adverse events (irAEs) remain a major concern [4]. These challenges highlight the need for strategies to enhance the efficacy and safety of immunotherapy.

Emerging evidence suggests that the gut microbiota, a complex community of trillions of microorganisms residing in the human intestine, plays a critical role in modulating host immunity and influencing the response to cancer immunotherapy [5]. The gut microbiota is often referred to as a "super organ" due to its profound

impact on host physiology, including immune regulation, metabolism, and maintenance of the tumour microenvironment (TME) [6]. Dysbiosis, or an imbalance in the gut microbial community, characterised by an increase in pathogenic bacteria and a decrease in beneficial species, has been linked to the development of both gastrointestinal and extra-gastrointestinal cancers [7]. Moreover, specific microbial taxa, such as *Bacteroidetes*, have been associated with enhanced anti-tumour immunity, whereas pathogenic *Proteobacteria* are correlated with immunosuppression [8]. These findings suggest that modulating the gut microbiota could be a viable strategy to improve the efficacy of cancer immunotherapy.

Fecal microbiota transplantation (FMT), the transfer of gut microbiota from a healthy donor to a recipient, has emerged as a promising intervention to restore microbial balance and enhance therapeutic outcomes. FMT has shown remarkable success in treating recurrent *Clostridioides difficile* infection (CDI), with efficacy rates of approximately 90% [9]. Beyond CDI, FMT is being explored for its potential to modulate the gut microbiota in various diseases, including cancer. Preclinical and clinical studies have demonstrated that FMT can enhance the efficacy of ICIs by reshaping the gut microbiome to promote anti-tumour immunity [10,11] . For instance, animal studies have shown that modulating the gut microbiota can increase the sensitivity of solid tumours to ICIs [12]. However, challenges remain, including concerns about the safety, efficacy, and precision of FMT, as well as the need for rigorous donor screening and standardised protocols[13].

This review aims to provide a comprehensive overview of the intricate relationship between the gut microbiota and anti-tumour immunotherapy, with a focus on the clinical applications of FMT in enhancing therapeutic efficacy. We discuss the role of the gut microbiota in regulating immune responses, the potential of FMT to modulate the tumour microenvironment, and its application in specific cancer types.

Fecal microbiota transplantation (FMT): tumor immunotherapy

Several bacterial species have been associated with tumor progression, such as in gastric carcinoma, *Escherichia coli, Bacteroides fragilis* and *Fusobacterium nucleatum* in *H. pylori* colonic neoplasia and *Streptococcus bovis* in colorectal cancer [14]. Recent advances in metagenomic sequencing and metabolomic profiling have provided insights into the gut microbiota's role in modulating responses to immune checkpoint inhibitors (ICIs). Notably, distinct microbial profiles have been identified in ICI responders versus non-responders, suggesting a link between gut microbiota composition and immunotherapy efficacy [15]. Among the identified bacterial species, *Akkermansia muciniphila* has emerged as a consistent marker of ICIs responsiveness in melanoma, non-small-cell lung cancer (NSCLC) and renal cell carcinoma (RCC) patients [16]. However, discrepancies in findings across studies may arise due to differences in sample collection, DNA extraction protocols, genetic background, geography, diet and medication use [17]. Despite these challenges, gut microbiota signatures show promise in predicting treatment outcomes and guiding microbiota-targeted therapeutic interventions. Numerous clinical trials are currently in progress, and the potential of FMT to enhance anti-tumor immunotherapy has remained a topic of significant interest.

Microbiota profiling and immune modulation

Microbiota profiling has revealed a strong association between gut microbiota composition and tumor-infiltrating immune cells in the tumor microenvironment (TME), impacting the efficacy of immunotherapy. Several bacterial species, such as *Akkermansia muciniphila, Faecalibacterium, Ruminococcaceae, Bifidobacterium breve, Bifidobacterium adolescentis, Bifidobacterium longum, Collinsella aerofaciens* and *Enterococcus faecium* have been identified as promoters of anti-PD-1 immunotherapy efficacy through enhanced antigen presentation and improved effector T cell function in both systemic circulation and the TME [18]. In contrast, a greater abundance of *Bacteroidales* correlates with elevated levels of regulatory T (Treg) cells and myeloid-derived suppressor cells (MDSCs), limited intratumoral lymphoid infiltration, and impaired antigen presentation, leading to poor prognosis in non-responders (NRs) [19].

FMT and immunotherapy resistance

FMT has garnered attention as a strategy to modulate gut microbiota composition and enhance anti-tumor immunity. By restoring microbial equilibrium, FMT has demonstrated potential in reversing ICI resistance and mitigating immune-related adverse events (irAEs). Clinical trials in metastatic melanoma patients have shown that FMT can increase the response rate to anti-PD-1 therapy, illustrating its clinical applicability [20] Mechanistically, FMT enhances gut microbiota diversity and promotes the persistence of beneficial microbial populations, thereby improving immune system modulation and tumor suppression [21].

Altering gut microbiota diversity through antibiotic use negatively impacts ICI response in NSCLC and RCC patients, underscoring the microbiota's role in shaping immunotherapy outcomes

[22]. FMT offers a more comprehensive approach than single-strain probiotic supplementation, which may disrupt microbial diversity. By transferring an entire donor microbial ecosystem, FMT facilitates ecological homeostasis, thereby increasing treatment efficacy. Notably, melanoma patients who responded to FMT exhibited sustained gut microbiota diversity over time, reinforcing the potential of FMT in long-term cancer management [21]. However, further research is needed to standardize FMT protocols and identify optimal donor microbiota compositions to maximize therapeutic benefits.

FMT has demonstrated promising results in overcoming immunotherapy resistance, particularly in clinical models of refractory melanoma. FMT from responders (Rs) resulted in beneficial alterations in immune cell infiltration, gene expression in the gut lamina propria, and increased CD8+ T cell activation, dendritic cell (DC) maturation and IFN-γ signaling within the TME [21]. In contrast, FMT from NRs led to an increased prevalence of immunosuppressive cell populations, including RORγT+ T helper 17 cells and CD4+FoxP3+ Treg cells, impairing the host immune response [23] Moreover, the restoration of PD-1 blockade efficacy by *A. muciniphila* supplementation highlights its role in recruiting CCR9+CXCR3+CD4+ T lymphocytes into the TME, enhancing IFN-γ release, and promoting IL-12 secretion by DCs [24]. Furthermore, species such as *Bacteroides fragilis, Bacteroides thetaiotaomicron* and *Burkholderia* have been implicated in enhancing the effects of CTLA-4 blockade by driving IL-12-dependent Th1 immune responses and promoting intratumoral DC maturation (Figure) [25]. Key gut microbiota traits linked to enhanced clinical outcomes in cancer patients treated with immune checkpoint inhibitors (ICIs) are listed in table.

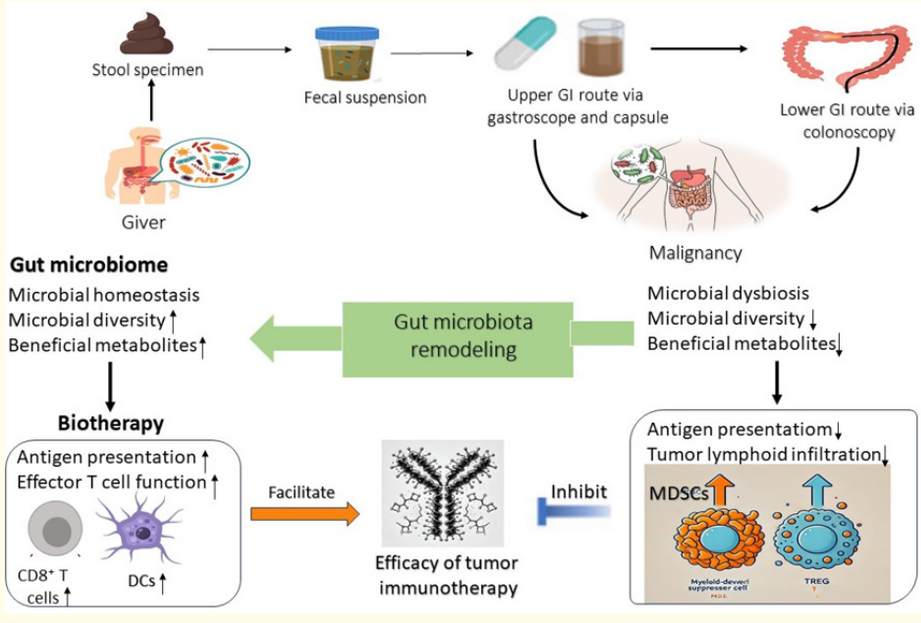

Figure 1: Fecal Microbiota Transplantation (FMT)-mediated gut microbiota remodeling enhances tumor immunotherapy efficacy via modulation of immune responses.

Microbial Taxon	Cancer Types	Mechanisms of Action	Clinical Outcomes	References
Akkermansia muciniphila	NSCLC, HCC, Melanoma, CRC	Enhances IFN-γ+ CD8+ CXCR3+ CD4+ T cell infiltration; improves gut barrier integrity; produces SCFAs, Induced dendritic cells to secrete IL-12	Longer PFS/OS; better response to anti-PD-1/PD-L1 therapy	[26]
Bifidobacterium spp.	Melanoma, NSCLC, CRC	Activates dendritic cells; promotes CD8+ T cell proliferation; modulates IL-12 signalling and enhanced Th1 immune responses.	Improved tumor control; enhanced anti-CTLA-4 and anti-PD-1 efficacy	[27]
Faecalibacterium prausnitzii	CRC, NSCLC	Produces butyrate; reduces inflammation; enhances anti-tumor T cell activity and modulated CD8+	Higher response rates; prolonged survival; Anti-PD-1	[26]
Ruminococcaceae family	NSCLC, HCC, CRC	Promotes SCFA production; supports immune activation and T cell priming; unsaturated fatty acid biosynthesis, and vitamin and starch biosynthesis, correlating with higher efficacy and no toxicity development	Longer OS; improved disease control (PR/SD); Anti-PD-1/PD-L1	[26]
Alistipes spp.	NSCLC, HCC	Modulates indole metabolism; anti-inflammatory effects; Enriched in responders; associated with enhanced treatment response.	Predictive of durable clinical benefit; Anti-PD-1	[26]
Eubacterium spp.	NSCLC, CRC	Enhances SCFA synthesis (e.g., butyrate); regulates histone deacetylase inhibition	Correlated with prolonged PFS	[28]
Prevotella copri	Advanced cancer	Associated with favorable outcomes; correlated with prolonged overall survival.	Anti-PD-1/PD-L1	[29]
Lactobacillus spp.	Melanoma, CRC	Produces indole-3-aldehyde (I3A); activates AhR signaling in CD8+ T cells	Increased tumor-infiltrating lymphocytes; improved anti-PD-1 response	[30]
Lachnospiraceae bacterium	Hepatobiliary cancer	High abundance linked to longer progression-free survival and improved treatment response.	Anti-PD-1	[31]
Bacteroides ratio	HCC, CRC	Higher ratio linked to immune activation; reduces immunosuppressive microenvironment	Better prognosis in HCC; improved nivolumab response	[28,32]
Clostridiales (specific strains)	Melanoma, CRC	Induces Treg suppression; enhances CD8+ T cell infiltration; Significantly more abundant in long-term responders; associated with durable response.	Synergistic effects with ICIs; reduced tumor growth; Anti-PD-1/PD-L1	[30,33]
High microbial diversity	Multiple cancers (NSCLC, CRC, Melanoma)	Maintains immune homeostasis; enriches beneficial taxa	Stronger ICI response; reduced antibiotic-induced resistance	[26]

Table 1: Summarizing key gut microbiota characteristics associated with improved clinical benefits of immune checkpoint inhibitors (ICIs) in cancer patients.

Clinical applications of FMT in cancer immunotherapy

Gastric Cancer

The carcinogenesis of gastric cancer has been closely associated with *H. pylori* and specific oral microbiota such as *Fusobacterium nucleatum*, *Parvimonas micra*, and *Peptostreptococcus stomatis [34]*. Studies have demonstrated significant enrichment of *P. stomatis*, *P. micra*, *Streptococcus anginosus*, *Dialister pneumosintes*, *Slackia exigua*, *Clostridium colicanis*, and *Fusobacterium nucleatum*, alongside a notable depletion of *Helicobacterium* in gastric cancer tissues [35] [36]. These microbial alterations reflect a dysbiotic microbial community with potential predictive value in gastric cancer. Moreover, increasing evidence supports that eradication therapy for *H. pylori* can significantly reduce the risk of gastric cancer [37]. Collectively, these findings highlight the critical role of gastric microbiota in gastric carcinogenesis.

Colorectal Cancer (CRC)

ICIs have shown limited efficacy in CRC, with only a subset of patients deriving therapeutic benefits. Preclinical studies suggest that FMT from CRC patients impairs anti-PD-1 efficacy compared to FMT from healthy individuals. However, FMT combined with anti-PD-1 therapy has been associated with increased butyrate-producing bacteria, enhanced T cell infiltration, and improved immune activation. Additionally, metabolites such as punicic acid have been linked to improved treatment response [21].

With the colonic epithelium in constant proximity to microbial populations, it is increasingly evident that gut microbiota contribute to colorectal cancer development. Specific pathogenic bacteria can induce CRC via mechanisms such as toxin production, chronic inflammation, mucosal barrier disruption, and bacterial translocation. Notably, enterotoxigenic *Bacteroides fragilis* has been shown to exert pro-tumorigenic effects by producing harmful substances [37]. Clinical studies also indicate distinct shifts in microbial composition between healthy individuals and CRC patients, characterized by a CRC-specific bacterial signature [38]. In CRC patients, beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* are reduced, while opportunistic taxa like *Staphylococcaceae*, *Fusobacteria*, and *Peptostreptococcus anaerobius* are elevated [39]. This microbial dysbiosis has prompted investigation into fecal microbiota profiling as a noninvasive diagnostic tool for early CRC detection.

Several studies support the protective effects of probiotics against CRC. For instance, butyrate-producing probiotics such as *Clostridium butyricum* and *Bacillus subtilis* have shown inhibitory effects on 1,2-dimethylhydrazine (DMH)-induced colon tumors in mice [40]. *Lactobacillus casei* strain BL23 not only suppressed CRC development in mice but also corrected CRC-induced gut Dysbiosis [41]. Additionally, clinical evidence demonstrates that oral administration of *Bifidobacterium* triple viable preparations can alleviate gut dysbiosis and mitigate small intestinal bacterial overgrowth in CRC patients [42].

Our group further identified the role of intestinal dysbiosis induced by deoxycholic acid (DCA), a carcinogenic secondary bile acid, in CRC development. Fecal microbiota transplants (FMT) from DCA-treated mice significantly promoted intestinal tumorigenesis compared to controls [43]. A parallel clinical study confirmed that fecal microbiota from CRC patients increased tumor formation and reduced microbial diversity in germ-free and conventional mice exposed to carcinogens [44]. Compared to laboratory strains, mice with wild-derived microbiota showed increased resistance to CRC and inflammation [45], suggesting that FMT may possess therapeutic potential in CRC management.

Breast cancer

The hypothesis linking gut microbiota to breast cancer was first proposed in 1971, based on shared epidemiological features with colorectal cancer [46]. However, direct studies remain limited. Goedert et al. reported that postmenopausal women with breast cancer exhibited significantly lower alpha diversity and distinct fecal microbiota profiles compared to healthy controls [47].

Potential mechanisms underlying this association include alterations in estrogen metabolism, immune modulation, and metabolic changes related to obesity [48]. Experimental studies have supported a protective role for gut microbiota modulation. For instance, oral supplementation with *Lactobacillus acidophilus* delayed breast cancer development in mice, potentially by enhancing anti-tumor immune responses [49]. Further mechanistic studies are needed to clarify these relationships and explore the potential of gut microbiota manipulation in breast cancer management.

Pancreatic cancer

Recent research has highlighted significant alterations in the microbiota composition of pancreatic cancer patients, particularly those with pancreatic ductal adenocarcinoma (PDAC). These alterations are characterized by an increased abundance of *Malassezia* spp., Pseudomonas aeruginosa, and *Fusobacterium* spp., alongside a marked reduction in beneficial microbes such as butyrate-producing bacteria and *Lactobacillus* spp. [50]. These dysbiotic changes have been linked to tumor-promoting inflammation and immune suppression.

Notably, microbiota ablation in murine models has been shown to decrease the population of myeloid-derived suppressor cells (MDSCs), promote differentiation of M1 macrophages, and enhance CD8+ T cell activation. These immune-modulatory effects led to improved responses to ICIs, suggesting that targeting the microbiota could enhance the efficacy of immunotherapy in pancreatic cancer [32]. Lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria, has been implicated in PDAC progression. In mouse models, LPS activates TLR4 on immune cells, which in turn promotes tumor formation [51]. Additionally, microbiota profiling of PDAC patients revealed that 76% had intratumoral bacterial colonization. Among these, *Gammaproteobacteria* were capable of inactivating gemcitabine a first-line chemotherapeutic agent for PDAC through enzymatic degradation. This microbial-induced resistance could be reversed using the antibiotic ciprofloxacin [37].

Oral microbiota also appears to differ significantly between healthy individuals and PDAC patients. In particular, PDAC patients show increased levels of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis,* and reduced levels of phylum *Fusobacteria* and genus *Leptotrichia.* These distinct microbial signatures suggest the potential utility of oral microbiota as a non-invasive diagnostic biomarker for pancreatic cancer [52].

Importantly, a high abundance of *Fusobacterium* species in pancreatic tissue has been independently associated with poor prognosis, indicating its potential role as a prognostic marker [53]. Moreover, FMT from PDAC-bearing mice into germ-free mice significantly accelerated tumor progression, further underscoring the role of the microbiota in modulating tumor behavior [54]. Collectively, these findings suggest that the microbiota not only influences PDAC pathogenesis and progression but also affects treatment outcomes. Microbiota-targeted therapies including antibiotics, probiotics, or FMT may represent promising adjunct strategies for the management of pancreatic cancer.

Melanoma

Emerging evidence has firmly established a link between gut microbiota composition and the efficacy of ICIs in melanoma. In particular, responders to ICIs such as ipilimumab, nivolumab, and pembrolizumab have shown an enrichment of *Bacteroides caccae* and elevated levels of anacardic acid, suggesting a microbiota-metabolite axis that modulates immune response [55]. A prospective clinical study in patients with metastatic melanoma further demonstrated that individuals with *Ruminococcaceae* dominant microbiota exhibited significantly better clinical responses to ICIs compared to those with *Bacteroidaceae* dominated profiles [18]. These findings indicate that specific gut microbial signatures can influence treatment outcomes.

Two landmark clinical trials (NCT03353402 and NCT03341143) showed that FMT from ICI-responsive melanoma patients to non-responders led to significant microbiome shifts, increased tumor immune infiltration, and reversal of PD-1 blockade resistance [3,20]. These results highlight the potential of microbiota-based interventions as adjuvant immunotherapy.

Preclinical evidence further supports these clinical observations. In murine models housed in separate facilities with differing microbial environments, melanoma growth and responsiveness to anti-PD-L1 therapy varied dramatically. Mice from the Jackson Laboratory (JAX), which harbored beneficial gut microbes, showed significantly improved responses compared to those from Taconic Farms (TAC). Genomic analysis identified *Bifidobacterium* species as key modulators enhancing the anti-tumor effects of PD-L1 blockade [56]. Moreover, a study of 39 metastatic melanoma patients receiving ICIs found a strong correlation between gut microbiota composition and therapeutic response. Specifically, responders harbored higher levels of *Bacteroides thetaiotaomicron, Faecalibacterium prausnitzii* and *Holdemania filiformis* all known to be involved in anti-inflammatory and immune-modulating processes [19].

Importantly, fecal microbiota from responding melanoma patients, when transferred into germ-free or antibiotic-treated mice, was able to enhance the efficacy of ICIs, further demonstrating the causative role of the microbiota in immunotherapy response [55]. The therapeutic impact of transferring microbiota from PD-1 responders to non-responders is investigated in a clinical trial (NCT03341143), which supports the translational potential of this strategy by demonstrating that FMT and anti-PD-1 altered the gut microbiome and reprogrammed the tumour microenvironment to overcome anti-PD-1 resistance in a subset of PD-1 advanced melanoma [57]. Taken together, these studies underscore the critical role of gut microbiota in shaping anti-tumor immunity and suggest that FMT or other microbiota-targeted strategies could be integrated into melanoma treatment to improve immunotherapeutic outcomes.

Non-small cell lung cancer (NSCLC)

Despite ICIs being a cornerstone therapy for metastatic NSCLC, response rates remain below 25%. Gut microbiota alterations, including increased *Prevotella, Gemmiger* and *Roseburia,* have been associated with immune dysregulation in NSCLC patients. FMT, combined with ginseng polysaccharides and αPD-1 monoclonal antibodies, has been proposed as a strategy to enhance anti-PD-1 responses by modifying gut microbiota composition and restoring immune homeostasis [58].

Hepatocellular carcinoma (HCC)

The liver, connected to the intestine via the portal vein, is continuously exposed to gut-derived products such as lipopolysaccharide (LPS) and deoxycholic acid [59]. This anatomical and functional linkage, known as the gut–liver axis, plays a key role in liver pathophysiology. Intestinal dysbiosis is frequently observed in liver diseases, with microbial metabolites implicated in the progression of chronic liver disease and hepatocellular carcinoma [60].

Although it remains unclear whether dysbiosis is a cause or consequence of liver disease, mounting evidence suggests a causal role. For example, microbiota transplantation from mice with high-fat diet-induced liver injury led to aggravated liver damage in recipient mice [61]. Similarly, stools from patients with severe alcoholic hepatitis increased susceptibility to liver disease in animal models [62]. Additional studies have shown that microbial disruption in-

duced by antibiotics or chemicals like dextran sulfate sodium exacerbates hepatotoxicity in mice [63]. Colonization by *Clostridium* species, which modulate bile acid metabolism, has been linked to enhanced tumor growth in gram-positive bacteria-depleted mice [60].

Probiotics are being actively explored as a therapeutic option for liver disease and HCC. VSL#3, a probiotic formulation containing *Bifidobacterium*, *Lactobacillus*, and *Streptococcus thermophilus*, has been shown to reduce hospital stays in cirrhosis patients with hepatic encephalopathy [64]. A randomized multicenter trial involving 117 patients with alcoholic hepatitis revealed that probiotic supplementation with *Lactobacillus subtilis* and *Streptococcus faecium* significantly reduced serum LPS levels compared to placebo [65].

FMT is also showing promise in managing liver diseases. It has been demonstrated to attenuate high-fat diet-induced liver injury and improve lipid metabolism in mice [66]. FMT from resistant donor mice conferred protection against alcohol-induced liver damage [67]. In clinical settings, a pilot study reported improved survival and resolution of ascites in patients with severe alcoholic hepatitis following FMT [68]. In a landmark case reported by Philips et al., FMT improved appetite and bilirubin levels in a corticosteroid-nonresponsive patient with alcoholic hepatitis [68]. In patients with persistent HBeAg positivity, FMT successfully induced HBeAg clearance, suggesting a potential role in chronic hepatitis B treatment [69]. Furthermore, a Phase I trial confirmed the efficacy of FMT in restoring microbiota balance in cirrhosis patients after antibiotic use [70]. In both animal and human models, FMT has been shown to alleviate cognitive symptoms and hepatic necrosis associated with hepatic encephalopathy [71]. Clinical studies have documented improvements in serum ammonia levels, cognition, and quality of life post-FMT [72], underlining its therapeutic relevance.

Renal Cell Carcinoma (RCC)

Gut microbiota has also been implicated in RCC pathogenesis and response to ICIs. A phase II trial (NCT03013335) reported that recent antibiotic use significantly reduced response rates to nivolumab, correlating with *Clostridium hathewayi* dominance [3]. Preclinical studies further demonstrated that FMT from responders could compensate for resistance in RCC-bearing mice, with the transplantation of beneficial commensals (*A. muciniphila* and *Bacteroides salyersiae*) restoring ICI efficacy [22].

Conclusion

FMT enhances the efficacy of cancer immunotherapy by overcoming resistance to immune checkpoint ICIs through remodelling of the tumour microenvironment. In malignancies such as melanoma, NSCLC, RCC, and gastrointestinal cancers, FMT from ICI responders introduces beneficial microbial taxa most notably *Akkermansia muciniphila* and members of the *Ruminococcaceae* family. This microbial enrichment promotes the activation of $CD8^+$ T cells, dendritic cells, and IFN-γ production, while suppressing immunosuppressive cell populations, ultimately correlating with improved clinical outcomes. Moving forward, large-scale clinical trials and personalized FMT strategies potentially integrated with dietary interventions or probiotics are critical to optimize its therapeutic benefit. FMT is becoming a pioneering approach in precision oncology, utilizing the gut microbiome to improve immunotherapy effectiveness and transform cancer treatment strategies.

Bibliography

1. Z Wu., *et al.* "Global burden of cancer and associated risk factors in 204 countries and territories, 1980-2021: a systematic analysis for the GBD 2021". *Journal of Hematology and Oncology* 17 (2024).

2. GD Sepich-Poore., *et al.* "The microbiome and human cancer". *Science* 80.371 (2021).

3. Y Yang., *et al.* "Fecal microbiota transplantation: no longer cinderella in tumour immunotherapy". *EBioMedicine* 100 (2024): 7-9.

4. TM Halsey., *et al.* "Microbiome alteration via fecal microbiota transplantation is effective for refractory immune checkpoint inhibitor-induced colitis". *Science Translational Medicine* 15 (2024).

5. Z Shi., *et al.* "Emerging roles of the gut microbiota in cancer immunotherapy". *Frontiers in Immunology* 14 (2023): 1-13.

6. J Yang., *et al.* "High-Fat Diet Promotes Colorectal Tumorigenesis Through Modulating Gut Microbiota and Metabolites". *Gastroenterology* 162 (2022): 135-149.e2.

7. R He., *et al.* "Dysbiosis and extraintestinal cancers". *Journal of Experimental and Clinical Cancer Research* 44 (2025): 1-21.

8. A Schwan., *et al.* "Relapsing Clostridium Difficile Enterocolitis Cured By Rectal Infusion of Homologous Faeces". *Lancet* 322 (1983): 845.

9. R Singh., *et al.* "The potential beneficial role of faecal microbiota transplantation in diseases other than Clostridium difficile infection". *European Society of Clinical Microbiology and Infectious Diseases* 20 (2014): 1119-1125.

10. C Rajendran., *et al.* "Durable coexistence of donor and recipient strains after fecal microbiota transplantation". *Science* 80.352 (2016): 583-586.

11. L Fernández., *et al.* "Phage or foe: An insight into the impact of viral predation on microbial communities". *ISME Journal* 12 (2018): 1171-1179.

12. E Meader., *et al.* "Evaluation of bacteriophage therapy to control clostridium difficile and toxin production in an invitro human colon model system". *Anaerobe* 22 (2013): 25-30.

13. K Selle., *et al.* "Delivered CRISPR-Cas3 Antimicrobials RESULTS". *MBio* 11 (2020): 10-1128.

14. JP Zackular., *et al.* "The gut microbiome modulates colon tumorigenesis". *MBio* 4 (2013): 1-9.

15. DJ Lin., *et al.* "Analysis of influencing factors of washed microbiota transplantation in treating patients with metabolic syndrome". *Frontiers in Nutrition* 12 (2025).

16. N Med., *et al.* "HHS Public Access" 28 (2022): 315-324.

17. Y Ren., *et al.* "Comparative evaluation of various DNA extraction methods and analysis of DNA degradation levels in commercially marketed Chestnut rose juices and beverages". *BMC Biotechnology* 25 (2025): 9.

18. R James and PW. "Cancer, Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients". *Science* 80.359 (2018): 97-103.

19. V Matson., *et al.* "The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients". *Science* 80.359 (2019): 104-108.

20. EN Baruch., *et al.* "Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients". *Science* 5920 (2020): 1-16.

21. D Davar., *et al.* "Fecal microbiota transplant overcomes resistance to anti - PD-1 therapy in melanoma patients". *Science* 602 (2021): 595-602.

22. L Derosa., *et al.* "Gut Bacteria Composition Drives Primary Resistance to Cancer Immunotherapy in Renal Cell Carcinoma Patients". *European Urology* 78 (2020): 195-206.

23. MC Andrews., *et al.* "Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade". *Nature Medicine* 27 (2021): 1432-1441.

24. M Santoni., *et al.* "Re: Gut Microbiome Influences Efficacy of PD-1-based Immunotherapy Against Epithelial Tumors". *European Urology* 74 (2018): 521-522.

25. Christopher R John. "350 (2020).

26. A Grenda., *et al.* "Gut microbial predictors of first-line immunotherapy efficacy in advanced NSCLC patients". *Scientific Reports* 15 (2025): 6139.

27. C Zhang., *et al.* "Gut microbiota in colorectal cancer: a review of its influence on tumor immune surveillance and therapeutic response". *Frontiers in Oncology* 15 (2025): 1-15.

28. C Laface., *et al.* "HCC and Immunotherapy : The Potential Predictive Role of Gut Microbiota and Future Therapeutic Strategies". *Oncology* 5 (2025): 1-19.

29. JWC Chang., *et al.* "Gut microbiota and clinical response to immune checkpoint inhibitor therapy in patients with advanced cancer". *Biomedical Journal* 47 (2024): 100698.

30. I Zalila-kolsi., *et al.* "The Gut Microbiota and Colorectal Cancer : Understanding the Link and Exploring Therapeutic Interventions". *Biology (Basel)* 14 (2025).

31. H Jiang and Q Zhang. "Gut microbiota influences the efficiency of immune checkpoint inhibitors by modulating the immune system (Review)". *Oncology Letters* 27 (2024): 1-14.

32. J Sun., *et al.* "Gut microbiota as a new target for anticancer therapy: from mechanism to means of regulation". *Npj Biofilms Microbiomes* 11 (2025): 1-20.

33. X Zhao., *et al.* "Combination of thalidomide and Clostridium butyricum relieves chemotherapy-induced nausea and vomiting via gut microbiota and vagus nerve activity modulation". *Frontiers in Immunology* 14 (2023): 1-13.

34. E Dias-Jácome., *et al.* "Gastric microbiota and carcinogenesis: The role of non-Helicobacter pylori bacteria - A systematic review". *Revista Espanola De Enfermedades Digestivas* 108 (2016): 530-540.

35. YY Hsieh., *et al.* "Increased Abundance of Clostridium and Fusobacterium in Gastric Microbiota of Patients with Gastric Cancer in Taiwan". *Scientific Reports* 8 (2018): 1-11.

36. RM Ferreira., *et al.* "Gastric microbial community profiling reveals a dysbiotic cancer-associated microbiota". *Gut* 67 (2018): 226-236.

37. D Chen., *et al.* "Fecal microbiota transplantation in cancer management: Current status and perspectives". *International Journal of Cancer* 145 (2019): 2021-2031.

38. H Tsoi., *et al.* "Peptostreptococcus anaerobius Induces Intracellular Cholesterol Biosynthesis in Colon Cells to Induce Proliferation and Causes Dysplasia in Mice". *Gastroenterology* 152 (2017): 1419-1433.e5.

39. J Yu., *et al.* "Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer". *Gut* 66 (2017): 70-78.

40. ZF Chen., *et al.* "Probiotics Clostridium butyricum and Bacillus subtilis ameliorate intestinal tumorigenesis". *Future Microbiol* 10 (2015): 1433-1445.

41. E Jacouton., *et al.* "Probiotic strain Lactobacillus casei BL23 prevents colitis-associated colorectal cancer". *Frontiers in Immunology* 8 (2017): 1-10.

42. S Liang., *et al.* "Effect of probiotics on small intestinal bacterial overgrowth in patients with gastric and colorectal cancer". *Turkish Journal of Gastroenterology* 27 (2016): 227-232.

43. EK Plowman., *et al.* "This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record". *Please c, Laryngoscope* (2014): 2-31.

44. SH Wong., *et al.* "Gavage of Fecal Samples From Patients With Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-Free and Conventional Mice". *Gastroenterology* 153 (2017): 1621-1633.e6.

45. SP Rosshart., *et al.* "Wild Mouse Gut Microbiota Promotes Host Fitness and Improves Disease Resistance". *Cell* 176 (2017): 139-148.

46. MJ Hill., *et al.* "Gut Bacteria and Ætiology of Cancer of the Breast". *Lancet* 298 (1971): 472-473.

47. JJ Goedert., *et al.* "Postmenopausal breast cancer and oestrogen associations with the IgA-coated and IgA-noncoated faecal microbiota". *British Journal of Cancer* 118 (2018): 471-479.

48. J Yang., *et al.* "Gastrointestinal microbiome and breast cancer: correlations, mechanisms and potential clinical implications". *Breast Cancer* 24 (2017): 220-228.

49. H Maroof., *et al.* "Lactobacillus acidophilus could modulate the immune response against breast cancer in murine model". *Journal of Clinical Immunology* 32 (2012): 1353-1359.

50. A Argyraki., *et al.* "Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine, 2015 IEEE Summer Top. Meet. Ser. SUM 2015. 10 (2018): 1-13.

51. S Bullman., *et al.* "Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer". *Science* 358 (2018): 1443-1448.

52. X Fan., *et al.* "Abstract 4350: Human oral microbiome and prospective risk for pancreatic cancer: a population based, nested case control study". *Cancer Research* 76 (2016): 4350-4350.

53. K Mitsuhashi., *et al.* "Association of Fusobacterium species in pancreatic cancer tissues with molecular features and prognosis". *Oncotarget* 6 (2015): 7209-7220.

54. R MICHA. "The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression". *Physiology and Behavior* 176 (2017): 100-106.

55. V Gopalakrishnan., *et al.* "Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients". *Science* 80.11 (2017).

56. A Sivan., *et al.* "Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy". *Science* 80.350 (2015): 1084-1089.

57. D Davar., *et al.* "Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy". *Science* 80. 371 (2022): 595-602.

58. J Huang., *et al.* "Ginseng polysaccharides alter the gut microbiota and kynurenine/tryptophan ratio, potentiating the antitumour effect of antiprogrammed cell death 1/programmed cell death ligand 1 (anti-PD-1/PD-L1): immunotherapy". *Gut* 71 (2022): 734-745.

59. H Malhi and M Camilleri. "Modulating bile acid pathways and TGR5 receptors for treating liver and GI diseases". *Current Opinion in Pharmacology* 37 (2017): 80-86.

60. C Ma., *et al.* "Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells". *Science* 360 (2019): 1-23.

61. S De Minicis., *et al.* "Dysbiosis contributes to fibrogenesis in the course of chronic liver injury in mice". *Hepatology* 59 (2014): 1738-1749.

62. M Llopis., *et al.* "Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease". *Gut* 65 (2016): 830-839.

63. C Qin., *et al.* "Microbiota transplantation reveals beneficial impact of berberine on hepatotoxicity by improving gut homeostasis". *Science China Life Sciences* 61 (2018): 1537-1544.

64. RK Dhiman., *et al.* "Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: A randomized, controlled trial". *Gastroenterology* 147 (2014): 1327-1337.e3.

65. SH Han., *et al.* "Effects of probiotics (cultured Lactobacillus subtilis/ Streptococcus faecium): in the treatment of alcoholic hepatitis: Randomized-controlled multicenter study". *European Journal of Gastroenterology and Hepatology* 27 (2015): 1300-1306.

66. D Zhou., *et al.* "Total fecal microbiota transplantation alleviates high-fat diet-induced steatohepatitis in mice via beneficial regulation of gut microbiota". *Scientific Reports* 7 (2017): 1-11.

67. G Ferrere., *et al.* "Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice". *Journal of Hepatology* 66 (2017): 806-815.

68. CA Philips., *et al.* "Healthy Donor Fecal Microbiota Transplantation in Steroid-Ineligible Severe Alcoholic Hepatitis: A Pilot Study". *Clinical Gastroenterology and Hepatology* 15 (2017): 600-602.

69. YD Ren., *et al.* "Fecal microbiota transplantation induces hepatitis B virus e-antigen (HBeAg): clearance in patients with positive HBeAg after long-term antiviral therapy". *Hepatology* 65 (2017): 1765-1768.

70. M Klingenberg., *et al.* "Ernst, The lncRNA CASC9 and RNA binding protein HNRNPL form a complex and co-regulate genes linked to AKT signaling". *Hepatology* 777 (2017): 1-36.

71. WW Wang., *et al.* "Fecal microbiota transplantation prevents hepatic encephalopathy in rats with carbon tetrachloride-induced acute hepatic dysfunction". *World Journal of Gastroenterology* 23 (2017): 6983-6994.

72. JS Bajaj., *et al.* "Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial". *Hepatology* 66 (2017): 1727-1738.