Trends in Cancer

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Review

Gut microbial metabolites for potentiating cancer therapy

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The gut microbiome exerts distant and local effects on tumours, healthy epithelial cells, and the immune system through the production of bioactive metabolites. This influences cancer therapy responses across treatment modalities and cancer types. In this review, we discuss promising approaches to boost beneficial microbiota-derived metabolites to enhance existing cancer therapies, including prebiotics, probiotics, postbiotics, and live biotherapeutic products. Each approach faces challenges in achieving physiological concentrations and tissue distribution, as well as different regulatory regimes and commercial landscapes. With promising early clinical trials and significant scientific and commercial activity in these areas, there is hope that targeted, metabolite-focused interventions will soon benefit cancer patients.

Highlights

Many cancer therapies have overall low response rates, which can be partly explained by microbiome variation and dysbiosis. Bacterial metabolites, most prominently indole acids and short-chain fatty acids, are emerging as determinants of therapy response.

Interventions, including prebiotics, probiotics, postbiotics, faecal microbiota transplants, and live biotherapeutic products, could increase beneficial metabolite levels to boost response rates.

We discuss current evidence for each intervention's efficacy and the biological, regulatory, and commercial challenges that interventions face on the route to the clinic, either as dietary supplements or drug products.

Interventions need to work across heterogeneous microbiomes and must consider the context-dependent action of bacterial metabolites.

Bacterial metabolites affect cancer therapy

The enzymatic repertoire of the gut microbiome vastly exceeds that of human cells [1], and the metabolic outputs of these pathways, many unique to bacteria, shape human physiology and disease. In oncology, recent breakthroughs have demonstrated mechanistic links between bacterial metabolites and therapy responses (Figure 1, Key figure) [2–10]. Short-chain fatty acids (**SCFAs**) (see Glossary), indole acids, urolithins, and others interact with cancer therapies, including immunotherapy, chemotherapy, and radiotherapy, often via multiple, context-dependent and cell-type-dependent mechanisms in the gut, systemically, or within the tumour. Differences in microbiota composition and the levels of gut-derived metabolites, therefore, contribute to the heterogeneous response commonly observed during cancer treatment, where it is not uncommon that 50% of patients or more do not respond to the administered treatment (Figure 2A) [7,11–13]. In this review, we briefly summarise the current knowledge on metabolite–therapy interactions and then discuss different interventions aiming to translate these findings into the clinic.

Metabolite–therapy interactions in oncology

The gut microbiota utilise nutrients derived from food, such as fibre and partially digested proteins, as well as host-derived compounds such as mucin. These metabolic processes produce fermentation end products and secondary metabolites, which are released into the gut environment, where they exert effects on the epithelium and can be absorbed and distributed throughout the body.

Indole acids

Indole acids, such as indole-3-propionic acid (**3-IPA**), indole-3-lactic acid (**3-ILA**), indole-3-acetic acid (**3-IAA**), and indole-3-aldehyde (I3A), are bacterial metabolites derived from the essential amino acid tryptophan. They broadly influence cancer therapy responses across different modalities and cancer types. Canonically, they bind the aryl hydrocarbon receptor (AhR), which

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is expressed in many cell types and acts as a transcription factor to elicit broad changes in immunity and metabolism. Treatment-modulating downstream effects vary depending on the cancer type, specific indole acid, and cancer model, as demonstrated by the diverse AhR-dependent mechanisms recently discovered. In many of these, indole acids act on AhR in immune cells. In mice, I3A alters AhR engagement in $CD4^+$ T cells, thereby reducing kynurenine-mediated formation of regulatory T cells and improving the efficacy of immune checkpoint blockade (**ICB**) [14]. In another study, 3-IPA increases $CD8^+$ T cell infiltration and thereby enhances the response to chemotherapy in colorectal cancer mouse models, again dependent on AhR [15]. Indole acids produced by tumour-colonising bacteria can similarly increase T cell function and ICB responses, as demonstrated in mouse models of colorectal cancer for 3-IAA [16] and in melanoma for I3A [17]. In bladder cancer, increased AhR expression is associated with longer overall survival. Moreover, 3-IAA induces downregulation of fatty acid synthase (FASN) and ferroptosis via AhR in human bladder cancer cells *ex vivo* [18]. Conversely, in pancreatic cancer mouse models under tryptophan deprivation (reducing microbiota-derived indoles), tumour growth was suppressed, while 3-ILA or 3-IAA supplementation for 2 weeks restored growth by activating tumour-associated macrophages (TAMs) through AhR [19]. Overall, these studies demonstrate a remarkable ability of indole acids to affect diverse immune cell types via AhR.

Additionally, different, apparently AhR-independent treatment-modulatory mechanisms of indole acids are emerging. Jia *et al.* describe how IPA increases ICB response through promoting H3K27 acetylation at the *transcription factor 7* (*Tcf7*) super-enhancer, thereby promoting progenitor-exhausted $CD8^+$ T cells (enriched for TCF1, the product of *Tcf7*) [3]. In pancreatic cancer mouse models, 3-IAA is oxidised by myeloperoxidase (MPO) from neutrophils to generate reactive oxygen species and reduce autophagy, thereby enhancing chemotherapy response [7].

Finally, acting locally in the gut, indole acids may ameliorate treatment-related side effects. Indole acids help reduce colonic inflammation and could thereby reduce dose limitations and improve patient well-being [4,20–22]. Overall, microbiota-derived indole acids modulate tumour-reactive T cell functionality and can influence chemotherapy responses, largely via AhR but also through other mechanisms, such as H3K27 acetylation or MPO/neutrophils. While many enhance antitumour immunity, in certain contexts or when active over certain periods, they sometimes appear to suppress it, warranting further study (Box 1).

SCFAs

Microbial fermentation products, such as SCFAs, including acetate, propionate, butyrate, and formate, are byproducts of bacterial carbohydrate metabolism. They act as metabolic substrates for human cells (especially locally on the gut epithelium, where butyrate is a major nutrient for colonocytes and is important for barrier maintenance) but are also distributed systemically to act on immune and tumour cells. Canonically, butyrate inhibits histone deacetylation, thereby changing chromatin structure and gene expression. In immune cells, this can result in improved T cell function, synergistic with ICB. For example, in preclinical colorectal cancer mouse models, supplementation with the butyrate-producing *Roseburia intestinalis* enhanced the effectiveness of programmed cell death protein 1 (PD-1) inhibitor treatment [2]. Similarly, direct administration of butyrate augments the cytotoxic function of antitumour $CD8^+$ T cells during chemotherapy-induced immune responses in a murine subcutaneous MC38 model [6]. *In vitro* pretreatment of receptor tyrosine kinase-like orphan receptor 1 (ROR1)-specific chimeric antigen receptor (CAR) T cells with butyrate or pentanoate improved tumour control in mice challenged with ROR1-expressing pancreatic cancer cells [31].

Notably, in mice, increased bacterial formate production via exercise-induced one-carbon metabolism leads to Nrf2-dependent heightened Tc1 T cell responses, which are able to control

Glossary

3-IAA: indole-3-acetic acid, a bioactive tryptophan metabolite.
3-ILA: indole-3-lactic acid, a bioactive tryptophan metabolite.
3-IPA: indole-3-propionic acid, a bioactive tryptophan metabolite.
FMT: faecal microbiota transplant, the procedure of transferring a preparation of donor-derived microorganisms for the treatment of disease.
GMP: Good Manufacturing Practice, a comprehensive regulatory quality control system used for drug production.
ICB: immune checkpoint blockade, a form of cancer immunotherapy that inhibits suppressive interactions between ligands (such as PD-L1) and inhibitory receptors on T cells (such as PD-1 and CTLA-4). Blocking these checkpoints reactivates cytotoxic T cells, enabling them to recognise and destroy cancer cells.
LBP: live biotherapeutic product, a drug product consisting of live microorganisms for the treatment or prevention of disease, which is not a vaccine.
PK/PD: pharmacokinetics/pharmacodynamics describe how a drug is taken up, modified, distributed in, and cleared from the body over time.
Postbiotic: a preparation or synthetic version of gut bacterial components (in the context of this review, metabolites) that aims to confer health benefits when administered to humans.
Prebiotic: a dietary component or supplement that promotes the growth or activity of beneficial microbes in the gut.
Probiotic: live microorganisms marketed as dietary supplements that aim to confer a health benefit to the host.
SCFA: short-chain fatty acids, a class of molecules produced through carbohydrate fermentation by gut bacteria, which include butyrate, propionate, and acetate.

Key figure

Interventions to boost beneficial metabolites and mechanisms by which they influence therapy response

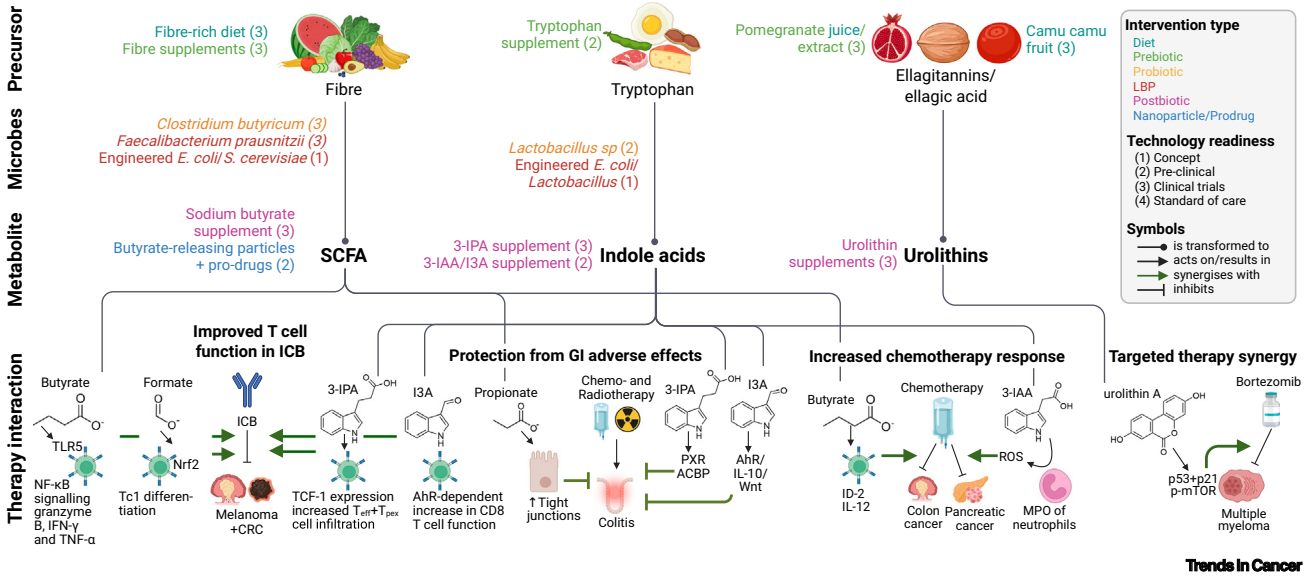

Figure 1. Dietary precursors (top) are converted by gut microbiota to bioactive metabolites (middle), which influence cancer therapy response via diverse mechanisms (bottom). Different (proposed) interventions, which increase the availability of precursors, beneficial microbes, or metabolites directly, are shown in coloured fonts. 3-IAA: indole-acetic acid; 3-IPA: indole-propionic acid; ACBP: acyl-CoA-binding protein; AhR: aryl hydrocarbon receptor; CRC: colorectal cancer; ICB: immune checkpoint blockade; IFN-γ: interferon-gamma; IL: interleukin; I3A: indole-carboxaldehyde; NF-κB: nuclear factor-κB; Nrf2: nuclear factor-erythroid-2-related factor 2; PXR: pregnane X receptor; SCFA: short-chain fatty acids; Tc1: type 1 cytotoxic lymphocytes; T_{eff}: T-effector cells; TNF-α: tumor necrosis factor-alpha; T_{pex}: progenitor exhausted $CD8^+$ T cells; Wnt: Wingless/Integrated signalling pathway; MPO: myeloid peroxidase; ROS: reactive oxygen species; TLR5: Toll-like receptor 5. Created in BioRender. Kamrad, S. (2025) https://BioRender.com/cdk0w17.

BRAF^{V600E} melanoma in mice [9]. Additionally, SCFAs, particularly propionate, have radioprotective effects in mice by strengthening the intestinal barrier and mucus layer [10,32]. These preclinical findings are supported by clinical correlations. In a prospective cohort dataset of mixed solid tumours, higher concentrations of SCFAs, such as butyrate and propionate, were observed in patients who benefited from treatment [33]. In melanoma patients receiving immunotherapy, higher fibre consumption was associated with improved outcomes [34]. Overall, these data indicate that SCFAs profoundly influence antitumour immune activity and intestinal inflammation, thereby potentially influencing therapy responses.

Other metabolites

Other microbiota-derived or microbiota-modulated metabolites with implications for cancer therapy have been described. Bile acids can modulate natural killer T cells via CXCL16 in liver cancer models [35], and secondary bile acids regulate endoplasmic reticulum stress in $CD8^+$ T cells, impairing response to immunotherapy [36]. Trimethylamine *N*-oxide (TMAO), generated from dietary choline, L-carnitine, and betaine, can increase macrophage activation (in mouse and human monocyte-derived macrophages) and enhance $CD8^+$ T cell antitumour activity (in mice), improving ICB efficacy [25]; however, opposing effects have been observed in other cancer types (Box 1).

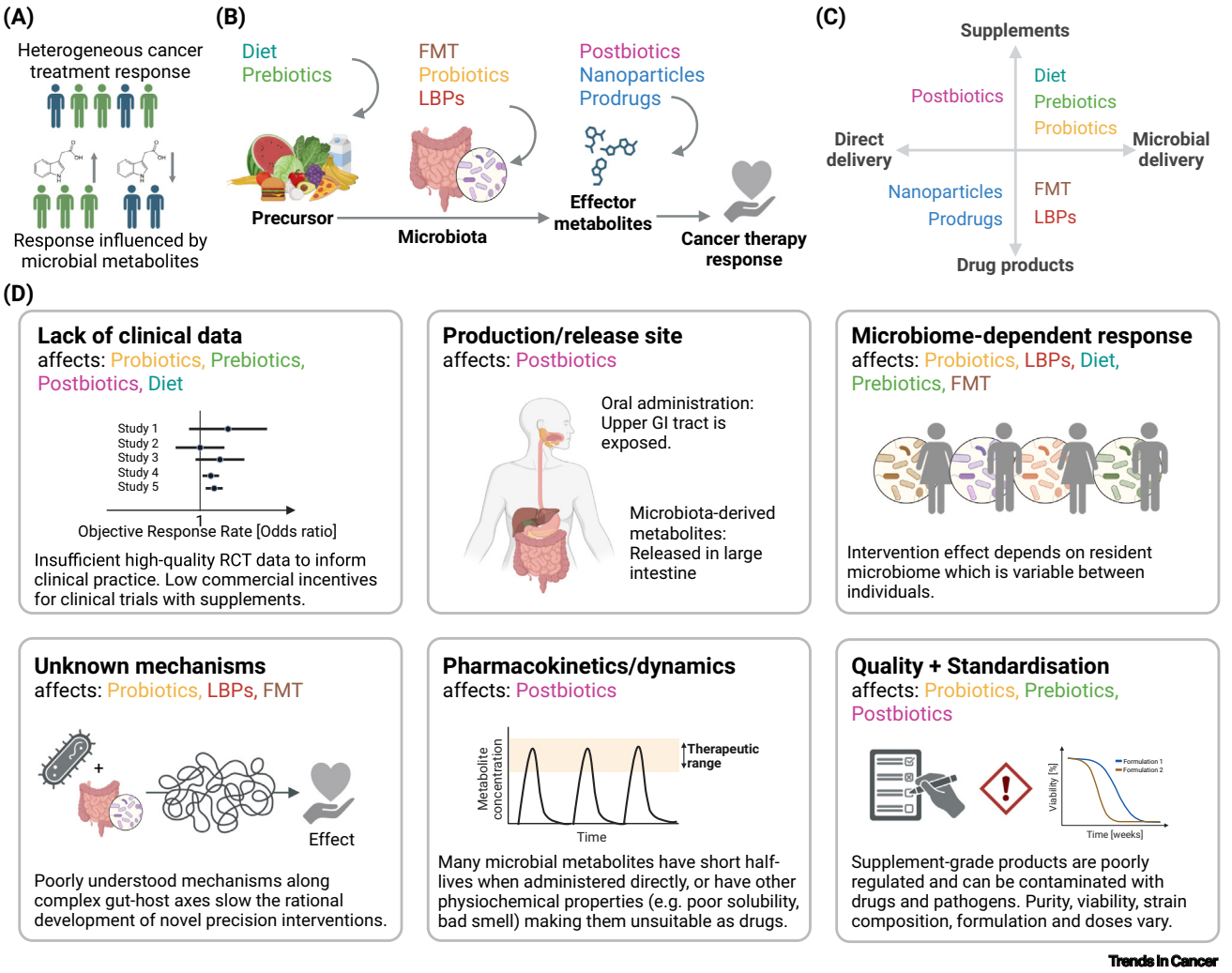

Figure 2. Key challenges of different metabolite-boosting interventions. (A) Illustration of the paradigm in which the microbiota influence therapy response by production of bioactive metabolites. (B) Interventions that act on different steps of the production of bioactive metabolites by increasing the supply of precursors, introducing additional metabolic activity in the microbiome, or directly increasing metabolite concentrations without need for microbial production. (C) Classification of interventions according to the origin of metabolites (x-axis) and regulatory route (y-axis). (D) Key challenges faced by different interventions. FMT: faecal microbiota transplant; GI: gastrointestinal; LBP: live biotherapeutic product; RCT: randomised controlled trial. Created in BioRender. Kamrad, S. (2025) https://BioRender.com/cdk0w17.

Ageing-related dysbiosis has been linked to systemic disease, and the microbiota-derived metabolite adenosine diphosphate heptose (ADP-heptose), produced by Gram-negative bacteria during lipopolysaccharide (LPS) core biosynthesis, activates alpha-protein kinase 1 (ALPK1) signalling in haematopoietic stem and progenitor cells, altering clonal haematopoiesis [37]. Microbial inosine activates antitumour T cells and synergises with ICB in mice [38]. Moreover, urolithins, produced by gut bacterial metabolism of dietary ellagitannins and ellagic acid (found in pomegranates, berries, nuts, and camu camu), can arrest the cell cycle of aberrant plasma cells in multiple myeloma [8], and improve T cell [39] and natural killer activity of peripheral blood mononuclear cells of prostate cancer patients against K562 (human chronic myelogenous leukaemia) cells in *ex vivo* assays [40].

Overall, microbial metabolites are emerging as key determinants of treatment response across modalities and cancer types. Microbial metabolites can act locally in the gut, systemically, and

Box 1. Divergent effects of microbial metabolites in different contexts

Gut bacterial metabolites can have divergent health effects depending on the dose and disease state. For example, bacterial formate has been described as an oncogenic driver in colorectal cancer [23] but also stimulates antitumour immunity in melanoma [9] (both in mice). Similarly, trimethylamine *N*-oxide (TMAO) has tumorigenic properties [24] but could be beneficial in a therapy-synergy context, boosting ICB response in pancreatic cancer [25] (in mice) and triple-negative breast cancer (human cohort and validation in mice) [26]. To further complicate the picture, another study reports an association between TMAO and reduced ICB response in hepatocellular carcinoma patients [27], suggesting further context-dependence on cancer types or other covariates. Similarly, 3-IAA can boost chemotherapy response [7] and is anti-inflammatory [21,28], but may be toxic in the (mouse) gut at prolonged high levels [29]. AhR signalling of indole acids is beneficial in the context of suppressing therapy-induced colitis [4,5], but prolonged activation could also promote pancreatic tumour growth [19]. Heterogeneous AhR expression [30] and activity by tumour cells and immune cells in the tumour microenvironment (TME) could furthermore contribute to the divergent effects of indole acids by making different cell populations sensitive or insensitive. In general, such context-dependence is not surprising; the therapeutic benefit of pharmaceutical drugs is also only achieved for certain indications and at the right dose. It highlights that there are likely no one-size-fits-all solutions and that metabolite-boosting interventions need to consider the patient, disease, and therapy context carefully.

within tumours, influencing both the immune system and therapy response (Box 2). Metabolite–treatment interactions are often mediated by the immune system and are context-dependent. While indoles and SCFAs are often recognised as health-promoting and can improve cancer therapy in many settings, they can display strong context dependence, sometimes exerting opposite effects (Box 1). Open questions, therefore, remain about the generalisability of mechanisms across cancers and the translatability of mouse experiments to diverse patient cohorts. Nonetheless, microbial metabolites present attractive starting points for novel therapeutics that synergise with existing cancer treatments by increasing response rates and/or reducing adverse effects.

Leveraging bacterial metabolites as synergistic therapeutics

How can new discoveries of therapy-synergising metabolites be translated to the clinic? Diets, supplementation of metabolic precursors (**prebiotics**), administration of live bacteria [**probiotics**, faecal microbiota transplant (**FMT**), and live biotherapeutic products (**LBPs**)], and direct administration of effector molecules (**postbiotics**) have all been proposed as therapy-supportive measures (Figure 2B). These solutions can be broadly classified along two axes: (i) distinguishing between direct delivery of these metabolites and delivery by microbes; and (ii) the extent to which genetic engineering and pharmaceutical technology are required in their development/production and, thereby, the regulatory regime they fall under (Figure 2C).

Box 2. Pharmacokinetics/pharmacodynamics of metabolites during interventions

A key property of pharmaceutical drugs is their pharmacokinetics/pharmacodynamics, which describe how drug molecules are taken up, distributed in, and cleared from the body over time. Similar concepts can be applied to gut bacterial metabolites, which can act locally on the gut epithelium but are, in many cases, also taken up into the bloodstream and distributed across various tissues [41]. While it is not always clear where microbial metabolites interact with the immune system or other widely distributed cell types, some treatment-synergising effects require metabolites to be located in specific tissues. Several studies (e.g., [7,17]) have described metabolites acting locally in the TME, but how metabolic output in the gut relates to metabolite concentrations in the TME is not fully understood and will depend on factors such as organ/tissue type, vascularisation, and other structural characteristics of the TME. In mice, I3A released by intratumoral *Lactobacillus reuteri* locally drives antitumour immunity [17], raising the question of whether systemic, gut-derived I3A can be equivalent and/or how to target lactic acid bacteria to tumours in humans. Similarly, chemotherapy response is increased by intratumoral 3-IAA, which increases reactive oxygen species locally via myeloidperoxidase of tumour-associated neutrophils [7]. To effectively target 3-IAA to tumours, tumour-colonising live biotherapeutic products (LBPs) have been proposed [16], although injecting genetically modified live bacteria into the bloodstream of severely ill patients comes with significant risks. Conversely, 3-IPA acts locally in the colon to suppress therapy-induced damage and inflammation [4,5]. In this context, it could be beneficial to increase bacterial production of 3-IPA by prebiotics, probiotics, or LBPs, as this closely replicates the natural location and dynamics of 3-IPA release in the gut. Oral administration of 3-IPA will likely fail to deliver steady, slowly increasing metabolite levels and could result in the majority of it being absorbed in the small intestine. Considering the desired site of action of target metabolites and the potential adverse effects of supraphysiological concentrations in other tissues is, therefore, key to designing safe and effective metabolite-boosting interventions.

Direct delivery of bacterial metabolites

Chemically produced or purified bacterial metabolites can be directly administered orally or intravenously, and some are available as dietary supplements, often referred to as postbiotics. Particularly, preparations of tryptophan-derived indole acids have proven effective in potentiating chemotherapy, radiotherapy, and immunotherapy responses in mouse models. Oral supplementation of 3-IAA increases the response to chemotherapy in orthotopic pancreatic ductal adenocarcinoma (PDAC) [7]; I3A [5] and 3-IPA [4] potentially protect the gut against radiotherapy-induced damage and inflammation. Furthermore, oral 3-IPA supplementation successfully raised 3-IPA serum levels and enhanced ICB therapy in a mouse model of colorectal cancer [3] (Figure 1). However, in humans, no mature data on basic pharmacokinetics and therapeutic uses are available yet, although a clinical trial exploring different doses of 3-IPA in healthy adults is currently underway (NCT06674018).

Butyrate (usually as a sodium salt) is widely available as a dietary health supplement, but its effect in different disease contexts is not yet clearly established. In general, it has poor pharmacological properties, as it is rapidly cleared from the body and has a strong, unpleasant smell. The systemic half-life of intravenously administered butyrate is approximately 6 min [42]. For orally ingested SCFA supplements, serum levels peak within 60 min and return to baseline after 120 min, with no increase in baseline levels observed after 1 week of twice-daily supplements [43]. In mouse models, sodium butyrate has shown potential to ameliorate adverse effects of irinotecan chemotherapy [44]. Clinical trials in cancer patients are sparse: one prospective study suggests oral, encapsulated sodium butyrate improves radiotherapy-associated adverse effects [45], while a larger randomised controlled trial (RCT) found no benefit of sodium butyrate enemas for the same purpose [46].

Urolithins are characterised by low water solubility and bioavailability, complicating oral delivery. Preclinically, intraperitoneal urolithin A showed promising anticancer activity and synergy with bortezomib against melanoma [8]. In humans, a commercially available oral urolithin A supplement substantially increases plasma levels in healthy people over a timeframe of >24 h [47] and is currently being trialled in postoperative care of prostate cancer (NCT06022822).

Overall, there are limited clinical data on the direct administration of microbial metabolites in cancer patients, but with trials underway, this could change soon. Still, fundamentally, postbiotics come with several drawbacks (Figure 2D): exogenous administration can fail to replicate the location and dynamics of natural metabolite production by microbiota. This is because many metabolites display unfavourable pharmacokinetics, as they are rapidly metabolised and/or excreted.

Given the drawbacks of direct metabolite administration, nanoparticle formulations and prodrugs have been proposed to improve pharmacological properties. For example, esterified forms of butyrate [48], prodrug-like nanoparticles [49–51], or slow-release particles [52,53] show improved **PK/PD** in mouse models. Similarly, a porous nanoparticle loaded with urolithin B could facilitate slow release and circumvent solubility limitations [54]. Furthermore, combining metabolites with cancer drugs, for example, the chemotherapy drug paclitaxel and 3-IAA [55], could specifically exploit their synergistic effects. Yet, mature clinical data on actual applicability in humans are lacking.

Modulating the resident microbiome

The microbiome and its metabolism are dynamic and responsive to factors under an individual's control, most notably diet [56] and medications [57]. This offers opportunities to therapeutically modulate the microbiome to enhance the production of beneficial metabolites using diet, prebiotics, or pharmaceuticals.

Diet is an obvious starting point for improving microbiome health and its metabolic activity in the context of cancer [58]. In the context of immunotherapy, dietary fibre intake and, in particular, increased omega-3 (fish) consumption, collectively reflecting a Mediterranean dietary pattern, are associated with substantially improved response rates across multiple cancer types, correlating with an increased abundance of SCFA-producing bacteria [34,59,60]. One randomised controlled trial in patients with hepatocellular carcinoma undergoing oncologic treatment (including immunotherapy in a subset of patients) evaluated a structured dietary programme combining a multispecies probiotic, a prebiotic (inulin/fructooligosaccharides), and individualised dietary counselling [61]. The intervention arm showed improved progression-free survival and overall survival compared with control (Table 1). A prospective Phase I trial showed encouraging activity for camu camu supplementation in ICB-refractory melanoma and non-small cell lung cancer [73], which is backed by preclinical data [74]. A randomised controlled trial is currently underway, and results are expected soon (NCT06049576). Multiple other dietary or prebiotic intervention trials are ongoing to improve side effects or response rates and are reviewed elsewhere [58]. Moreover, even short-term dietary interventions lasting 4–5 days can increase the production of microbiome-derived metabolites in mice and humans [7,75,76]. However, while dietary interventions show some promise, they are generally difficult to standardise. A possible solution to this is to provide all meals for patients during a trial, as in an ongoing study of immunotherapy for melanoma [71]. While this design enables the collection of robust, controlled data, it is challenging to apply in routine clinical practice over the long term. Results are expected soon, but preliminary data [71] confirm that such dietary interventions are feasible and may enhance responses to ICB in randomised controlled trials (Table 1).

Isolating the dietary components responsible for beneficial effects of diets offers a potential solution to these shortcomings, resulting in oral supplements with defined compositions that can be easily standardised and administered. When targeting the microbiome, these are referred to as prebiotics, that is, food-derived formulations of compounds specifically designed to promote the growth and activity of beneficial microbiota. Fibre supplements have been proposed as supportive treatments to mitigate gastrointestinal (GI) adverse effects of chemotherapy and radiotherapy. However, a recent meta-review found largely no differences in treatment-associated diarrhoea and no differences in SCFA levels upon fibre supplementation [77], although small study sizes, variation in type of fibre, dose, and differences in symptom assessment make it difficult to draw definitive conclusions.

Supplementation of the precursor tryptophan could offer an avenue to boost the production of beneficial indole acids. Increased tryptophan intake resulted in increased serum indole acids in a mouse pancreatic cancer model [7]; however, no correlation between tryptophan intake and indole-propionic acid levels was observed in a human cohort [78], which instead showed a correlation with fibre. Tryptophan supplementation might present risks, as it is the starting point for a number of competing host and microbial pathways. For example, indoxyl sulphate, a uremic indole metabolite, has been linked to kidney cancer progression in a mouse model [79]. Supplementation with pomegranate juice, containing urolithin precursors such as ellagic acid, has been proposed and successfully trialled in various cancers [80,81], although the contribution of direct versus microbiome-dependent (i.e., urolithin-mediated) mechanisms is not firmly established. Another source of urolithin precursors is camu camu, which has been used in preclinical models and in cancer patients treated with ICB and is currently being evaluated as a treatment adjunct in a randomised controlled trial (NCT06049576).

Novel or repurposed small-molecule drugs could be used to modulate microbiota metabolism in a targeted way. For example, there is evidence that metformin can boost SCFA production

Table 1. Prospective clinical trials to increase therapy efficacy via the microbiota

Category	Intervention	Product (FMT/probiotic)	Dose/amount consumed	Indication
Probiotic	CBM588 + nivolumab/ipilimumab	CBM588 (*C. butyricum* MIYAIRI 588)	4×10^8 spores/day orally	Metastatic RCC on ICI
Probiotic	Cabozantinib + nivolumab ± CBM588	CBM588 (*C. butyricum* MIYAIRI 588)	4×10^8 spores/day orally	Treatment-naïve advanced RCC
Probiotic	Probiotic during CCRT (NPC)	Multistrain probiotic (*B. longum*, *L. lactis*, and *E. faecium*)	Three capsules twice daily for 7 weeks	Nasopharyngeal carcinoma on chemoradiotherapy
Probiotic	*S. salivarius* K12	*S. salivarius* K12 lozenges	Three lozenge/day during radiotherapy	Head & neck cancer on radiotherapy
Probiotic	BB-12 + LGG during irinotecan chemotherapy	BB-12 + LGG (Probio-Tec BG-Vcap-6.5)	2.7×10^9 CFU per capsule (50/50 BB-12 and LGG) during chemo cycles	Advanced/metastatic colorectal cancer
Probiotic/Prebiotic	LGG ± guar gum	*L. rhamnosus* GG	$1–2 \times 10^{10}$ CFU/day; 11 g guar gum on days 7–14 of each chemo cycle	CRC on 5-FU chemotherapy
Probiotic	VSL#3 during pelvic radiotherapy	VSL#3 probiotic	Two sachets/day (~9×10^{11} CFU/day)	Sigmoid/rectal/cervical cancer
Probiotic/Prebiotic	Perioperative synbiotic (CRC surgery)	Commercial synbiotic (probiotic + prebiotic)	7 days preoperative (dose varied)	Resectable colorectal cancer
Prebiotic/Diet	Structured dietary intervention	Daily multispecies probiotic + 10 g prebiotic powder (inulin/FOS) + dietary counselling	$\geq 1 \times 10^{10}$ CFU/day probiotic; 10 g prebiotic daily	Hepatocellular carcinoma
Prebiotic/Diet	Controlled high-fibre/plant-forward diet	Prepared meals (high-fibre plant-based)	30–50 g fibre/day (ramp-up) versus 20 g control	Melanoma on ICI
Postbiotic	Sodium butyrate enemas	Sodium butyrate	1–4 g/day (dose-finding)	Prostate cancer radiotherapy
FMT	FMT + pembrolizumab/axitinib	Donor FMT (capsules + enemas)	Colonoscopy under sedation after 4 l macrogol bowel prep. Maintenance at weeks 12 (±2) and 24 (±2): 150 frozen capsules per course (five capsules three times per day for 10 days), stored at –20 °C and taken ≥1 h after meals.	First-line metastatic RCC

CCRT: concurrent chemoradiotherapy; CFU: colony forming units; FOS: fructooligosaccharides; HR: hazard ratio; ICI: immune checkpoint inhibitor; NPC: nasopharyngeal carcinoma; OM: oral mucositis; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; QoL: Quality of Live; RCC: renal cell carcinoma.

[82–84] and that sulfasalazine increases butyrate production by *Faecalibacterium prausnitzii* [85]. The first systematic screens of drug–bacteria–metabolite interactions are now available [86], providing a framework for discovering pharmacological modulators of microbiome metabolism.

Overall, dietary/prebiotic supplements support has the potential to boost cancer therapy via modulation of the microbiota and the provision of metabolic precursors; however, current data are too preliminary to recommend specific diets to boost specific microbiota-derived metabolites as adjunctive therapy.

Design	Primary endpoint	Main microbiome result	Metabolite result	Main clinical result	Refs
Open-label 2:1 RCT (Phase 1)	Change in *Bifidobacterium* spp.	Increase in *Bifidobacterium* spp. only in patients receiving CBM588 who responded to treatment (exploratory)	Overall serum SCFA response not significant; increased isobutyrate and acetate; and high butyrate in responders	Primary endpoint not met. Longer PFS with CBM588 (12.7 versus 2.5 months; secondary endpoint)	[62,63]
Phase 1 randomised	Change in *Bifidobacterium* spp.	No difference in the relative abundance of *Bifidobacterium* spp.. Enrichment of Ruminococcaceae genera with CBM588 (exploratory)	Not reported	Primary endpoint not met. Higher ORR (74% versus 20%; secondary endpoint)	[64]
Double-blind RCT	Incidence of severe oral mucositis	Reduced radiochemotherapy-induced microbial disturbance	Not reported	Reduced grade ≥3 mucositis (45.7% versus 15.5%)	[65]
Double-blind RCT	Incidence of severe oral mucositis	Reversed increase of *Selenomonas* and *Acinetobacter* during RT	Not reported	Reduced incidence/duration of severe oral mucositis (36.6% versus 54.2%)	[66]
Phase 3 double-blind RCT	Prevention of grade 3/4 diarrhoea	Not reported	Not reported	Grade 3/4 diarrhoea not significantly reduced (11.8% placebo versus 7.9% probiotic)	[67]
Randomised factorial study	Chemo-related diarrhoea	Not reported	Not reported	Reduced severe diarrhoea with LGG (22% versus 37%)	[68]
Double-blind RCT	Radiation-induced diarrhoea	Not reported	Not reported	Lower incidence/severity of diarrhoea (51.8% versus 31.6%)	[69]
Double-blind RCT	Postoperative complications	Not reported	Not reported	Reduced surgical site infections (2% versus 21.4%) and reduce dIL-6 and CRP after 7 days in the intervention group	[70]
RCT	PFS/OS and QoL	Increased α-diversity; enrichment of Bifidobacterium and Lactobacillus	Not reported	PFS 9.4 vs 7.3 months; OS 27.7 versus 22.6 months	[61]
Randomised 2:1 feeding RCT	Microbiome structure and function	To be published	Not reported	Exploratory ORR: 77% (diet) versus 29% (control)	[71]
Phase 2 dose-finding RCT	Acute radiation proctitis	Not reported	Not reported	No clinical benefit	[46]
Phase 2a RCT	12-month PFS rate	Donor strain engraftment with increased α-diversity and larger β-diversity shifts versus baseline; specific strain acquisition/loss, but not total engraftment, correlated with the primary endpoint.	Not reported	12-month PFS: 70% d-FMT versus 41% p-FMT (P = 0.053; primary endpoint not met); median PFS significantly improved (24.0 versus 9.0 months; HR = 0.50, P = 0.035).	[72]

Delivery of metabolites by live bacteria

Diets and prebiotics share a key weakness (Figure 2D): interventions will have different effects depending on pre-existing microbiome composition and physiology. For example, the effect of fibre supplementation varies substantially between individuals due to their pre-existing microbiome [87–89] and potentially the consumption of other dietary compounds, such as omega-3 fatty acids. Similarly, upon ellagic acid supplementation, the urolithin profile will depend on the individual, and some individuals will not produce urolithins at all [47,90]. These interventions will therefore not be effective if the patient's microbiome is not able to convert the precursors into beneficial metabolites.

To overcome this limitation, bacteria performing the desired metabolic functions can be administered in the form of probiotics, FMT, or LBPs. With all three approaches, host microbiomes usually confer resistance to colonisation by introduced strains [91–93]. Gut dysbiosis associated with infection and treatment lowers this resistance [93], and antibiotics such as vancomycin can be used as pretreatment to open niches [92]. However, this may also induce detrimental effects on gut microbiota composition and potentially impair responses to ICB [94]. In the last part of this review, we focus on the ability of administered bacteria to boost beneficial metabolite levels. Other effects, such as antigenic immune modulation, are not considered, as they fall outside the scope of this review and are described elsewhere [95].

Taking probiotics is common among cancer patients (e.g., in a large melanoma immunotherapy cohort, 31% of patients did so [34]); however, it is often not clear whether this is beneficial or potentially harmful. In terms of microbiome metabolism, classical probiotics (*Lactobacilli* and *Bifidobacteria*) have no conclusive impact on SCFA levels [96], and their overall impact on clinical outcomes for ICB is debated, with nonsignificant trends in both positive [97] and negative [34] directions reported. A recent meta-analysis of 13 studies (out of which only two were randomised controlled trials) covering >3000 patients and diverse probiotic species found significant benefits of probiotics on ICB response in terms of overall survival (hazard ratio 95% CI: 0.46–0.73) and objective response rate (odds ratio 95% CI: 1.27–2.40) [98].

In preclinical models, probiotics have shown some potential to boost tryptophan-derived indole acids [99–101]. However, in paediatric diabetes patients, *Lactobacillus* probiotics had no effect on tryptophan metabolites [102], while in an elderly cohort, *Bifidobacteria* increased levels of 3-IPA [103]. Two randomised controlled trials reported that probiotic supplementation with either *Bifidobacterium longum, Lactobacillus lactis*, and *Enterococcus faecium* [65], or *Streptococcus salivarius* K12 [66], was associated with reduced mucositis during radiotherapy. Furthermore, two randomized controlled trials indicated that *Lactobacillus rhamnosus* GG (LGG), given either in combination with *Bifidobacterium animalis* subsp. *lactis* [67] or with guar gum soluble fibre [68], was associated with reduced chemotherapy-associated diarrhoea in patients with colorectal cancer (Table 1). Most reported randomised controlled trials of microbiome interventions do not report the impact of the intervention on metabolism, which could provide key insights into efficacy and mechanisms. A notable exception is clinical trials of the next-generation probiotic *Clostridium butyricum*, which show promise in boosting immunotherapy [62,64,104]. Follow-ups showed overall no significant increase in serum butyrate (compared with baseline), although patients with increases in butyric acid upon treatment had a higher objective response rate (ORR) compared with those who did not respond [63]. Overall, clinical research on probiotics in oncology is characterised by a lack of sufficiently powered studies and is complicated by the large number of available products and dose regimens. For example, different strains (as part of different commercial products) of the same probiotic species can vary widely in their effects on health [105]. Moreover, the engraftment of species [91] and appropriate dosages of different probiotics are often unclear.

FMT can transfer treatment-supportive microbial communities from responder patients to nonresponders, offering a potentially more potent but also more invasive treatment option. This introduces a broad diversity of microbes, including unculturable microbes, and does not require knowledge of the species and mechanisms responsible for the effect. In other diseases, FMT has been shown to increase beneficial metabolites such as SCFAs [106,107]. FMT shows promise in boosting response rates to immunotherapy in melanoma [108] and affects serum metabolites, including bile acids, histidine, propionate, and benzoate metabolites [109,110] (Table 1). A multi-donor FMT-like product (MaaT013) was found to increase SCFA and bile acid levels [111]. While there is clearly promise in using FMT to increase therapy response, as demonstrated

by recent randomised controlled trials [72,112,113], there is a risk of disturbing the metabolic balance across different sections of the GI tract [114], as well as significant challenges related to the need for donors, infection risk, and standardisation, as reviewed elsewhere [115].

Given the considerable drawbacks and complexities of FMT, it is becoming attractive to isolate the causal microbes and formulate these into standardised, scalable treatments of live microorganisms, referred to as LBPs. Several therapeutic start-ups are developing such products (reviewed in [116]), which, within the cancer field, are mainly aimed at increasing response rates to ICB. Exeliom is currently trialling an LBP containing the butyrate producer *F. prausnitzii* [117]. An eight-species consortium LBP by Vedanta Biosciences was shown to boost SCFA and secondary bile acids in healthy volunteers [92]. While the isolation methods and selection criteria of LBPs are often not made public, the available data focus on interactions between the transferred bacterial community and the immune system. Screening of metabolic activities appears to be secondary, representing a missed opportunity.

To exploit known mechanisms of beneficial bacterial metabolites and to increase efficacy, metabolic engineering could be applied to confer or increase production capacity for known therapeutic metabolites [118]. This is attractive because it could allow tighter control over metabolite production while simultaneously using species with well-established safety profiles and/or species that are genetically tractable. For example, an engineered *Bacillus subtilis* strain increased butyrate levels [119] in mice. As a rare example of using yeast for metabolite delivery, engineered *Saccharomyces cerevisiae* equipped with fine-tuned butyrate production capacities alleviated colitis in a mouse model [120]. The earlier studies use model microbes, which, while easy to engineer, might not thrive in the human gut environment. Among probiotic species, *Escherichia coli* Nissle is now established as a chassis for synthetic biology and metabolic engineering for microbiome applications (e.g., [29,121]), with several completed clinical trials. Alternatively, probiotic lactic acid bacteria are a potentially attractive, safe chassis for delivering molecules in the gut [122]; however, developments on this front have been slow due to poor genetic tractability. The use of laboratory evolution techniques to increase beneficial metabolite production [123–125] represents a possible alternative to classical genetic engineering. Overall, metabolic engineering has the potential to improve precision microbiome interventions; however, it also adds significant regulatory hurdles and might hamper acceptance by patients.

Regulatory and commercial considerations

Regulatory routes and oversight

Prebiotics, postbiotics, and probiotics are usually sold directly to consumers as dietary health supplements. Regulations vary across the world [126], but, in general, they follow food standards rather than those for drug products. The increasing number of available products, combined with loose regulation and enforcement, means that the purity of commercially available supplements varies drastically. Dietary supplements can be contaminated with undeclared pharmaceuticals [127], microplastics [128], or pathogens [129]. Likewise, probiotics can contain antimicrobial resistance genes [130]. These concerning developments require greater awareness by clinicians [131] and testing by independent third-party laboratories.

In the EU, clinical trials of supplements are not centrally registered in the Clinical Trials Information System (CTIS); approval from national competent authorities and ethics committees is required. Data from such trials can then be used to substantiate health claims associated with the products. Health claims are evaluated by the European Food Safety Authority (EFSA) and listed in the EU Register of Health Claims (https://ec.europa.eu/food/food-feed-portal/screen/health-claims/eu-register). Notably, it contains no approved health claims relating to probiotics or key postbiotics to date.

In contrast to prebiotics, postbiotics, and probiotics, LBPs are regulated as drug products [132,133]. The FDA has developed specific guidance for LBPs, relating to documenting strain origins and history, genetic and *in vitro* characterisation, and quality assurance. Commensal bacteria present low safety risks, as long as they contain no antimicrobial resistance genes, which streamlines toxicological assessments. However, drug-grade production standards (Good Manufacturing Practice, **GMP**) are usually required, making even small clinical trials expensive to set up.

Intellectual property and commercial landscape

The divergent regulatory pathways for supplements and drug products result in different commercial landscapes. For supplements in the EU, new health claims substantiated with clinical trials can be used exclusively for 5 years by the applicant who provided the data. This does, however, not exclude others from selling the same supplement, and, after the 5-year period, the claim can be applied generically to all identical compounds by any vendor. Overall, this means that intellectual property protection—and thereby commercial incentives—are substantially weaker compared with novel drug entities, meaning that promising preclinical findings and small investigator-led trials are often not followed up with larger trials. Furthermore, doctors can often only recommend supplements, but healthcare providers do not routinely cover their costs. While the supplement market is highly competitive, with many established brands, LBP development is driven largely by start-up companies [116]. The costs for research and development, manufacturing according to **GMP** standards, and clinical trials are substantial, and patent-protecting microbial strains for therapeutic use is not as straightforward as for novel drug molecules. These factors together result in a challenging business landscape for developers of LBPs. Although many early companies have failed [116], there are several ongoing clinical trials of LBPs for cancer applications due to report soon: for example, NCT06540391 (Phase 1b, Microbiotica); NCT06253611, NCT06448572, and NCT06551272 (all Phase 2 by Exeliom). Successful outcomes could raise prospects for renewed interest and investment in supplements and LBPs tailored to support cancer therapy.

Concluding remarks

It is now widely recognised that cancer therapy response can be influenced by microbiome-derived metabolites. As knowledge of context-dependent and differential effects across cancer types, therapy modalities, and action sites emerges (Boxes 1 and 2), translating these into precision interventions shows promise. Focusing on microbial metabolites (rather than individual species) is attractive, as they represent a point of convergence for functionally similar but compositionally different microbiomes. An advantage of metabolite-boosting interventions is that their effectiveness can be monitored by measuring metabolite levels in blood or stool, although these might not always provide an accurate picture of metabolic fluxes between the gut and host. For example, SCFAs are largely consumed by the colonic epithelium, and measuring faecal SCFAs might not capture the success or failure of SCFA-boosting interventions [134,135].

Despite the number of prebiotic, probiotic, and postbiotics available as supplements, there are still almost no scientifically validated therapeutic avenues available to patients and clinicians. Supplements face issues around standardisation, quality assurance, and limited high-quality in-human data across diverse cancer types and demographics. This is because the regulatory landscape offers low commercial incentives to conduct such trials. Academic and public science should do more in this area to identify existing products that can benefit cancer patients, and regulators and governments should consider how to better incentivise commercial clinical trials.

Contrarily, LBP development promises clinically validated, regulated drug products, although the approval of the first LBP supporting cancer therapy is likely at least a few years away. A key

Outstanding questions

How large are the effect sizes of metabolite-boosting interventions in clinical practice? That is, how much can microbiome interventions shift response rates?

What is the relative importance of microbial metabolites versus direct bacteria–host-driven immune modulations or other indirect effects (quorum sensing or microbiome–drug interactions) in boosting antitumour immune responses?

Where in the body do microbial metabolites act, and how can they be targeted to specific organs?

Do related microbial metabolites, such as different indole acids, have redundant functions?

With most mechanistic work done in mouse models, how do these findings translate to humans, particularly with regard to metabolite and therapy doses, physiological differences between mice and humans, and microbiome differences?

What is the context that determines metabolite–therapy response interactions? Why do some metabolites, such as indole acids, sometimes appear to have procancer and sometimes anticancer effects?

What are the metabolic and ecological interactions of probiotics and live biotherapeutic products with diverse microbiomes? How can these be stabilised to achieve consistent outcomes?

How can we measure the success of metabolite-based interventions? How meaningful are serum and faecal concentrations as biomarkers?

Is there potential in metabolite-based interventions for cancer prevention? Are different metabolites required for prevention versus therapy, or are they the same?

How can we finance or better incentivise Phase 2/3 clinical trials on supplement-type products?

challenge in this area is the complex interactions of LBPs with heterogeneous microbiomes [136], and lessons have been learned from the failing of many/most first-generation LBP companies. For example, newer companies embrace precision engineering and microbial consortia, which act via a 'belts and braces' approach or can exploit synergisms such as cross-feeding.

The discovery of the clinical importance of microbiota-derived metabolites in the cancer therapy setting blurs the traditionally sharp distinction between dietary supplements (taken to support health) and therapeutics (taken to treat disease). As startups and large companies continue to innovate in the onco-microbiome field, different routes into clinical practice are conceivable: as therapeutics, as medical food ('food for special medical purposes'), via clinical dietitians' and nutritionists' advice, and over-the-counter supplements. With increasing research activity in this area (see Outstanding questions), there is hope that such solutions will offer cost-effective avenues to boost the response to existing cancer therapies for the benefit of patients and healthcare systems globally.

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Declaration of interests

K.R.P. is a cofounder of Cambiotics ApS and an inventor on related patents. K.R.P. is also an inventor on other patents relating to the metabolic engineering of lactic acid bacteria. T.D.L. is a cofounder and the Chief Scientific Officer (CSO) of Microbiotica Ltd and an inventor on related patents. The other authors declare no competing interests. N.G. has received funding via the UKE from Roche and GSK. All outside the submitted work.

References

1. Pascal Andreu, V. *et al.* (2023) gutSMASH predicts specialized primary metabolic pathways from the human gut microbiota. *Nat. Biotechnol.* 41, 1416–1423
2. Kang, X. *et al.* (2023) *Roseburia intestinalis* generated butyrate boosts anti-PD-1 efficacy in colorectal cancer by activating cytotoxic $CD8^+$ T cells. *Gut* 72, 2112–2122
3. Jia, D. *et al.* (2024) Microbial metabolite enhances immunotherapy efficacy by modulating T cell stemness in pan-cancer. *Cell* 187, 1651–1665.e21
4. Xiao, H.-w. *et al.* (2020) Gut microbiota-derived indole 3-propionic acid protects against radiation toxicity via retaining acyl-CoA-binding protein. *Microbiome* 8, 69
5. Xie, L.-W. *et al.* (2024) Microbiota-derived I3A protects the intestine against radiation injury by activating AhR/IL-10/Wnt signaling and enhancing the abundance of probiotics. *Gut Microbes* 16, 2347722
6. He, Y. *et al.* (2021) Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic $CD8^+$ T cell immunity. *Cell Metab.* 33, 988–1000.e7
7. Tintelnot, J. *et al.* (2023) Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. *Nature* 615, 168–174
8. Rodríguez-García, A. *et al.* (2025) Microbiota-derived urolithin A in monoclonal gammopathies and multiple myeloma therapy. *Microbiome* 13, 56
9. Phelps, C.M. *et al.* (2025) Exercise-induced microbiota metabolite enhances CD8 T cell antitumor immunity promoting immunotherapy efficacy. *Cell* 188, 5680–5700.e28
10. He, K.-Y. *et al.* (2023) *Akkermansia muciniphila* protects the intestine from irradiation-induced injury by secretion of propionic acid. *Gut Microbes* 15, 2293312
11. Morad, G. *et al.* (2022) Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. *Cell* 185, 576
12. Stein-Thoeringer, C.K. *et al.* (2023) A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy. *Nat. Med.* 29, 906–916
13. Ma, X. *et al.* (2021) Characterization of a real-world response variable and comparison with RECIST-based response rates from clinical trials in advanced NSCLC. *Adv. Ther.* 38, 1843–1859
14. Fong, W. *et al.* (2023) *Lactobacillus gallinarum*-derived metabolites boost anti-PD1 efficacy in colorectal cancer by inhibiting regulatory T cells through modulating IDO1/Kyn/AHR axis. *Gut* 72, 2272–2285
15. Xu, H. *et al.* (2024) Effect of indole 3-propionic acid from microbiota on the immunity of $CD8^+$ T cell to improve chemotherapy of colorectal cancer. *J. Clin. Oncol.* 42, e15194
16. Vaaben, T.H. *et al.* (2025) Modulating tumor immunity using advanced microbiome therapeutics producing an indole metabolite. *EMBO Rep.* 26, 1688–1708
17. Bender, M.J. *et al.* (2023) Dietary tryptophan metabolite released by intratumoral *Lactobacillus reuteri* facilitates immune checkpoint inhibitor treatment. *Cell* 186, 1846–1862.e26
18. Li, W. *et al.* (2025) Gut *Parabacteroides distasonis*-derived indole-3-acetic acid promotes phospholipid remodeling and enhances ferroptosis sensitivity via the AhR-FASN axis in bladder cancer. *Adv. Sci. (Weinh.)* 12, e04688
19. Hezaveh, K. *et al.* (2022) Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity. *Immunity* 55, 324–340.e8
20. Wang, G. *et al.* (2024) Microbiota-derived indoles alleviate intestinal inflammation and modulate microbiome by microbial cross-feeding. *Microbiome* 12, 59
21. Wang, J. *et al.* (2025) Gut microbiota derived indole-3-acetic acid ameliorates precancerous inflammatory intestinal milieu to inhibit tumorigenesis through IL-35. *J. ImmunoTher. Cancer* 13, e011155

22. Li, Q. *et al.* (2025) Microbial metabolite indole-3-propionic acid drives mitochondrial respiration in CD4$^+$ T cells to confer protection against intestinal inflammation. *Nat. Metab.* 7, 2510–2530
23. Ternes, D. *et al.* (2022) The gut microbial metabolite formate exacerbates colorectal cancer progression. *Nat. Metab.* 4, 458–475
24. Zhou, Y. *et al.* (2025) Gut microbiota derived metabolite trimethylamine N-oxide influences prostate cancer progression via the p38/HMOX1 pathway. *Front. Pharmacol.* 15, 1526051
25. Mirji, G. *et al.* (2022) The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer. *Sci. Immunol.* 7, eabn0704
26. Wang, H. *et al.* (2022) The microbial metabolite trimethylamine N-oxide promotes antitumor immunity in triple-negative breast cancer. *Cell Metab.* 34, 581–594.e8
27. Nakazawa, M. *et al.* (2025) Abstract 2222: trimethylamine-N-oxide (TMAO) mediates immunotherapy resistance in advanced HCC. *Cancer Res.* 85, 2222
28. Wang, N. *et al.* (2025) Gut microbiota-derived indoleacetic acid attenuates neuroinflammation and neurodegeneration in glaucoma through AhR/rage pathway. *J. Neuroinflammation* 22, 179
29. Wei, W. *et al.* (2024) Psychological stress-induced microbial metabolite indole-3-acetate disrupts intestinal cell lineage commitment. *Cell Metab.* 36, 466–483.e7
30. Kim, D.K. *et al.* (2024) Exploring aryl hydrocarbon receptor expression and distribution in the tumor microenvironment, with a focus on immune cells, in various solid cancer types. *Front. Immunol.* 15, 1330228
31. Luu, M. *et al.* (2021) Microbial short-chain fatty acids modulate CD8$^+$ T cell responses and improve adoptive immunotherapy for cancer. *Nat. Commun.* 12, 4077
32. Guo, H. *et al.* (2020) Multi-omics analyses of radiation survivors identify radioprotective microbes and metabolites. *Science* 370, eaay9097
33. Nomura, M. *et al.* (2020) Association of short-chain fatty acids in the gut microbiome with clinical response to treatment with nivolumab or pembrolizumab in patients with solid cancer tumors. *JAMA Netw. Open* 3, e202895
34. Spencer, C.N. *et al.* (2021) Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science* 374, 1632–1640
35. Ma, C. *et al.* (2018) Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science* 360, eaan5931
36. Varanasi, S.K. *et al.* (2025) Bile acid synthesis impedes tumor-specific T cell responses during liver cancer. *Science* 387, 192–201
37. Agarwal, P. *et al.* (2025) Microbial metabolite drives ageing-related clonal haematopoiesis via ALPK1. *Nature* 642, 201–211
38. Mager, L.F. *et al.* (2020) Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. *Science* 369, 1481–1489
39. Denk, D. *et al.* (2022) Expansion of T memory stem cells with superior anti-tumor immunity by urolithin A-induced mitophagy. *Immunity* 55, 2059–2073.e8
40. Rogovskii, V. *et al.* (2024) Urolithin A increases the natural killer activity of PBMCs in patients with prostate cancer. *Front. Pharmacol.* 15, 1503317
41. Han, S. *et al.* (2021) A metabolomics pipeline for the mechanistic interrogation of the gut microbiome. *Nature* 595, 415–420
42. Miller, A.A. *et al.* (1987) Clinical pharmacology of sodium butyrate in patients with acute leukemia. *Eur. J. Cancer Clin. Oncol.* 23, 1283–1287
43. Green, C.G. *et al.* (2024) Investigating serum concentration profiles of orally ingested short-chain fatty acid supplements. *Food Funct.* 15, 11525–11536
44. Cheatham, S. *et al.* (2024) Sodium butyrate alleviates chemotherapy induced gastrointestinal toxicity. *J. Pharmacol. Exp. Ther.* 389, 62–63
45. Cannizzaro, R. *et al.* (2025) Microencapsulated sodium butyrate in the prevention of acute radiotherapy proctitis: single-center prospective study. *J. Clin. Med.* 14, 4783
46. Maggio, A. *et al.* (2014) Daily sodium butyrate enema for the prevention of radiation proctitis in prostate cancer patients undergoing radical radiation therapy: results of a multicenter randomized placebo-controlled dose-finding phase 2 study. *Int. J. Radiat. Oncol. Biol. Phys.* 89, 518–524
47. Singh, A. *et al.* (2022) Direct supplementation with urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population. *Eur. J. Clin. Nutr.* 76, 297–308
48. Cao, S. *et al.* (2024) A serine-conjugated butyrate prodrug with high oral bioavailability suppresses autoimmune arthritis and neuroinflammation in mice. *Nat. Biomed. Eng.* 8, 611–627
49. Shashni, B. and Nagasaki, Y. (2023) Short-chain fatty acid-releasing nano-prodrugs for attenuating growth and metastasis of melanoma. *Acta Biomater.* 159, 226–236
50. Wang, R. *et al.* (2023) Treatment of peanut allergy and colitis in mice via the intestinal release of butyrate from polymeric micelles. *Nat. Biomed. Eng.* 7, 38–55
51. Mu, Y. *et al.* (2021) Polyvinyl butyrate nanoparticles as butyrate donors for colitis treatment. *ACS Appl. Bio Mater.* 4, 2335–2341
52. Sacco, P. *et al.* (2017) Butyrate-loaded chitosan/hyaluronan nanoparticles: a suitable tool for sustained inhibition of ROS release by activated neutrophils. *Macromol. Biosci.* 17, 1700214
53. Minelli, R. *et al.* (2012) Cholesteryl butyrate solid lipid nanoparticles inhibit the adhesion and migration of colon cancer cells. *Br. J. Pharmacol.* 166, 587–601
54. Nezhadhossein, B. *et al.* (2025) Efficacy of urolithin B-loaded mesoporous silica nanoparticles modified with graphene quantum dots against MCF-7 breast cancer cells. *Sci. Rep.* 15, 25473
55. Zhu, Y. *et al.* (2025) 3-indoleacetic acid-modified chondroitin sulfate-mediated paclitaxel nanocrystal assembly for the treatment of pancreatic cancer. *ACS Appl. Mater. Interfaces* 17, 9035–9046
56. David, L.A. *et al.* (2014) Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505, 559–563
57. Forslund, S.K. *et al.* (2021) Combinatorial, additive and dose-dependent drug–microbiome associations. *Nature* 600, 500–505
58. Abdeen, S.K. *et al.* (2025) Diet-microbiome interactions in cancer. *Cancer Cell* 43, 680–707
59. Simpson, R.C. *et al.* (2022) Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome. *Nat. Med.* 28, 2344–2352
60. Bolte, L.A. *et al.* (2023) Association of a Mediterranean diet with outcomes for patients treated with immune checkpoint blockade for advanced melanoma. *JAMA Oncol.* 9, 705–709
61. Shen, X. *et al.* (2026) Dietary intervention reshapes gut microbiota and lipid metabolism to enhance anti-tumor immunity and prognosis in hepatocellular carcinoma: a randomized controlled trial. *BMC Cancer* 26, 42
62. Dizman, N. *et al.* (2022) Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. *Nat. Med.* 28, 704–712
63. Dizman, N. *et al.* (2023) Assessment of short-chain fatty acid (SCFA) and circulating cytokine trends in a clinical trial of nivolumab/ipilimumab and CBM588 in metastatic renal cell carcinoma (mRCC). *J. Clin. Oncol.* 41, 4556
64. Ebrahimi, H. *et al.* (2024) Cabozantinib and nivolumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. *Nat. Med.* 30, 2576–2585
65. Jiang, C. *et al.* (2019) A randomized, double-blind, placebo-controlled trial of probiotics to reduce the severity of oral mucositis induced by chemoradiotherapy for patients with nasopharyngeal carcinoma. *Cancer* 125, 1081–1090
66. Peng, X. *et al.* (2024) *Streptococcus salivarius* K12 alleviates oral mucositis in patients undergoing radiotherapy for malignant head and neck tumors: a randomized controlled trial. *J. Clin. Oncol.* 42, 1426–1435
67. Mego, M. *et al.* (2023) Randomized double-blind, placebo-controlled multicenter phase III study of prevention of irinotecan-induced diarrhea by a probiotic mixture containing

Bifidobacterium BB-12® *Lactobacillus rhamnosus* LGG® in colorectal cancer patients. *Front. Oncol.* 13, 1168654
68. Österlund, P. *et al.* (2007) *Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. *Br. J. Cancer* 97, 1028–1034
69. Delia, P. *et al.* (2007) Use of probiotics for prevention of radiation-induced diarrhea. *World J. Gastroenterol.* 13, 912–915
70. Polakowski, C.B. *et al.* (2019) Impact of the preoperative use of synbiotics in colorectal cancer patients: a prospective, randomized, double-blind, placebo-controlled study. *Nutrition* 58, 40–46
71. Qiu, Y. *et al.* (2025) Clinical outcomes of the DIET study: a randomized controlled phase 2 trial of a high fiber diet intervention (HFDI) in patients with melanoma receiving immune checkpoint blockade (ICB). *J. Clin. Oncol.* 43, 9511
72. Porcari, S. *et al.* (2026) Fecal microbiota transplantation plus pembrolizumab and axitinib in metastatic renal cell carcinoma: the randomized phase 2 TACITO trial. *Nat. Med.* 32, 1316–1324
73. Maillou, J. *et al.* (2025) Abstract 2223: phase I clinical trial combining camu camu prebiotic enriched with castalagin modulates bile acids and metabolites in combination with cancer immunotherapy in patients with treatment-naïve lung cancer and PD-1 refractory melanoma (NCT05303493). *Cancer Res.* 85, 2223
74. Messaoudene, M. *et al.* (2022) A natural polyphenol exerts antitumor activity and circumvents anti-PD-1 resistance through effects on the gut microbiota. *Cancer Discov.* 12, 1070–1087
75. Siracusa, F. *et al.* (2024) Diet and immune response: how today's plate shapes tomorrow's health. *Trends Immunol.* 45, 4–10
76. Siracusa, F. *et al.* (2023) Short-term dietary changes can result in mucosal and systemic immune depression. *Nat. Immunol.* 24, 1473–1486
77. Gardiner, B. *et al.* (2025) The impact of fibre and prebiotic interventions on outcomes in cancer and haematopoietic stem cell transplantation: a systematic review. *Clin. Nutr.* 44, 86–100
78. Sehgal, R. *et al.* (2022) Indolepropionic acid, a gut bacteria-produced tryptophan metabolite and the risk of type 2 diabetes and non-alcoholic fatty liver disease. *Nutrients* 14, 4695
79. Li, J.-R. *et al.* (2025) Indoxyl sulfate promoted glutamine metabolism and cell proliferation in urothelial carcinoma involving Runx2. *Biomed. Pharmacother.* 193, 118865
80. Nuñez-Sánchez, M.A. *et al.* (2017) Gene expression changes in colon tissues from colorectal cancer patients following the intake of an ellagitannin-containing pomegranate extract: a randomized clinical trial. *J. Nutr. Biochem.* 42, 126–133
81. Tan, Z. *et al.* (2024) Ellagic acid inhibits tumor growth and potentiates the therapeutic efficacy of sorafenib in hepatocellular carcinoma. *Heliyon* 10, e23931
82. Mueller, N.T. *et al.* (2021) Metformin affects gut microbiome composition and function and circulating short-chain fatty acids: a randomized trial. *Diabetes Care* 44, 1462–1471
83. de la Cuesta-zuluaga, J. *et al.* (2017) Metformin is associated with higher relative abundance of mucin-degrading *Akkermansia muciniphila* and several short-chain fatty acid-producing microbiota in the gut. *Diabetes Care* 40, 54–62
84. Wu, H. *et al.* (2017) Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. *Nat. Med.* 23, 850–858
85. Lima, S.F. *et al.* (2024) The gut microbiome regulates the clinical efficacy of sulfasalazine therapy for IBD-associated spondyloarthritis. *Cell Rep. Med.* 5, 101431
86. Kamrad, S. *et al.* (2025) Impact of drugs and environmental contaminants on amine production by gut bacteria. *Mol. Syst. Biol.* 21, 1351–1370
87. Murga-Garrido, S.M. *et al.* (2021) Gut microbiome variation modulates the effects of dietary fiber on host metabolism. *Microbiome* 9, 117
88. Venkataraman, A. *et al.* (2016) Variable responses of human microbiomes to dietary supplementation with resistant starch. *Microbiome* 4, 33
89. Holmes, Z.C. *et al.* (2022) Microbiota responses to different prebiotics are conserved within individuals and associated with habitual fiber intake. *Microbiome* 10, 114
90. Tomás-Barberán, F.A. *et al.* (2014) Ellagic acid metabolism by human gut microbiota: consistent observation of three urolithin phenotypes in intervention trials, independent of food source, age, and health status. *J. Agric. Food Chem.* 62, 6535–6538
91. Zmora, N. *et al.* (2018) Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. *Cell* 174, 1388–1405.e21
92. Dsouza, M. *et al.* (2022) Colonization of the live biotherapeutic product VE303 and modulation of the microbiota and metabolites in healthy volunteers. *Cell Host Microbe* 30, 583–598.e8
93. Ianiro, G. *et al.* (2022) Variability of strain engraftment and predictability of microbiome composition after fecal microbiota transplantation across different diseases. *Nat. Med.* 28, 1913–1923
94. Glitza, I.C. *et al.* (2024) Randomized placebo-controlled, biomarker-stratified phase Ib microbiome modulation in melanoma: impact of antibiotic preconditioning on microbiome and immunity. *Cancer Discov.* 14, 1161–1175
95. Naghavian, R. *et al.* (2023) Microbial peptides activate tumour-infiltrating lymphocytes in glioblastoma. *Nature* 617, 807–817
96. de Almeida Brasiel, P.G. and Potente Dutra Luquetti, S.C. (2025) Effects of probiotics supplementation on short-chain fatty acids: a systematic review of randomized controlled trials. *Nutr. Rev.* 83, 1892–1907
97. Tong, L. *et al.* (2024) Evaluating oral probiotic supplements as complementary treatment in advanced lung cancer patients receiving ICIs: a prospective real-world study. *Cancer Control* 31, 10732748241253960
98. Zhao, S. *et al.* (2025) Assessing the impact of probiotics on immunotherapy effectiveness and antibiotic-mediated resistance in cancer: a systematic review and meta-analysis. *Front. Immunol.* 16, 1538969
99. Zhang, Q. *et al.* (2023) *Lactobacillus plantarum*-derived indole-3-lactic acid ameliorates colorectal tumorigenesis via epigenetic regulation of $CD8^+$ T cell immunity. *Cell Metab.* 35, 943–960.e9
100. Zhang, Z. *et al.* (2025) *Lactobacillus gasseri* LGV03-derived indole-3-lactic acid ameliorates immune response by activating aryl hydrocarbon receptor. *Microb. Cell Factories* 24, 34
101. Xia, Y. *et al.* (2023) *Lactobacillus*-derived indole-3-lactic acid ameliorates colitis in cesarean-born offspring via activation of aryl hydrocarbon receptor. *iScience* 26, 108279
102. Mondanelli, G. *et al.* (2020) Effect of probiotic administration on serum tryptophan metabolites in pediatric type 1 diabetes patients. *Int. J. Tryptophan Res.* 13, 1178646920956646
103. Kim, C.-S. *et al.* (2023) Gut microbiota indole-3-propionic acid mediates neuroprotective effect of probiotic consumption in healthy elderly: a randomized, double-blind, placebo-controlled, multicenter trial and *in vitro* study. *Clin. Nutr.* 42, 1025–1033
104. Tomita, Y. *et al.* (2023) Association of *Clostridium butyricum* therapy using the live bacterial product CBM588 with the survival of patients with lung cancer receiving chemoimmunotherapy combinations. *Cancers (Basel)* 16, 47
105. McFarland, L.V. *et al.* (2018) Strain-specificity and disease-specificity of probiotic efficacy: a systematic review and meta-analysis. *Front. Med. (Lausanne)* 5, 124
106. Paramsothy, S. *et al.* (2019) Specific bacteria and metabolites associated with response to fecal microbiota transplantation in patients with ulcerative colitis. *Gastroenterology* 156, 1440–1454.e2
107. El-Salhy, M. *et al.* (2021) Changes in fecal short-chain fatty acids following fecal microbiota transplantation in patients with irritable bowel syndrome. *Neurogastroenterol. Motil.* 33, e13983
108. Baruch, E.N. *et al.* (2021) Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. *Science* 371, 602–609
109. Davar, D. *et al.* (2021) Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science* 371, 595–602
110. Routy, B. *et al.* (2023) Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial. *Nat. Med.* 29, 2121–2132
111. Malard, F. *et al.* (2023) Pooled allogeneic faecal microbiota MaaT013 for steroid-resistant gastrointestinal acute graft-

versus-host disease: a single-arm, multicentre phase 2 trial. *EClinicalMedicine* 62, 102111
112. Duttagupta, S. *et al.* (2026) Fecal microbiota transplantation plus immunotherapy in non-small cell lung cancer and melanoma: the phase 2 FMT-LUMINate trial. *Nat. Med.* 32, 1337–1350
113. Fernandes, R. *et al.* (2026) Fecal microbiota transplantation plus immunotherapy in metastatic renal cell carcinoma: the phase 1 PERFORM trial. *Nat. Med.* 32, 1325–1336
114. DeLeon, O. *et al.* (2025) Microbiome mismatches from microbiota transplants lead to persistent off-target metabolic and immunomodulatory effects. *Cell* 188, 3927–3941.e13
115. Karimi, M. *et al.* (2024) Safety and efficacy of fecal microbiota transplantation (FMT) as a modern adjuvant therapy in various diseases and disorders: a comprehensive literature review. *Front. Immunol.* 15, 1439176
116. Pribyl, A.L. *et al.* (2025) A decade of advances in human gut microbiome-derived biotherapeutics. *Nat. Microbiol.* 10, 301–312
117. Bredon, M. *et al.* (2024) *Faecalibaterium prausnitzii* strain EXL01 boosts efficacy of immune checkpoint inhibitors. *Oncoimmunology* 13, 2374954
118. Ballister, E.R. *et al.* (2025) The emerging landscape of engineered bacteria cancer therapies. *Nat. Biotechnol.* 43, 672–676
119. Wang, L. *et al.* (2022) Positive interventional effect of engineered butyrate-producing bacteria on metabolic disorders and intestinal flora disruption in obese mice. *Microbiol. Spectrum* 10, e01147-21
120. Wu, J. *et al.* (2024) A tailored series of engineered yeasts for the cell-dependent treatment of inflammatory bowel disease by rational butyrate supplementation. *Gut Microbes* 16, 2316575
121. Dimopoulou, C. *et al.* (2023) An engineered *Escherichia coli* Nissle 1917 increase the production of indole lactic acid in the gut. *FEMS Microbiol. Lett.* 370, fnad027
122. Levit, R. *et al.* (2022) Use of genetically modified lactic acid bacteria and bifidobacteria as live delivery vectors for human and animal health. *Gut Microbes* 14, 2110821
123. Leeflang, J. *et al.* (2025) Evolutionary adaptation of probiotics in the gut: selection pressures, optimization strategies, and regulatory challenges. *NPJ Biofilms Microbiomes* 11, 96
124. Konstantinidis, D. *et al.* (2021) Adaptive laboratory evolution of microbial co-cultures for improved metabolite secretion. *Mol. Syst. Biol.* 17, e10189
125. Jouhten, P. *et al.* (2022) Predictive evolution of metabolic phenotypes using model-designed environments. *Mol. Syst. Biol.* 18, e10980
126. Di Martino, M. (2025) *Food Safety in Personalized Nutrition – A Focus on Food Supplements and Functional Foods*, FAO
127. White, C.M. (2022) Continued risk of dietary supplements adulterated with approved and unapproved drugs: assessment of the US Food and Drug Administration's tainted supplements database 2007 through 2021. *J. Clin. Pharmacol.* 62, 928–934
128. Panneerselvan, L. *et al.* (2024) Fibrous foes: first report on insidious microplastic contamination in dietary fiber supplements. *Environ. Pollut.* 363, 125248
129. Dlugaszewska, J. *et al.* (2019) Are dietary supplements containing plant-derived ingredients safe microbiologically? *Saudi Pharm. J.* 27, 240–245
130. Tian, Q. *et al.* (2025) Evaluating the health risk of probiotic supplements from the perspective of antimicrobial resistance. *Microbiol. Spectrum* 13, e0001924
131. Brykman, M.C. *et al.* (2022) What should clinicians know about dietary supplement quality? *AMA J. Ethics* 24, E382–E389
132. Rodriguez, J. *et al.* (2025) The regulatory framework for microbiome-based therapies: insights into European regulatory developments. *NPJ Biofilms Microbiomes* 11, 53
133. Paquet, J.-C. *et al.* (2021) Entering first-in-human clinical study with a single-strain live biotherapeutic product: input and feedback gained from the EMA and the FDA. *Front. Med. (Lausanne)* 8, 716266
134. Oliver, A. *et al.* (2021) High-fiber, whole-food dietary intervention alters the human gut microbiome but not fecal short-chain fatty acids. *mSystems* 6, e00115–e00121
135. Arnoldini, M. *et al.* (2025) Quantifying the varying harvest of fermentation products from the human gut microbiota. *Cell* 188, 5332–5342.e16
136. Henry, L.P. and Bergelson, J. (2025) Applying ecological principles to microbiome engineering. *Nat. Microbiol.* 10, 2111–2121