Cancer Screening and Prevention **2026** | Epub
DOI: 10.14218/CSP.2026.00033

Review Article

Fecal Microbiota Transplantation as a Therapeutic Adjuvant in Gastrointestinal Cancers: Potential Mechanisms, Therapeutic Applications, and a Functional Donor Screening Strategy

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Received: March 16, 2026 | **Revised:** April 15, 2026 | **Accepted:** May 22, 2026 | **Published online:** June 26, 2026

Abstract

Gastrointestinal (GI) cancers account for approximately one-third of annual cancer-related deaths globally, while outcomes remain poor despite advances in surgery, chemotherapy, radiotherapy, and immunotherapy. Given the challenges of persistent resistance and treatment-related toxicities in current therapies, the pivotal roles of the gut microbiota and fecal microbiota transplantation (FMT) in GI cancer therapy are increasingly recognized. This review aims to explore the potential and mechanisms of FMT as a therapeutic adjuvant in the treatment of GI cancers. FMT may enhance antitumor treatment efficacy and reduce treatment-related toxicity through multiple mechanisms, including enhancing antigen presentation, reshaping the tumor microenvironment, and preserving intestinal barrier function. Preliminary clinical evidence indicates that FMT combined with immune checkpoint inhibitors, chemotherapy, or radiotherapy can improve treatment response rates in some trials and may reverse resistance and alleviate associated intestinal toxicities in selected cases. However, clinical application is hindered by donor microbiota functional heterogeneity, substantial interindividual variability in engraftment, and the absence of validated predictive models. To advance FMT toward precision intervention, we propose a functional screening framework: the Healthy Donor-derived Microbiota Xenograft model as a preclinical functional screening platform and its subsequent clinical application, Xenograft-screened FMT, which links donor-level functional validation with personalized microbiota delivery. By integrating mechanistic insights, emerging preclinical and clinical evidence, and a functional screening framework, this review contributes to advancing FMT from an empirical intervention toward a precision adjuvant strategy and offers insights into future clinical investigation of FMT as a therapeutic approach in GI oncology.

Introduction

Gastrointestinal (GI) cancers are among the most prevalent and lethal malignancies worldwide, accounting for approximately one-third of annual cancer-related deaths.[1] Despite continuous advances in surgery, chemotherapy, radiotherapy, and targeted therapy, the overall prognosis for GI malignancies remains modest, with clinical benefit largely confined to molecularly defined subgroups such as MSI-H/dMMR colorectal cancer (CRC) and HER2-positive gastric cancer.[2,3] Acquired resistance and treatment-related toxicities remain persistent, unmet clinical challenges across treatment modalities. In recent years, cancer immunotherapy, most notably immune checkpoint inhibitors (ICIs), has dramatically transformed the oncological treatment landscape by blocking regulatory pathways that suppress T-cell function, thereby effectively unleashing the immune system and delivering considerable clinical benefit across a wide variety of cancers.[4] However, a substantial proportion of patients with GI malignancies develop primary, adaptive, or acquired resistance to ICI monotherapy, resulting in poor clinical responses,[5] and the mechanisms underlying this resistance are multifactorial and

Keywords: Fecal microbiota transplantation; Gastrointestinal cancers; Gut microbiota; Antitumor; Therapy; Donor selection.
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How to cite this article: Wang Y, Li Z, Kong X. Fecal Microbiota Transplantation as a Therapeutic Adjuvant in Gastrointestinal Cancers: Potential Mechanisms, Therapeutic Applications, and a Functional Donor Screening Strategy. *Cancer Screen Prev*. Published online: Jun 26, 2026. DOI: https://doi.org/10.14218/CSP.2026.00033.

incompletely understood. Improving therapeutic efficacy while minimizing treatment-related toxicity through rational combinatorial strategies therefore represents a critical unmet need in GI oncology.

As research in microbiome science advances, the gut microbiota has been recognized as playing a pivotal role in physiological and pathological processes, including metabolism, inflammation, and immune regulation. Notably, gut dysbiosis is closely associated with the initiation, progression, and prognosis of GI cancers, particularly CRC, although the underlying mechanisms have not been fully elucidated.[6] Beyond these oncological roles, dysbiosis can also precipitate or exacerbate treatment-related toxicities, including chemotherapy-induced diarrhea and radiation enteritis (RE), whether pre-existing or arising during treatment.[7,8] Moreover, by modulating systemic and intratumoral immune responses, dysbiosis further influences the efficacy of immunotherapy and correlates with adverse clinical outcomes.[9] Collectively, these considerations position the gut microbiome as a compelling therapeutic target with the potential to simultaneously enhance antitumor efficacy and reduce treatment-related toxicity in GI cancers.

Fecal microbiota transplantation (FMT) is an intervention that involves the transfer of fecal material from healthy donors into a recipient's gut, with the aim of reconstructing the recipient's gut microbial ecosystem. FMT has demonstrated remarkable success in treating recurrent *Clostridioides difficile* infection, underscoring its capacity for functional microbial restoration.[10] However, the translation of FMT to GI cancers remains in its early stages. Preliminary studies suggest that FMT has the potential to enhance antigen presentation, reshape the tumor microenvironment (TME), and preserve intestinal barrier function, providing a mechanistic rationale for its application as a therapeutic adjuvant to ICIs, chemotherapy, and radiotherapy.[11,12] Nevertheless, the precise sensitizing efficacy of FMT in GI cancers remains to be established in large-scale controlled trials, and its translation is hindered by donor microbiota functional heterogeneity, unpredictable engraftment, and the absence of validated predictive models.

This review examines the sensitizing potential of FMT in GI oncology. We delineate the putative mechanisms by which FMT may enhance antigen presentation, modulate the TME, and preserve intestinal barrier function, and critically evaluate clinical evidence and translational challenges associated with combining FMT with ICIs, chemotherapy, and radiotherapy. Additionally, we examine the formidable challenges impeding the evolution of FMT from an empirical intervention to a precision microbial therapy. To advance FMT toward precision intervention, we propose a functional screening framework: the Healthy Donor-derived Microbiota Xenograft (HDMX) model as a preclinical functional screening platform, and its subsequent clinical application, the Xenograft-screened FMT (XenoFMT), linking donor-level functional validation with personalized microbiota delivery. By integrating mechanistic insights, emerging preclinical and clinical evidence, and a functional screening framework, this review contributes to advancing FMT from an empirical intervention toward a precision adjuvant strategy and offers insights into future clinical investigation of FMT as a therapeutic strategy in GI oncology.

Potential mechanisms of FMT in antitumor immunity

FMT, as a potential strategy to sensitize antitumor therapy, is predicated on reshaping the patient's gut microbiota, thereby modulating host immune function and antitumor immune responses. Currently, investigations in this domain remain in the early phases, and the precise mechanisms underlying microbiota–host crosstalk have yet to be fully elucidated. Emerging preclinical evidence suggests that transplanted microbiota may exert therapeutic effects via multiple interrelated mechanisms (Fig. 1), as discussed in the subsections below.

Enhance antigen presentation

Efficient antigen presentation is a critical initiating step in adaptive antitumor immunity, with dendritic cells (DCs) serving as the principal professional antigen-presenting cells (APCs) orchestrating the induction of T-cell responses. DCs primarily derive from hematopoietic progenitors in the bone marrow. They differentiate through intermediates such as macrophage–DC progenitors and common DC progenitors to generate conventional DC (cDC) precursors that circulate via the bloodstream and colonize peripheral tissues.[13] Upon encountering antigenic and danger signals, DCs mature and migrate via lymphatics to draining lymph nodes, where they present processed peptide–major histocompatibility complex (MHC) complexes to T-cell receptors and deliver secondary signals through co-stimulatory molecules such as CD80 and CD86 to drive full T-cell activation and differentiation.[14]

Gut commensal bacteria harbor diverse microbe-associated molecular patterns that are recognized by pattern recognition receptors expressed on the surface of or within host immune cells.[15] Within the intestinal mucosa, such recognition can orchestrate DC activation and maturation, thereby initiating a cascade of immunoregulatory events.[16] Preclinical studies have identified a series of gut commensal bacteria capable of modulating DC-dependent antitumor immunity. Tanoue *et al*.[17] found in mice that colonization with 11 human gut bacterial strains increases colonic IFN-γ^+ $CD8^+$ T cells in germ-free mice, a process dependent on $CD103^+$ DCs and MHC class Ia molecules. In syngeneic tumor models, this bacterial consortium, combined with ICIs, attenuates tumor growth. Vétizou *et al*.[18] showed that *Bacteroides fragilis* gavage restored the antitumor effects of CTLA-4 blockade in microbiota-depleted mice, potentially via lamina propria $CD11b^+$ DCs that process its polysaccharides to drive Th1 responses and promote intratumoral DC maturation. FMT from a subset of ipilimumab-treated patients with metastatic melanoma and a Bacteroides-associated microbiota conferred similar responsiveness in germ-free mice.[18] Building on these findings, Lin *et al*.[19] isolated a strain, *Hominenteromicrobium* sp. YB328, from the feces of patients who responded to programmed cell death protein 1 (PD-1) blockade. In mouse models, YB328 enhanced anti–PD-1 efficacy by promoting the differentiation and migration of $CD103^+CD11b^-$ cDCs from the gut to the tumor via TLR7/9–MyD88 signaling, upregulating IRF8 through S6K/STAT3 phosphorylation. DCs conditioned by YB328 lowered the activation threshold for tumor-specific $CD8^+$ T cells and induced PD-1 expression, potentially enhancing ICI responses.[19] The interplay between gut microbiota and ICIs may be bidirectional. In a preclinical melanoma model, Choi *et al*.[20] showed that ICI

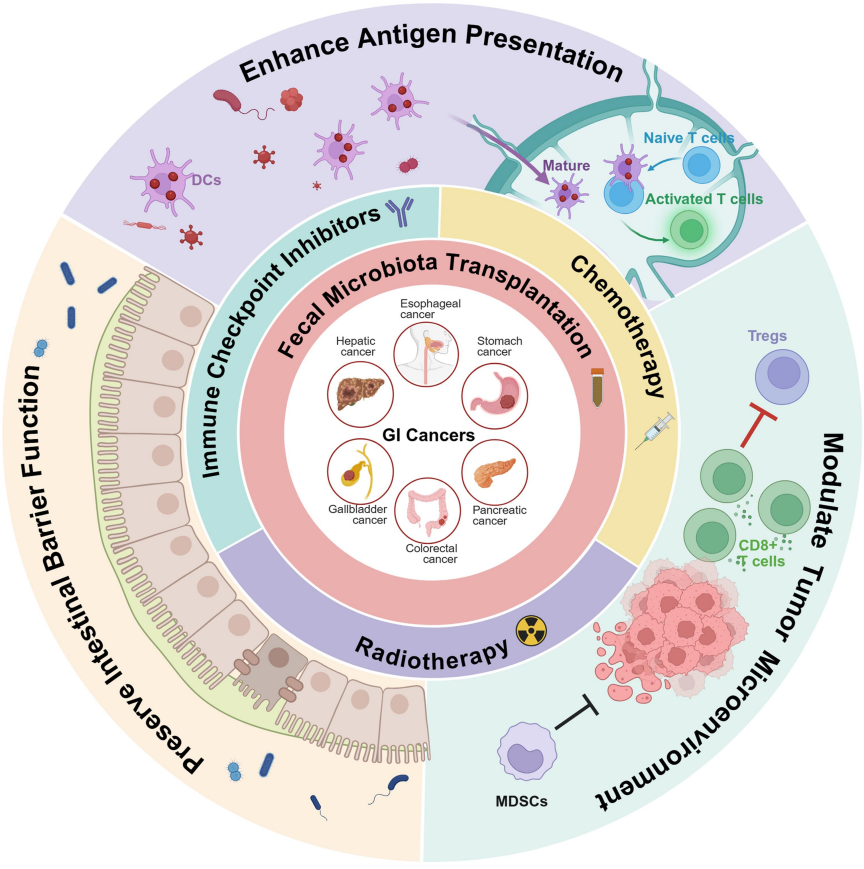

Fig. 1. Potential mechanisms underlying fecal microbiota transplantation as a therapeutic adjuvant to antitumor therapy. Fecal microbiota transplantation enhances therapeutic efficacy through three possible pathways: (i) enhancing antigen presentation, (ii) modulating the tumor microenvironment, and (iii) preserving intestinal barrier function. Created with BioRender.com. DC, dendritic cell; GI, gastrointestinal; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell.

therapy induces DC activation and CCR7-dependent migration, enabling specific gut bacteria to translocate to lymphoid organs and tumors, where these bacteria further activate DCs and prime antitumor $CD8^+$ T cells. Additional commensals implicated in DC-mediated immune modulation include *Akkermansia muciniphila*,[21] *Bifidobacterium*,[22-24] *Lactobacillus intestinalis*,[25] and nontoxigenic *Bacteroides fragilis*.[26] Baruch *et al*.[27] also found in a clinical trial in refractory melanoma patients that FMT combined with anti–PD-1 enhanced gut mucosal $CD68^+$ APC infiltration and MHC class I expression, with parallel enrichment of MHC class II and DC differentiation genes in the TME. However, commensal-driven DC activation does not uniformly support antitumor immunity. Hou *et al*.[28] showed that *Megasphaera elsdenii*, enriched in IBD and CRC, can activate colonic DCs via TLR4/NF-κB/IRF4, driving pathogenic Th1/Th17 responses and exacerbating colitis-associated tumorigenesis.

Molecular mimicry represents a second candidate mechanism, whereby commensal bacteria carried by FMT donors may prime T cells against specific microbial antigens that cross-react with homologous tumor epitopes, enabling immune-mediated tumor recognition.[29] Boesch *et al*.[30] also propose that increased microbial diversity following FMT is potentially associated with a higher probability of tumor neoantigen mimicry. In murine models, a TMP1 epitope derived from the prophage tail of intestinal *Enterococcus hirae* primes H-$2K^b$-restricted $CD8^+$ T cells that cross-react with a homologous epitope of the endogenous tumor antigen PSMB4. Crucially, targeted mutation of either the bacterial epitope or its tumor homolog abrogates efficacy, as confirmed by genetic manipulation studies in mice.[31] *In vitro* evidence shows that a SIN3A-reactive $CD4^+$ T-cell clone (TCC88), isolated from tumor-infiltrating lymphocytes of a single patient with glioblastoma, cross-recognizes dozens of peptide sequences derived from both commensal and pathogenic gut microbiota. These microbial peptides elicited TCC88 activation, while HGM3 was further shown to stimulate TCC88-mediated cytotoxicity against autologous glioblastoma cells *in vitro*.[32] Beyond cross-reactivity based on sequence similarity, segmented filamentous bacteria colonization in preclinical models has been shown to imprint gut-primed TH17 cells that migrate to tumors engineered to express the cognate microbial antigen, transdifferentiate into TH1-like effectors producing IFN-γ and TNF, and synergize with anti–PD-1 therapy to enhance $CD8^+$ T-cell-mediated tumor control.[33] However, molecular mimicry may also promote the occurrence of immune-related adverse events

(irAEs) through cross-reactivity between microbial antigens and autoantigens. Correlative evidence has identified homologous sequences shared between gut microbial epitopes and human autoantigens in some patients with irAEs.[34] This mechanism suggests that microbiota interventions may not only sensitize the immune response but also carry a risk of toxicity.

Specialized microbial metabolites can function as signaling molecules regulating DC function. FMT may reshape the microbial metabolite landscape, thereby providing a possible mechanism for regulating DC differentiation, maturation, and antigen-presenting capacity. Moreover, the immunomodulatory effects of these metabolites are tightly governed by the cellular and tissue microenvironment, rendering modulation of DC antigen presentation highly context-dependent.[35] Evidence from mouse models and *in vitro* cell culture experiments suggests that under homeostatic conditions, certain metabolites produced by gut commensals play a role in actively maintaining immune tolerance rather than merely eliciting immune responses. For instance, short-chain fatty acids (SCFAs) at physiological concentrations regulate the differentiation, maturation, and function of DCs and directly promote the differentiation of regulatory T (Treg) cells.[36-39] Similarly, iso-deoxycholic acid antagonizes the farnesoid X receptor in DCs, thereby suppressing the expression of genes involved in antigen processing and presentation. This tolerogenic reprogramming promotes the differentiation of RORγt$^+$ Tregs.[40] Collectively, these studies indicate that microbial metabolites of healthy individuals act in concert to limit DC activation, lowering the intrinsic activation potential of cDCs and imposing a broad tolerogenic effect on the adaptive immune system.[14] Under tumor- or inflammation-associated microecological perturbations, alterations in the concentration of specific metabolites can reprogram DC metabolism and epigenetic states. Recent work demonstrates that low-dose radiation-mediated remodeling of the intestinal microenvironment reduces immunosuppressive metabolites such as lactic acid and certain butyrate derivatives while increasing immunostimulatory secondary bile acids and cholesterol, shifting the milieu from tolerogenic to immunostimulatory. These metabolites potentiate the antigen-presenting function of DCs and promote CCR7+ DC trafficking to tumor-draining lymph nodes.[41] In a murine CRC model, the metabolite indole-3-lactic acid derived from the probiotic *Lactobacillus plantarum* L168 was found to enhance DC IL-12 production by increasing histone H3K27 acetylation at the Il12a enhancer, thereby potentiating CD8$^+$ T-cell-mediated antitumor immunity.[42] As demonstrated in preclinical studies, butyrate represents an example of how treatment context determines a metabolite's net immunological outcome through its context-dependent effects on DC-mediated antigen presentation. Butyrate attenuates inflammation under steady-state conditions by suppressing myeloid APC maturation and co-stimulatory molecule expression.[43] Under radiotherapy conditions, butyrate suppresses antitumor immunity by downregulating CD86 on DCs and impairing antigen cross-presentation *in vitro*, while in mice, vancomycin depletion of butyrate-producing bacteria enhanced CD8$^+$ T-cell-dependent, IFN-γ-mediated antitumor immunity.[44] Yang *et al*.[45] also showed that butyrate blocks TBK1 and IRF3 phosphorylation in DCs, dampening STING-dependent type I IFN induction. Notably, in the context of oncolytic virotherapy, butyrate may activate cGAS–STING, potentially upregulating MHC-I and enhancing CD8$^+$ T-cell-dependent antitumor immunity.[46]

Modulate the TME

As a critical determinant of tumor progression and therapeutic response, the TME represents a dynamic network comprising malignant cells, heterogeneous non-malignant cells (including immune cells, cancer-associated fibroblasts, and endothelial cells), the extracellular matrix, and an array of soluble factors. The immunosuppressive TME constitutes a major barrier to effective antitumor immunity and therapeutic response, characterized by functional exhaustion or physical exclusion of effector T cells and pronounced infiltration of immunosuppressive cell populations.[47] FMT has the potential to modulate the TME via the gut microbiota, thereby enhancing antitumor immune responses.[48]

Modulating the composition and function of tumor-infiltrating immune cells is a potential mechanism underlying the therapeutic effects of FMT. A recent preclinical single-cell transcriptomic study provides mechanistic clues that anti-PD-1 therapy in mice with an intact gut microbiota may not only increase the proportions of tumor-infiltrating CD8$^+$, CD4$^+$, and γδ T cells but also drive reprogramming of tumor-associated macrophages (TAMs), shifting the balance from immunosuppressive SPP1$^+$ TAMs toward immunostimulatory, antigen-presenting CD74$^+$ TAMs. Supporting this, reanalysis of a clinical FMT trial suggested similar TAM reprogramming trends, though data remain preliminary.[49] Similarly, the early foundational work by Routy *et al*.[50] showed that oral supplementation of *Akkermansia muciniphila* in mice receiving FMT from anti-PD-1 non-responders restored efficacy, potentially by recruiting CCR9$^+$ CXCR3$^+$CD4$^+$ T cells and increasing the intratumoral CD4$^+$/Foxp3$^+$ ratio in an IL-12-dependent manner. Beyond direct intratumoral effects, preclinical work in a murine model of colitis-associated CRC indicates that FMT may also remodel the TME indirectly through systemic immune modulation. FMT from healthy donors reduced splenic Th1 and Th17 cells and intratumoral inflammation, while also reversing epithelial-mesenchymal transition and inhibiting Wnt/β-catenin signaling.[51] These preclinical observations are partially corroborated by emerging clinical evidence. A systematic review indicates that cancer patients receiving FMT combined with immunotherapy exhibited increased intratumoral CD8$^+$ T-cell infiltration in responders, alongside reductions in Tregs and myeloid-derived suppressor cells (MDSCs) in some studies.[52] Consistent with these findings, Kim et al. reported that recipient R7, a patient with hepatocellular carcinoma (HCC) who achieved a partial response after FMT combined with anti-PD-1 therapy, exhibited not only elevated intratumoral CD8+ T cells and persistently low levels of Tregs but also a marked increase in tumor-infiltrating MHC-II+ M1 macrophages.[53] In addition, the gut microbiota has been shown to modulate the local expression of immune checkpoint molecules,[54] and some evidence suggests that FMT may influence this process,[55] though consistent conclusions have yet to be drawn across studies. Beyond bacterial communities, the gut mycobiome may also shape the TME. Shiao *et al*.[56] demonstrated in murine tumor models that intestinal fungi actively drive an immunosuppressive TME through Dectin-1-mediated β-glucan sensing, promoting CD206$^+$ suppressive macrophage polarization

and PD-1 upregulation on $CD8^+$ T cells. However, few clinical FMT studies to date have assessed mycobiome engraftment in recipients, leaving the fungal dimension of FMT-mediated TME modulation largely uncharted and warranting dedicated investigation in future studies.

Microbial metabolites introduced by FMT may also serve as mediators of TME remodeling. SCFAs, particularly butyrate, introduced by FMT or specific bacterial strains, are potential metabolic mediators. In a murine gastric cancer model, FMT from healthy donors was associated with elevated butyrate and enhanced $CD8^+$ T-cell immunity via GPR109A/HOPX.[57] In murine CRC, *Roseburia intestinalis*-derived butyrate enhanced $CD8^+$ T-cell infiltration and cytotoxicity, possibly through TLR5/NF-κB activation, while simultaneously reducing MDSCs and improving anti-PD-1 efficacy.[58] Acetate, another SCFA restored by FMT or by *Lactobacillus reuteri* supplementation, suppressed IL-17A production in group 3 innate lymphoid cells via HDAC inhibition and Sox13 acetylation, thereby reducing immunosuppression and fibrosis while enhancing cytotoxic T lymphocyte (CTL) infiltration, and synergized with anti-PD-1 therapy in HCC mouse models.[59] Furthermore, the gut microbiota-derived secondary bile acid metabolite 3-oxoLCA has been shown to inhibit differentiation of pro-inflammatory TH17 cells, while isoalloLCA promotes differentiation of Tregs by inducing mitochondrial reactive oxygen species production.[60,61] Whether FMT specifically alters the intratumoral bile acid landscape in human tumors remains an open question. Purine metabolites may also participate in TME remodeling. In mouse tumor models, *Bifidobacterium pseudolongum*-derived inosine was shown to translocate upon ICI-induced gut barrier impairment and promote Th1/CTL antitumor immunity through T-cell A_2A receptor signaling, but this effect was conditional on sufficient co-stimulation.[62] An emerging mechanism involves gut microbiota-dependent biotransformation of dietary compounds into immunologically active metabolites. The dietary flavonoid quercetin can be metabolized by gut microbiota into 3,4-dihydroxyphenylacetic acid (DOPAC), which in preclinical models enhances $CD8^+$ T-cell antitumor activity through KEAP1–NRF2-mediated mitophagy.[63] Clinically, *Eubacterium ramulus*, a bacterium capable of producing DOPAC, was found to be significantly enriched in melanoma patients who responded to anti-PD-1 immunotherapy combined with FMT,[64] though this association remains observational. However, not all microbiota-derived metabolites exert antitumor effects. Tumor-promoting metabolites, including *Fusobacterium nucleatum*-derived formate,[65] *Peptostreptococcus anaerobius*-derived trans-3-indoleacrylic acid,[66] and deoxycholic acid,[67,68] have also been documented in preclinical models, highlighting the need for careful donor selection in FMT.

Preserve intestinal barrier function

The intestinal wall constitutes a sophisticated system comprising the mucosa, submucosa, muscularis, and serosa or adventitia. It is composed of a diverse array of cell types, including epithelial cells, immune cells, enteric neurons, and smooth muscle cells, and coordinates a spectrum of vital functions, including digestion, absorption, secretion, motility, barrier maintenance, and immune defense. Alterations in the composition or metabolism of the gut microbiota can result in changes to intestinal permeability and barrier function. Preclinical evidence suggests that intestinal dysbiosis can activate pro-inflammatory signaling pathways,[69,70] perturb antimicrobial peptide expression,[71] and compromise tight junction integrity.[72] These disruptions collectively impair epithelial barrier integrity and increase mucosal permeability. This barrier dysfunction permits the translocation of bacteria and microbial products into the systemic circulation, triggering local and systemic inflammatory responses that have been implicated in diverse pathologies, including colorectal carcinogenesis and tumor progression.[73] In turn, preclinical evidence suggests that established malignancies can reciprocally exacerbate bacterial translocation through pro-inflammatory cytokine secretion and disruption of intestinal vascular barrier integrity.[74,75] In piglet models, FMT was associated with upregulated tight junction protein expression, increased mucin secretion, and attenuated mucosal inflammatory responses.[76] Preclinical studies have begun to elucidate the potential mechanisms by which FMT may ameliorate chemotherapy-induced intestinal injury. In CRC mouse models, FMT administration was accompanied by restored goblet cell numbers and ZO-1 expression, suppressed claudin-2 upregulation, and attenuated TLR–MyD88–NF-κB signaling pathway activity following FOLFOX-induced intestinal injury.[77] Complementarily, in cisplatin-treated murine models, FMT promoted Muc3 mucin secretion, epithelial repair, reduced bacterial translocation, and attenuated systemic inflammation. However, *Ruminococcus gnavus*, which was selectively depleted after cisplatin treatment, failed to reproduce the full protective effects of intact FMT when supplemented alone.[78] FMT may also play a role in preserving intestinal barrier function after radiotherapy. In murine models of acute radiation enteropathy, sex-matched FMT has been shown to protect against radiation-induced barrier damage, potentially by increasing goblet cell numbers, thickening the mucus layer, and upregulating Muc2 and Tff3.[79] Tu *et al*.[80] further observed that FMT-associated mitigation of RE coincided with restoration of *Lachnospiraceae* and tryptophan metabolites such as indole-3-acetaldehyde, along with upregulation of ZO-1, attenuation of Muc2 suppression, and decreased Granzyme B.

Gut microbial metabolites may also influence intestinal barrier function. Preclinical findings suggest that certain metabolites may support intestinal barrier integrity by reinforcing tight junction assembly,[81-84] fortifying the chemical barrier through mucus layer maintenance and mucosal repair and attenuating inflammation-driven epithelial damage.[85-87] *In vitro* studies by Feng *et al*.[86] also suggest that SCFAs may protect the intestinal barrier from lipopolysaccharide-induced disruption by inhibiting activation of the NLRP3 inflammasome and autophagy. Guo *et al*.[88] used a multi-omics approach to show that SCFAs, particularly propionate, have potential to enhance radiation tolerance by reducing DNA damage and suppressing reactive oxygen species (ROS). In contrast, tryptophan metabolites such as 1H-indole-3-carboxaldehyde and kynurenic acid may serve as long-lasting radioprotectants, though these remain preclinical findings.[88] Ma *et al*.[89] also concluded that SCFA-producing bacteria and their metabolites act as overall protective factors in radiotherapy. Dong *et al*.[90] recently found that *Roseburia intestinalis* and its metabolite butyrate promote radiation-induced autophagic cell death in CRC cells, significantly enhancing radiotherapy efficacy.

Furthermore, the same study confirmed in a mouse model that this strain alleviates RE.[90] Butyrate has also been characterized as a positive allosteric modulator of the 5-HT transporter, reducing the local concentration of 5-HT, which has emetic properties, potentially mitigating GI toxicity during radiotherapy.[91] However, the MARS study observed elevated SCFA-producing bacteria such as *Roseburia* in radiation enteropathy, alongside decreased SCFA pathway capacity and depleted homeostatic cytokines. This may reflect bacterial shedding from a damaged epithelium rather than protective expansion, indicating a disrupted host–microbe equilibrium.[92] Tryptophan-derived metabolites have also been implicated in intestinal barrier maintenance. *In vitro* studies suggest that indole-3-propionic acid (IPA) may activate the pregnane X receptor (PXR) to suppress TLR4 signaling and upregulate tight junction proteins.[93] Preclinical findings further indicate that oral IPA administration may attenuate radiation-induced intestinal permeability and tissue damage in mice, possibly through a PXR/ACBP-dependent pathway.[94] However, this protective effect is not universal, as metabolites such as secondary bile acids may disrupt the chemical barrier.[95] Significant heterogeneity exists in the effects of different metabolites, which may depend on metabolite type, concentration, receptor affinity, and host pathological status.

In summary, FMT may enhance antitumor therapeutic efficacy and alleviate treatment-related toxicity through at least three interconnected mechanisms: augmenting antigen presentation, reshaping the TME, and preserving intestinal barrier function. The effects of individual commensal strains and metabolites across each of these axes are heterogeneous or even immunosuppressive and are profoundly context-dependent. Specific microbial configurations may paradoxically sustain immune tolerance or precipitate irAEs. Rigorous functional donor screening is therefore essential prior to clinical application of FMT. Direct mechanistic evidence linking FMT-driven microbiota reconstitution to antitumor immune responses in humans across each of these pathways remains to be established.

FMT combined with basic therapies to enhance treatment sensitivity

FMT combined with ICIs

While the application of ICIs has revolutionized the pharmacological treatment paradigm for GI cancers, their efficacy is universally challenged by primary, adaptive, and acquired resistance. This resistance manifests as a complex, multifactorial, and multilayered network. At the intrinsic tumor-cell level, tumors directly evade T-cell recognition through mechanisms such as impaired antigen presentation and upregulation of multiple immune checkpoints.[96] Concurrently, mutations and persistent activation of diverse oncogenic signaling pathways reinforce the immune evasion capacity of tumor cells. Within the TME, at the cellular level, extensive infiltration of immunosuppressive cells, including Tregs, M2 macrophages, and suppressive neutrophils, forms a robust inhibitory network.[97] At the functional level, the TME undergoes profound metabolic reprogramming, characterized by sustained hypoxia, lactate accumulation, and depletion of critical nutrients such as glucose, directly impairing T-cell function and inducing exhaustion.[98] Simultaneously, networks of inhibitory cytokines such as TGF-β further undermine antitumor immunity. Critically, these mechanisms do not operate in isolation but are embedded within and modulated by broader host systemic factors. Among these, gut microbiota dysbiosis plays a particularly important role, driving systemic immune dysfunction. Beyond the microbiome, diet, environmental exposures, and lifestyle collectively constitute the macro-level context that ultimately shapes the immunotherapy response.[99]

FMT may reverse ICI resistance by reshaping the gut microbiota, thereby modulating immune responses and restoring therapeutic efficacy. Preclinical studies indicate that specific gut microbial communities or FMT from ICI responders can induce tumor regression, potentiate T-cell responses, and enhance the antitumor efficacy of ICIs. In preclinical CRC models, FMT from microsatellite-stable (MSS) CRC patients with high *Fusobacterium nucleatum* (Fn) abundance or from anti-PD-1-responsive mice conferred sensitivity to anti-PD-1 therapy, whereas FMT from low-Fn or non-responsive donors proved ineffective.[100,101] Furthermore, oral administration of *Bifidobacterium catenulatum* potentiated anti-PD-1 efficacy; this effect was transferable by FMT and accompanied by enhanced intratumoral $CD8^+$ T-cell infiltration.[102] Currently, numerous clinical studies have evaluated FMT combined with ICI therapy across different cancer types, though efficacy data from large-scale randomized trials remain lacking.[103] Melanoma has been one of the earliest cancer types investigated in FMT–ICI combination research, with early studies showing preliminary feasibility and safety of FMT in overcoming ICI resistance. Two single-arm trials provided preliminary clinical signals suggesting that responder-derived FMT combined with anti-PD-1 therapy resensitized a subset of refractory melanoma patients to immunotherapy.[27,104] Routy *et al*.[64] further reported in a phase I trial that FMT from healthy donors combined with anti-PD-1 therapy achieved an objective response rate (ORR) of 65% (13 of 20) in previously untreated patients with advanced melanoma, with an unexpected median overall survival (mOS) of 52.8 months compared with RCTs and real-world data (30.0–39.6 months mOS).[105] Although these findings require validation in larger controlled trials and safety considerations warrant ongoing attention, they offer valuable exploratory insights that may inform future investigation of FMT in GI tumors, where clinical evidence remains emerging.

FMT combined with ICI therapy is increasingly being investigated in GI tumors, with preliminary clinical signals suggesting potential value, particularly in ICI-resistant patients. While the current evidence is largely derived from early-phase trials and small-cohort studies, clinical signals across diverse GI cancer subtypes, such as colorectal, gastric, esophageal, and hepatocellular carcinoma, provide preliminary support for the therapeutic potential of FMT in combination with anti-PD-1 therapy with or without anti-angiogenic agents. These studies report disease control rates (DCRs) generally ranging from 40% to 95%, with some patients achieving marked tumor regression or durable long-term disease stability. In a study by Kim *et al*.,[53] 13 patients with metastatic GI cancers received responder-derived FMT combined with continued nivolumab treatment, with an ORR of 7.7% and a DCR of 46.2%. Four cases of ESCC and one of HCC achieved stable disease, while one HCC patient achieved a partial response (PR) with a maximum tumor reduction of 47.7%

and a progression-free survival (PFS) of 8.7 months.[53] In a phase I trial reported by Zhang *et al*.,[106] healthy-donor FMT combined with nivolumab was evaluated in patients with anti-PD-1-refractory MSS GI cancer (n = 10). The study demonstrated an ORR of 20% overall and a DCR of 40%, while the ORR was 25% and the DCR was 50% when restricted to the eight gastric cancer patients, with two patients achieving PR. Responses were accompanied by donor microbial engraftment and systemic immune activation.[106] In a phase II trial (RENMIN-215) involving 20 patients with MSS metastatic CRC, the combination of FMT, tislelizumab, and fruquintinib as third-line or later therapy achieved an ORR of 20%, a DCR of 95%, and an mOS of 13.7 months. A post hoc subgroup analysis suggested that patients without liver metastases might derive more pronounced benefit, with median PFS not reached.[107] Furthermore, Cheng *et al*.[108] reported a case of a patient with proficient mismatch repair and MSS stage IVB colon cancer who, after failing multiple lines of chemotherapy and targeted therapy, received a chemotherapy-free triple regimen comprising tislelizumab, bevacizumab, and fecal microbiota capsules. The tumor regressed markedly, enabling surgical resection, and postoperative pathology confirmed a pathological complete response.[108] These early-phase findings provide hypothesis-generating evidence for FMT–ICI combinations in GI cancers, with DCRs generally ranging from 40% to 95% across heterogeneous study designs and patient populations. Nevertheless, the available studies are limited by small sample sizes, lack of randomization, insufficient follow-up data, and inadequate safety monitoring for FMT-specific risks. Furthermore, the current literature is heavily weighted toward positive findings, with limited reporting of null results or cases of disease progression following FMT. Several ongoing clinical trials are further investigating the efficacy of FMT combined with ICIs in GI cancers (NCT05750030; NCT05690048; NCT05273255; NCT04729322).

After FMT–ICI combination treatment, the gut microbiota of GI cancer patients may undergo remodeling, especially in CRC. In preclinical studies, multi-omics analysis of CRC mouse models suggested that FMT combined with anti-PD-1 therapy enriched beneficial bacteria such as *Bacteroides thetaiotaomicron* and *B. fragilis*, while suppressing potentially detrimental species like *Bacteroides ovatus* and *Lactobacillus murinus*. These alterations were accompanied by shifts in microbial functional profiles and changes in the host plasma metabolome, though their direct translational relevance to human disease requires further validation.[109] At the phylum level, Zhao *et al*.[107] found that the proportion of *Proteobacteria* was significantly higher in responders, while *Actinobacteriota* and the genus *Bifidobacterium* were more abundant in non-responders. At the family and genus levels, *Lachnospiraceae* emerged as a critical beneficial group, and its genera *Roseburia* and *Lachnospira* were significantly increased in responders. Peng *et al*.[110] also observed that after treatment, patients' gut microbiota composition shifted toward that of their corresponding healthy donors, and those who achieved clinical benefit showed significantly higher similarity to the donor. Through exploratory analysis, a group of species potentially associated with clinical benefit were identified in responders, such as *Bacteroides coprocola*, *Bacteroides stercoris*, and *Parabacteroides goldsteinii*, which were hypothesized to have originated from successful donor colonization.[106]

FMT has been proposed to potentially reduce the incidence of irAEs, though this association requires further validation in larger prospective studies. In available early-phase trials and retrospective analyses, most irAEs or treatment-related adverse events (AEs) associated with FMT–ICI combination were grade 1 or 2, primarily involving the GI tract and presenting as nausea and constipation.[53,106] However, it should be noted that FMT itself carries inherent safety risks, including pathogen transmission, bacteremia, and potential immune dysregulation, particularly in immunocompromised oncology patients. ICI-associated colitis is a common and potentially severe adverse reaction, typically presenting as diarrhea but capable of progressing to fever, hematochezia, bowel obstruction, megacolon, peritonitis, intestinal perforation, and death.[111] Emerging evidence suggests that FMT may represent a promising, though not yet established, treatment approach for ICI-associated colitis. Three case reports suggest that FMT is associated with symptom alleviation, restoration of mucosal integrity, and remodeling of gut microbial composition and local immune homeostasis.[112,113] Additionally, two larger clinical analyses reported similarly notable clinical remission rates.[114,115]

FMT combined with traditional therapies

FMT combined with chemotherapy

Preclinical and emerging clinical evidence suggests that chemotherapeutic agents can rapidly reduce tumor volume and remodel the TME by inducing immunogenic cell death, promoting CTL infiltration, and depleting or reprogramming immunosuppressive cells.[116] The immunological effects of chemotherapy depend on the drug type, dosage, and administration regimen. High-dose chemotherapy may suppress immune effector cells such as $CD8^+$ T cells and NK cells, whereas low-dose chemotherapy has shown the potential to enhance immune responses by reducing the number of MDSCs and Tregs, although it is often insufficient to achieve complete responses alone.[117] While inhibiting the growth, division, or DNA replication of cancer cells, chemotherapy also affects normal cells that are actively dividing, such as those in the bone marrow, GI tract, and hair follicles, leading to adverse effects such as nausea, vomiting, alopecia, myelosuppression, and immunosuppression. Prior studies have reported that chemotherapy can also damage the intestinal epithelium, disrupt microbiota balance, and impair immune homeostasis.[118]

The interaction between the gut microbiota and chemotherapy is bidirectional. Gut microbiota influence drugs through multiple processes, including bacterial translocation, reduced diversity, drug deactivation and reactivation, immune modulation, and biotransformation.[119] These mechanisms may act in concert to ultimately shape therapeutic efficacy and toxicity by altering drug activity, the TME, and host metabolic status. For instance, the antitumor efficacy of cyclophosphamide (CTX) observed in preclinical mouse models is potentially mediated by the activities of specific gut commensal bacteria. CTX promotes translocation of Gram-positive bacteria such as *Enterococcus hirae*, which is associated with induction of Th1/Th17 immune responses.[120] CTX also appears to facilitate the accumulation of Gram-negative bacteria such as *Barnesiella intestinihominis* in the colon.[121]

Notably, these beneficial effects are markedly attenuated when the gut microbiota is disrupted by antibiotics. Similarly, the efficacy of platinum-based drugs such as oxaliplatin may also depend on the gut microbiota. In mice with disrupted microbiota, treatment failure was associated with a blunted ROS response by tumor-infiltrating myeloid cells and suggested a correlation between specific bacterial genera such as *Alistipes* and improved therapeutic outcomes.[122] More recently, Xu *et al*.[123] further showed that *Akkermansia muciniphila* may enhance oxaliplatin sensitivity in gastric cancer via its metabolite pentadecanoic acid, which putatively targets FUBP1 to inhibit tumor glycolysis. In pancreatic ductal adenocarcinoma mouse models, the microbiota-derived metabolite indole-3-acetic acid (3-IAA), produced by *Bacteroides* species, potentially enhanced FIRINOX or gemcitabine/nab-paclitaxel chemotherapy through ROS accumulation and autophagy downregulation in cancer cells. The same study further observed that in two patient cohorts, higher serum 3-IAA correlated with better response and longer survival, though the mechanism in humans remains to be confirmed.[124] However, the gut microbiota may also contribute to potentiating the toxicity of chemotherapeutic agents. Wallace *et al*.[125] provided preclinical evidence that irinotecan-induced diarrhea is mechanistically driven by bacterial β-glucuronidase, which reactivates the glucuronide conjugate SN-38G back to the active metabolite SN-38, thereby directly damaging the intestinal mucosa. Sun *et al*.[126] further found that the ratio of SN-38 to SN-38G in intestinal tissue correlates most closely with diarrhea severity. Furthermore, certain bacterial species directly undermine therapeutic efficacy by activating resistance pathways in cancer cells. *Bacteroides fragilis* promotes resistance to 5-fluorouracil and oxaliplatin in CRC mice by directly binding to the Notch1 receptor on cancer cells via its surface proteins, which in turn activates Notch1 signaling and induces epithelial-mesenchymal transition and stemness.[127] Collectively, these findings suggest that the gut microbiota may function as a contributor to chemotherapy outcomes, influencing both efficacy and toxicity through distinct microbial mechanisms. While causal relationships in humans remain largely unestablished, the microbiota-dependent nature of these processes raises the possibility that modulating microbial composition could represent one avenue to improve therapeutic responses, a hypothesis that has prompted investigation into microbiome-directed strategies, including FMT.

Preclinical studies have provided initial evidence that FMT may both enhance chemotherapy efficacy and alleviate chemotherapy-induced toxicity through modulation of gut microbiota composition, restoration of intestinal barrier integrity, and attenuation of pro-inflammatory signaling. In rodent models of chemotherapy-induced intestinal injury, FMT has demonstrated beneficial effects. Le Bastard *et al*.[128] showed that FMT after 5-fluorouracil and antibiotics restored microbial diversity and butyrate-producing commensals, recovered metabolic functions, and suppressed pathogen outgrowth. Wardill *et al*.,[129] using methotrexate, further delineated that autologous pre-treatment FMT, but not post-chemotherapy FMT, reduced diarrhea, with benefit linked to Muribaculaceae engraftment and mucosal recovery. Li *et al*.[130] also found that healthy-donor FMT alleviated weight loss and colon shortening in 5-FU-treated mice, while FMT from 5-FU-treated donors transferred these injuries to vancomycin-pretreated recipients. These findings were further corroborated in tumor-bearing CRC models, where FMT not only alleviated chemotherapy-induced mucosal injury but also enhanced antitumor efficacy. Arshad *et al*.[131] showed that FMT synergized with capecitabine to reverse microbial dysbiosis and potentiate antitumor immunity. Similarly, Chang *et al*.[77] demonstrated that FMT safely mitigated FOLFOX-induced intestinal mucositis and diarrhea without compromising the antitumor efficacy of chemotherapy, while Unrug-Bielawska *et al*.[132] reported that FMT might potentiate FOLFOX's antitumor activity in specific CRC patient-derived xenograft models. Moreover, several animal studies have shown that FMT can transmit intestinal mucosal protection or chemotherapy sensitization conferred by gut microbiota-modulating agents to recipient animals.[133-136] Whether these findings translate into clinical benefit remains uncertain. A clinical study of 62 CRC patients reported that FMT alleviated refractory FOLFIRI-induced diarrhea, along with reduced markers of intestinal permeability.[137] In a randomized, double-blind, phase II trial involving 24 cachectic patients with advanced gastroesophageal cancer, administration of allogenic FMT from healthy obese donors prior to first-line chemotherapy significantly improved the DCR (83% vs. 42%) and showed a trend toward improved mOS and PFS compared with autologous FMT, although the primary endpoint of improving cachexia was not met.[138] Given the small sample sizes and limited cancer types investigated so far, larger-scale studies are needed to replicate these findings. Several ongoing clinical trials include ChiCTR2400094513, NCT06405113, and NCT06346093.

FMT combined with radiotherapy

Radiotherapy, as one of the cornerstone treatments for malignant tumors, is administered to approximately 50% of cancer patients during their disease course, with about 40% achieving cure through this modality.[139] It directly kills tumor cells and inhibits their proliferation by inducing DNA damage while exerting dual immunomodulatory effects. On one hand, radiotherapy activates antitumor immune responses through immunogenic cell death, tumor antigen release, and enhanced antigen presentation, remodeling the TME and potentially mediating the abscopal effect on distant metastases, although the reverse abscopal effect may also occur via independent pathways.[140] On the other hand, it may drive immunosuppression by impairing immune cells, expanding MDSCs and Tregs, upregulating TGF-β expression, and reducing $CD8^+$ T-cell infiltration, thereby undermining treatment durability.[141] The cytotoxic effects of radiotherapy inevitably extend to surrounding healthy tissues, particularly rapidly proliferating epithelia such as those of the GI tract, oral mucosa, and skin. Approximately 90% of patients receiving abdominal, pelvic, or rectal radiotherapy develop RE.[142] RE is characterized by acute intestinal mucositis and chronic fibrosis affecting the small intestine and rectum, with clinical manifestations including abdominal pain, diarrhea, and hematochezia, significantly impairing quality of life and potentially necessitating treatment discontinuation.[143]

A bidirectional interaction exists between the gut microbiota and radiotherapy. Ionizing radiation rapidly and dose-dependently alters the composition and function of the microbiota and may even directly damage microbial DNA or induce horizontal gene

transfer among gut microbes.[144,145] A preclinical study also reported that radiation may reshape the gut virome. Dysregulation of the viral community can lead to excessive activation of RIG-I and Notch signaling pathways, further impairing intestinal stem cell regeneration and differentiation, and potentially contributing to exacerbated intestinal injury in mouse models.[146] While ionizing radiation alters the composition and function of the gut microbiota, the microbiota in turn modulates the efficacy and toxicity of treatment. A healthy gut microbiota can play a key protective role in mitigating radiotherapy-induced toxicity by modulating host immune and oxidative stress responses. Dysbiosis may weaken radiotherapy responses, amplify radiotherapy-induced toxicity, and even indirectly increase the risk of tumor progression or metastasis. A prospective study of 172 patients with esophageal carcinoma showed that pathological complete responders maintained stable gut microbial diversity during neoadjuvant chemoradiotherapy, whereas diversity significantly declined in non-responders. Additionally, lower pre-surgery diversity independently predicted worse PFS.[147] Neoadjuvant concurrent chemoradiotherapy (nCRT) is the standard treatment for locally advanced rectal cancer (LARC), yet both therapeutic response and toxicity vary considerably among individuals. Two small exploratory studies have provided initial evidence of compositional and dynamic changes in the gut microbiome during nCRT. At baseline, Clostridium sensu stricto 1 and *Shuttleworthia* were enriched in responders, whereas genera such as *Murimonas* and *Faecalibacterium* were more abundant in non-responders.[148,149] During nCRT, microbial diversity showed a declining trend in patients with poor response, and a longitudinal decrease in *Intestinimonas* was predictive of a good pathological response.[149] In addition, Shi *et al*.[148] observed that genera including *Bifidobacterium* and *Clostridia* were more abundant in patients with less severe diarrhea. A larger study of 126 LARC patients found that non-responders showed a significant post-treatment enrichment of *Bacteroides vulgatus* and enhanced microbial nucleotide biosynthesis activity in feces and tumor tissues. The study further demonstrated in preclinical models that *B. vulgatus*-derived nucleosides can be taken up by tumor cells via nucleoside transporters and enhance DNA damage repair, thereby directly contributing to chemoradiotherapy resistance.[150] Huang *et al*.[151] further found in mouse models that *Bacteroides* enrichment may exacerbate radiation proctitis by depleting colonic NAD^+ and impairing mucosal proliferative capacity, thereby amplifying normal tissue injury.

The combination of radiotherapy and FMT may represent a strategy to potentiate antitumor immunity, mitigate radiation-induced intestinal injury, and restore gut microbial homeostasis, thereby improving both the efficacy and tolerability of radiotherapy. Studies in murine models have shown that the protective effects of low-intensity exercise against radiation-induced intestinal injury can be transferred to recipient mice via FMT. In the same work, direct administration of *Akkermansia muciniphila* similarly reduced radiation-induced gut toxicity.[152] Li *et al*.[153] reported that transplanting gut microbiota from radiotherapy responders into antibiotic-treated HCC mouse models via FMT restored the antitumor efficacy of radiotherapy through the cGAS–STING signaling pathway, in which microbiota-derived c-di-AMP and radiotherapy-induced dsDNA from damaged tumor cells synergistically triggered IFN-β production and CTL activation. FMT also reshapes gut microbiota structure in irradiated mice, improves GI tract function and intestinal epithelial integrity, and thereby significantly increases survival rates and alleviates radiation-induced GI toxicity.[79] However, direct clinical investigation of FMT combined with radiotherapy in GI cancers remains virtually absent, and the translational relevance of these preclinical findings has yet to be established in controlled human studies.

Preliminary clinical evidence suggests a potential reparative role of FMT in radiation-induced intestinal injury, though current data remain limited and largely derived from gynecological cancer patients. Three clinical case studies involving cervical cancer patients provided initial evidence for the efficacy of FMT. Wang *et al*.[154] and Zheng *et al*.[155] reported that multi-course FMT significantly alleviated the clinical symptoms of chronic RE and improved long-term outcomes, while the gut microbiota profiles of these patients were shifted toward those of healthy donors. Furthermore, a case report confirmed that FMT with the patient's son as the donor effectively alleviated symptoms in a patient with recurrent RE 18 years after radiotherapy, underscoring the therapeutic potential of FMT for RE at different disease stages.[156] In addition, Ding *et al*.[157] administered washed microbiota transplantation to five patients with refractory chronic RE; three achieved a clinical response at 8 weeks post-transplantation, with improvement in intestinal symptoms and mucosal injury, and no severe treatment-related AEs were reported. Microbiological analysis showed that the gut microbiota profiles of responders shifted toward the donor lineage, accompanied by enriched beneficial taxa such as *Phascolarctobacterium*, *Lachnoclostridium* , and *Blautia*. Furthermore, Cui *et al*.[158] conducted a prospective cohort study in 45 patients with RE complicated by intestinal obstruction. Compared with conventional treatment, perioperative FMT combined with nutritional support significantly shortened the time to postoperative GI function recovery and hospital stay, and effectively reduced the incidence of postoperative inflammatory obstruction. More importantly, this combined regimen significantly improved postoperative nutritional parameters and GI quality-of-life scores, though the study design and sample size again limit the strength of conclusions that can be drawn.[158]

HDMX-based donor screening strategy for XenoFMT

In the clinical application of FMT in GI oncology, donor selection has largely been restricted to safety-based screening criteria with taxonomic characterization, encompassing pathogen exclusion and infectious disease testing, with limited systematic attention to microbiota characteristics potentially relevant to therapeutic efficacy. In the ICI setting, two primary donor sources have been utilized in studies, namely healthy donors and treatment-responding donors who have achieved a complete or PR to ICI, with the former being more commonly reported. In GI cancers, post hoc analyses of donors associated with clinical benefit in FMT–ICI combination therapy suggest that therapeutic efficacy may depend on the enrichment of immunostimulatory bacterial strains and the exclusion of immunosuppressive strains,[53,107] and may also be linked to the establishment of functionally cooperative microbial consortia.[106] However, donor analyses to date have been largely retrospective and lack prospective

application. Given interstudy heterogeneity and the absence of RCTs, determination of the optimal donor source remains unresolved. In clinical trials of FMT combined with chemotherapy or radiotherapy, even retrospective profiling is absent, with available studies focused exclusively on toxicity mitigation and symptomatic management,[137,138,156-158] with no characterization of donor microbiota in relation to response. A preclinical study in CRC patient-derived xenograft models further suggested that identical healthy-donor FMT enhanced FOLFOX efficacy in only two of four tumor models, with differential responses potentially attributable to specific host–microbiota–tumor interactions rather than the overall extent of microbiota restructuring, supporting the idea that compositional profiling alone may be insufficient to predict chemotherapy sensitization across distinct tumor contexts.[132] Current FMT-oncology clinical trials have yet to incorporate functional donor characterization as a design criterion. Few strategies incorporate functional evaluation of how the donor microbiota, as an integrated community, modulates host antitumor responses. Moreover, the efficacy of microbiome-based interventions varies substantially among individuals. Even strains within the same bacterial species may produce divergent outcomes due to genomic variation.[34,159] In addition, microbiota-mediated effects are profoundly context-dependent, shaped by tumor type, treatment modality, and host immune status, rendering static taxonomic profiling insufficient as a basis for donor selection.

To address this limitation, we propose an integrated preclinical-to-clinical framework comprising two sequential components (Fig. 2). The first is the HDMX model, a preclinical platform in which recipient mice undergo antibiotic-mediated microbiota depletion, followed by transplantation of microbiota from individual donors within a prospectively assembled donor pool. After tumor inoculation and immunotherapy administration, this system evaluates the ability of each donor microbiota to modulate therapeutic efficacy and host immune responses in a disease-relevant context.

Although illustrated here in the setting of tumor immunotherapy, the HDMX framework is broadly applicable to a range of microbiota-associated diseases, including inflammatory bowel disease, irritable bowel syndrome, metabolic disorders such as type 2 diabetes and obesity, and neuropsychiatric conditions such as depression and Alzheimer's disease. In these contexts, the sequence of microbiota transplantation and disease induction can be adjusted according to disease-specific experimental designs.

The second component is XenoFMT, in which fecal microbiota preparations from donors functionally validated through the HDMX platform are administered to eligible patients. Unlike conventional approaches that rely primarily on safety screening and taxonomic profiling, XenoFMT incorporates functional preclinical validation as a prerequisite for donor selection. Together, the HDMX–XenoFMT pipeline proposes an integrated framework linking functional donor evaluation in a standardized preclinical system with personalized microbiota delivery in the clinical setting, with the potential to inform precision microbiome-based therapeutic strategies.

Safety concerns

Although FMT is usually regarded as safe and associated with mild AEs,[160] such as transient diarrhea, abdominal pain, low-grade fever, and constipation, its safety requires more attention in oncology patients whose immune competence may be altered by the underlying malignancy and concurrent systemic therapies. A pertinent concern in this context is pathogen transmission. In 2019, DeFilipp *et al*.[161] reported that two patients—one with advanced cirrhosis and one who had undergone allogeneic hematopoietic cell transplantation—developed extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* bacteremia after FMT. One patient died. Genomic sequencing linked both cases to the same stool donor, and SNP analysis suggested that the isolates from the donor and the patients were clonal organisms. The donor had no multidrug-resistant risk factors, and the screening protocol at the time did not include ESBL testing, underscoring that standard screening cannot eliminate all transmissible pathogens. Zellmer *et al*.[162] reported in 2020 that seven patients with *Clostridioides difficile* infection developed AEs after receiving FMT from a single donor. Although the donor had repeatedly tested negative for Shiga toxin-producing *Escherichia coli* (STEC), retrospective testing later revealed asymptomatic carriage of STEC.[162] Ultimately, it was determined that four serious AEs were associated with STEC transmitted via FMT. Transmission of norovirus via FMT has also been reported in a leukemia patient, causing gastroenteritis and graft-versus-host disease after transplantation.[163] Encouragingly, Chang *et al*.[164] achieved zero pathogen transmission in 109 FMT products via stringent screening, including clinical assessment, respiratory and stool testing, and multidrug-resistant organism surveillance, with no reported SARS-CoV-2 or MDRO infections in 29 recipients. These findings suggest that current donor screening practices may require further refinement. While direct evidence of pathogen transmission through FMT in GI cancer patients is currently lacking, analogous risks cannot be excluded given the shared immunocompromised status of the affected populations described above, underscoring the need for more rigorous donor screening and prospective safety evaluation in this population.

In the context of combination oncology regimens, FMT-associated safety considerations are further compounded by treatment interactions. In GI cancer patients, underlying malignancy and compromised intestinal architecture may already perturb immune homeostasis.[165] FMT may introduce microbial taxa or metabolites that have the potential to attenuate antitumor immune responses.[40,45,65,66] When combined with ICIs, FMT may alter the irAE risk profile, though a causal role of FMT specifically in precipitating irAEs has not been fully demonstrated across diverse ICI regimens and donor sources. Furthermore, FMT has been explored as a salvage therapy for refractory ICI-related colitis in patients who have failed standard treatment, while evidence from Duttagupta *et al*.[166] links gut microbiota composition to irAE risk in ICI-treated melanoma patients. At the individual patient level, FMT–ICI interactions remain unpredictable, presenting both therapeutic opportunity and safety uncertainty. Although preclinical studies have provided initial evidence that FMT may attenuate intestinal injury related to chemotherapy or radiotherapy,[77,79,128-130,152,153] available clinical data remain limited to small underpowered trials and case series mostly in non-GI malignancies,[137,138,154-158] precluding definitive conclusions. In this context, the timing of FMT administration warrants particular caution. Although chemotherapy-associated

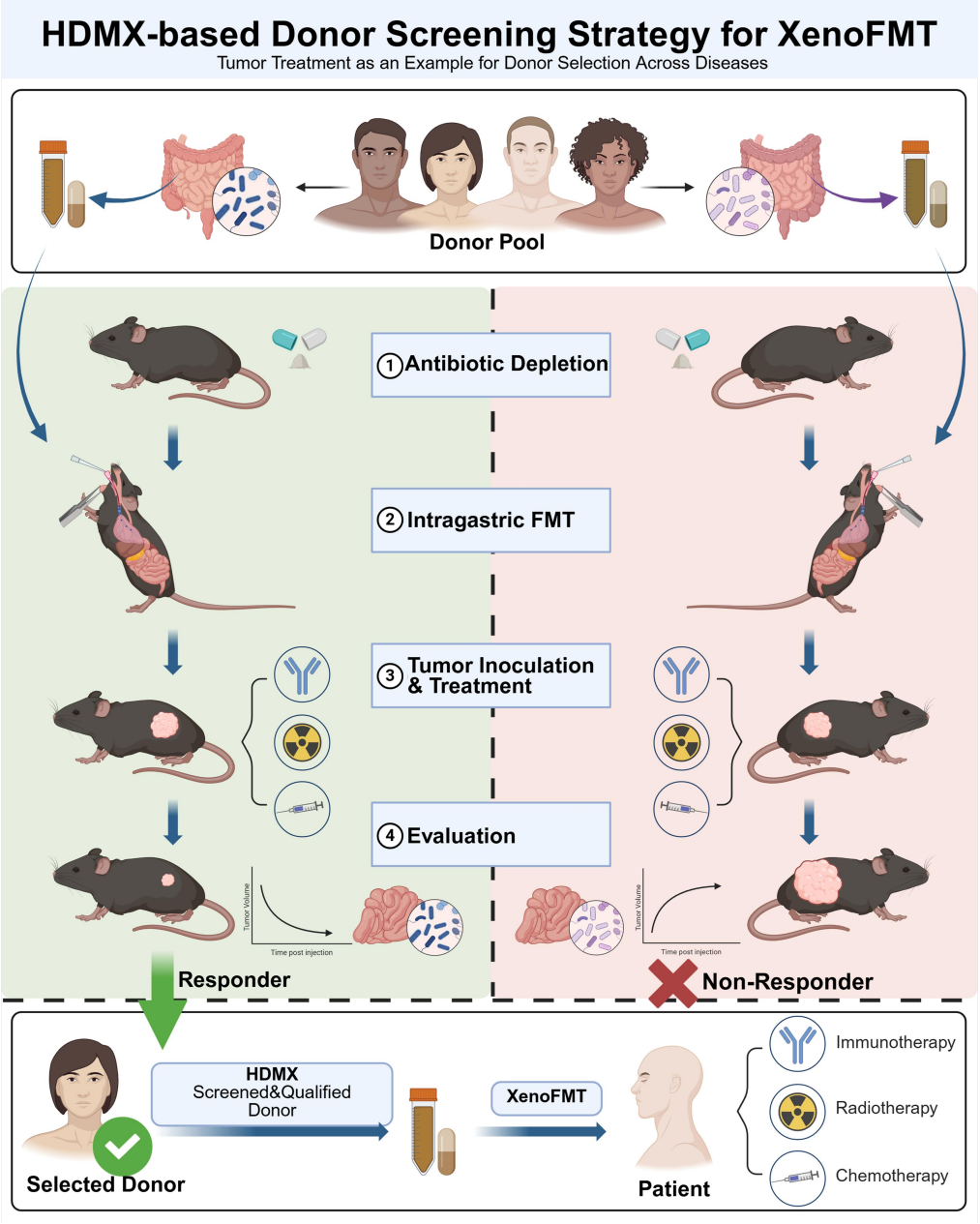

Fig. 2. HDMX-based Donor Screening Strategy for XenoFMT. Fecal samples from a donor pool are transplanted into microbiota-depleted mice for functional screening. Microbiota from validated donors are then selected for clinical XenoFMT in patients with GI cancers, combined with immunotherapy, chemotherapy, or radiotherapy. Created with BioRender.com. FMT, fecal microbiota transplantation; GI, gastrointestinal; HDMX, Healthy Donor-derived Microbiota Xenograft; XenoFMT, Xenograft-screened fecal microbiota transplantation.

epithelial disruption and neutropenia,[167,168] as well as radiation-induced mucositis,[169] are individually recognized risk factors for bacteremia in oncology patients, whether FMT delivery during these periods further amplifies this risk in GI cancers has not been directly investigated. The conditions under which FMT can be safely administered in FMT–chemotherapy or FMT–radiotherapy combination therapy remain unestablished. Separately, FMT-oncology studies often have limited safety reporting, and follow-up durations may be insufficient to capture delayed infectious or immune-mediated complications. These safety-related reports suggest that the true incidence and severity of FMT-associated AEs in GI cancer patients remain uncertain, presenting challenges for clinical decision-making regarding FMT in this population.

Limitations

This review has several limitations. First, the clinical evidence included is predominantly derived from early-phase trials, single-

arm studies, and preclinical models. Large-scale randomized controlled trials in GI cancers remain scarce, precluding firm conclusions regarding clinical efficacy and long-term safety. Second, substantial heterogeneity exists across the included studies in donor sources, cancer subtypes, and combination regimens, compounded by the use of divergent donor screening criteria in the absence of consensus. Third, microbial engraftment is highly variable and unpredictable across individuals, fundamentally limiting the standardization of FMT dosing and precluding objective comparisons of biological efficacy across studies. Fourth, many mechanistic insights discussed are extrapolated from murine models or *in vitro* systems, and their translational validity remains uncertain. Moreover, the context-dependent and frequently dual immunomodulatory effects of microbial metabolites hinder the prediction of net outcomes in human tumors. Fifth, the proposed HDMX–XenoFMT framework is a theoretical construct that has not been clinically validated, and supporting evidence remains preclinical. Furthermore, its predictive value should be interpreted with caution, as these models may not fully mirror the complexity of the human TME or the infectious susceptibility profiles of immunocompromised oncology patients. Consequently, safety and efficacy data derived from HDMX require careful clinical validation before broad application in this vulnerable population. Sixth, the evidence base is unevenly distributed across GI cancer subtypes, with colorectal and gastric cancers overrepresented relative to esophageal, hepatocellular, and pancreaticobiliary malignancies. Finally, this review was limited to peer-reviewed publications in English and Chinese and may have missed relevant unpublished work or recently published studies not captured by our search.

Conclusions

FMT represents a promising adjuvant strategy in GI oncology, with putative mechanisms including enhancement of antigen presentation, reshaping of the TME, and preservation of intestinal barrier function, supporting its potential to enhance antitumor efficacy and alleviate treatment-related toxicities. We further propose the HDMX–XenoFMT pipeline as an integrated framework linking functional preclinical validation with personalized microbiota delivery, aiming to advance FMT toward precision intervention. Despite this promise, translating FMT into clinical practice remains challenging, as donor microbiota functional heterogeneity, unpredictable engraftment, and incompletely characterized risks of pathogen transmission and treatment interactions in immunocompromised patients have yet to be systematically resolved. In addition, clinical validation of the HDMX–XenoFMT framework itself remains lacking. Future progress will require rigorous prospective validation of functional donor screening frameworks, large-scale randomized controlled trials, long-term safety surveillance, and multi-omics integration to establish FMT as a validated precision adjuvant in GI oncology.

Acknowledgments

None.

Funding

Supported in part by the National Key R&D Program of China (Grant No. 2024YFC3607503) and grants 82473057 and 82072760 (XYK) from the National Natural Science Foundation of China.

Conflict of interest

Zhaoshen Li serves as the Honorary Editor-in-Chief of *Cancer Screening and Prevention*. All other authors declare no competing interests.

Author contributions

Study conceptualization, framework establishment (YW, XK), figure design, visualization (YW), original draft (YW), revision, content development (YW), critical review, and academic oversight (ZL, XK). All authors have made significant contributions to this study and have approved the final manuscript.

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