Cancer Biome and Targeted Therapy
ISSN: 3070-9989
www.cancerbiometherapy.com

REVIEW · OPEN ACCESS

Microbiome-Modulating Nanoplatforms for Breast Cancer Therapy

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Received May 8, 2026
Accepted August 11, 2026
Published November 15, 2026
DOI: 10.66505/cbtt.v1i4.59

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Abstract

Breast tumors comprise interacting malignant, stromal, immune, and microbial compartments, while gut microbial communities can influence systemic immunity, drug metabolism, and therapeutic response. Emerging evidence therefore positions the microbiome as a potential modifier of breast cancer progression and treatment efficacy rather than merely a passive correlate of disease. Nanotechnology offers experimental approaches to couple tumor-directed drug delivery with selective manipulation of intratumoral or intestinal microbiota. Liposomal, lipid-based, inorganic, biomimetic, and biohybrid platforms have been used to reduce tumor-associated bacteria, alter microbial communities or metabolites, and modify antitumor immune responses. Several platforms further combine microbiota modulation with chemotherapy, immunotherapy, ferroptosis induction, or externally activated treatment. However, improved tumor control cannot necessarily be attributed to microbial modulation because many of these systems independently alter drug exposure, tumor-cell viability, oxidative stress, or immune activity. Evidence for microbiota dependence remains largely preclinical and is frequently derived from experimentally colonized or bacteria-enriched tumor models. Low microbial biomass, contamination risk, interpatient microbiome heterogeneity, methodological variability, ecological consequences of microbial depletion, manufacturing complexity, and the absence of clinical validation further constrain translation. This review critically evaluates microbiome-modulating nanoplatforms in breast cancer, distinguishes microbiota-associated from microbiota-dependent therapeutic effects, and defines the mechanistic, analytical, and clinical evidence needed to establish microbiome targeting as a viable component of precision breast cancer therapy.

Keywords: Breast cancer; intratumoral microbiome; gut microbiome; nanomedicine; microbiome-targeted therapy; therapeutic resistance; tumor microenvironment; precision oncology.

1. Introduction

Breast cancer remains a major contributor to cancer morbidity and mortality worldwide. Therapeutic challenges are particularly evident in triple-negative breast cancer (TNBC), where the absence of estrogen receptor, progesterone receptor, and HER2 expression limits established receptor-directed treatment options and contributes to substantial molecular and clinical heterogeneity (1–3). Traditionally, tumor biology has been interpreted primarily through genetic alterations and dysregulated cellular processes (4). Tumors comprise interacting malignant, stromal, immune, and microbial components that can influence disease progression and therapeutic response (5, 6).

The role of microorganisms in carcinogenesis has been recognized for centuries (7). Historical observations of tumor regression following bacterial infections prompted William B. Coley to investigate bacterial preparations as experimental cancer treatments. His early clinical reports described the use of bacterial products in patients with inoperable malignancies, providing a historical foundation for subsequent investigations of bacteria-based cancer therapy (7–9). In contrast, the identification of microorganisms capable of causing cancer, such as the Rous Sarcoma Virus and Epstein-Barr virus, indicates that microorganisms may initiate and promote tumorigenesis (10–12).

Next-generation sequencing and culture-independent methods have identified microbial signatures in multiple tumor types, challenging the historical view that tumor tissues are sterile (13, 14). Microbiota consisting of bacteria, fungi, and viruses have now been identified across a wide range of cancer types, including breast cancer (15, 16). Intratumoral microbiota may originate through translocation across disrupted epithelial barriers, migration from adjacent tissues, or hematogenous dissemination (17, 18). Notably, intratumoral microbiota exhibit tumor-type-specific heterogeneity and spatial organization within the tumor microenvironment (19, 20).

Experimental evidence indicates that at least some intratumoral microorganisms can influence tumor biology rather than functioning solely as passive residents (18). Mechanistically, microbes influence cancer progression through various pathways, such as epigenetic reprogramming, metabolic alterations, DNA damage, and modulation of oncogenic signaling (16, 21). They also shape the tumor immune microenvironment (TIME) by promoting immune evasion, regulating inflammatory responses, or enhancing antitumor immunity (22). In breast cancer, microbial dysbiosis has been increasingly associated with metastasis, tumor initiation, and resistance to chemotherapy and immunotherapy (23). Studies of human breast tissue have detected bacterial DNA and cultivable bacteria, including in samples from women without breast cancer (24, 25). Human breast-tissue profiling identified microbial differences between women with and without breast cancer, and selected bacterial isolates induced DNA damage in vitro (26, 27). Microbial differences associated with breast cancer have been reported, and selected tumor-resident bacteria promoted metastatic colonization in mouse models; these findings do not establish that microbial changes initiate breast cancer in patients (28, 29). Diet, adiposity, antibiotic exposure, hormonal status, aging, environmental exposures, and other host factors can influence microbial composition, although their specific contribution to breast-associated microbial communities remains incompletely defined (26, 28, 30).

The intratumoral microbiome has also been implicated in treatment resistance, although the magnitude and clinical relevance of this contribution appear to vary by tumor type, microbial taxa, and therapeutic context. Intratumoral bacteria can directly metabolize certain chemotherapeutic agents, as demonstrated by bacterial inactivation of gemcitabine and the resulting drug resistance in experimental tumor models (31). Microorganisms may also alter drug bioavailability and influence therapeutic penetration through

additional mechanisms (32). Furthermore, gut microorganisms can disrupt immune response pathways, limiting immunotherapy efficacy (33). This emphasizes the need to discover innovative ways to specifically control microorganisms associated with malignancies. Nanotechnology has enabled the development of drug-delivery systems that can improve the pharmacokinetic properties, biodistribution, and therapeutic performance of selected anticancer agents (34). Various smart nano-delivery systems, such as lipid-, inorganic, metallic, and polymer-based nanoparticles and liposomes, can deliver drugs, regulate drug release, and optimize pharmacokinetic properties (35, 36). Beyond conventional drug delivery, nanocarrier systems offer a unique opportunity to integrate multiple therapeutic modalities such as photothermal therapy, photodynamic therapy, and immunotherapy (37, 38). Importantly, nanotechnology has provided a versatile toolkit for interacting with the tumor microbiota (23, 39).

Microbiome-directed nanoplatforms therefore represent an emerging experimental strategy in breast cancer, but their therapeutic value remains clinically unestablished (23). Engineered nanoparticles have been investigated for localized antimicrobial delivery, biofilm disruption, and modulation of microbial communities (23, 40). Whether these interventions can reproducibly overcome microbiome-associated therapeutic resistance in patients remains unknown. Preclinical platforms have combined microbiota modulation with chemotherapy, ferroptosis induction, or immune activation, with several models reporting greater antitumor activity than individual interventions (41, 42). Such results do not yet establish that microbiota modulation will provide comparable therapeutic benefit in clinically heterogeneous breast cancers. Despite these advances, challenges remain, including accurate characterization of low-biomass intratumoral microbiota, potential contamination during analysis, interpatient heterogeneity, and safety concerns associated with microbiome-targeted interventions (13, 15). Addressing these challenges will require multidisciplinary approaches integrating microbiology, oncology, immunology, and nanotechnology.

This review examines the contribution of intratumoral and gut microbiota to breast cancer progression, metastasis, and therapeutic resistance, and evaluates emerging nanoplatforms designed to manipulate these microbial compartments. This review emphasizes the strength of mechanistic evidence, the distinction between microbiota-associated and microbiota-dependent effects, and the biological and technical barriers that currently limit clinical translation.

2. Role of Microbiota in Breast Cancer

Beyond their impact on the tumor microenvironment, the gut-mammary axis expands our understanding of microbiota effects on breast cancer as a two-way communication pathway between gut microbes and host immunity and tumor biology (43, 44). Microbial short-chain fatty acids can modulate CD8+ T-cell function and enhance adoptive T-cell therapy in experimental cancer models (45, 46). Selected microbial species and their products can activate Toll-like receptors and downstream inflammatory signaling pathways, although these effects depend on the microbial species, host, and tumor context (47, 48). In breast cancer models, small extracellular vesicles derived from *Fusobacterium nucleatum* have been shown to promote cancer cell proliferation, migration, and invasion, as well as tumor growth and metastasis, through a TLR4-dependent mechanism (49). These findings illustrate how specific microbial products may contribute to breast cancer progression but should not be generalized to the intratumoral microbiome as a whole. Some bacterial strains, such as *F. nucleatum*, can stimulate epithelial-mesenchymal transition, increasing tumor invasiveness and metastasis (50, 51). In contrast, intratumoral microbiota can significantly modify the immune microenvironment. These bacteria attract and expand immunosuppressive populations, such as MDSCs and M2-like macrophages, and decrease the cytotoxic activity of $CD8^+$ T cells (17, 52). These immunosuppressive changes may contribute to an immunologically “cold” tumor microenvironment and reduced responsiveness to immunotherapy

(53). Experimental studies in pancreatic cancer models have demonstrated that microbial depletion can reprogram the tumor immune microenvironment, reduce immunosuppressive myeloid populations, enhance antitumor T-cell responses, and improve responsiveness to immune checkpoint blockade (54). Together with broader evidence of microbiome-immunotherapy interactions (55), these findings support microbiota-directed interventions as a potential therapeutic strategy, although their applicability to breast cancer requires further investigation.

The therapeutic relevance of breast-associated microbiota may differ across molecular subtypes and disease stages. Triple-negative, hormone receptor-positive, and HER2-positive breast cancers exhibit distinct tumor microenvironments, immune landscapes, metabolic characteristics, and treatment sensitivities, which may influence microbial colonization and host–microbe interactions. Differences between primary tumors and metastatic lesions may further affect microbial distribution, nanoparticle delivery, and therapeutic response. However, evidence establishing reproducible subtype-specific microbial targets or microbiome-dependent treatment responses remains limited. Future investigations should therefore integrate molecular subtype, disease stage, metastatic site, and treatment history into microbiome profiling and therapeutic evaluation rather than assuming that findings from individual TNBC models apply broadly to breast cancer.

Together, these observations support a functional contribution of selected intratumoral microorganisms to tumor progression and treatment response in experimental models. However, microbial effects are unlikely to be uniform across breast cancer subtypes or microbial communities, and causal evidence in patients remains limited. A central limitation of this literature is the difficulty of distinguishing microbial causation from microbial selection by the tumor microenvironment. Tumor hypoxia, altered nutrients, immune suppression, necrosis, and treatment exposure may themselves reshape microbial communities. Consequently, microbial enrichment within breast tumors does not establish that the enriched organism initiated or sustained the malignant phenotype. Longitudinal human studies and experimental systems incorporating microbial depletion, recolonization, and defined microbial consortia are needed to resolve directionality.

3. Gut Microbiota-Tumor Axis

Beyond the local tumor niche, the gut microbiome contributes to systemic regulation of breast cancer via the gut-tumor axis, which involves bidirectional communication through microbial, metabolic, and immune signaling pathways that shape tumor progression and therapeutic response (44, 56). In experimental tumor models, gut commensals enhanced dendritic-cell function and antitumor T-cell responses (57), while microbiota disruption impaired therapy-associated myeloid-cell responses (57, 58).

Key signaling molecules produced by the microbiota, such as tryptophan metabolites, bile acid metabolites, and SCFA metabolites, mediate this communication (59, 60). Microbial metabolites can also influence immune regulation: butyrate promoted peripheral regulatory T-cell generation in mice (61, 62). Moreover, recent studies have shown that microbial metabolites regulate oxidative stress and ferroptosis pathways, linking gut microbiota to cancer cell fate determination (63, 64).

Preclinical evidence links gut microbiota perturbation to nanomedicine disposition and treatment response, but the mechanisms should not be generalized across platforms. In mice bearing 4T1 breast tumors, antibiotic-mediated gut microbiota depletion increased tumor vascular permeability and intratumoral accumulation of liposomal doxorubicin, accompanied by improved therapeutic outcomes (65). Broader interactions among microbial metabolites, the tumor microenvironment, and

nanomedicine have been discussed in reviews (66, 67), but direct evidence that specific metabolites determine nanoparticle penetration or distribution remains limited. Microbiota-associated immune regulation and macrophage polarization may link to nanocarrier behavior (68, 69); however, direct experimental testing is needed to assess their effects on nanoparticle uptake, retention, and clearance. Similarly, microbial effects on anticancer drug metabolism should not be interpreted as demonstrating microbial control of nanocarrier stability or payload release (70). These uncertainties support evaluating selective microbiota modulation while monitoring its ecological consequences (71). Combining microbial interventions with drug-delivery systems remains an experimental strategy (23, 44, 66), whose value will depend on demonstrating benefits beyond altered drug exposure and the independent activities of the therapeutic cargo.

Apart from breast cancer, there is a growing amount of evidence suggesting that alteration of the gut microbiota can have far-reaching systemic impact on the biology of tumors in a variety of cancers (72). Approaches like probiotics, prebiotics, diet, fecal microbiota transplantation, selective antibiotics, and microbiome-based nanotherapies can alter microbial composition and function, thereby affecting immune responses, metabolism, and inflammation (73, 74).

Specific microbiota-directed interventions have altered dendritic-cell, T-cell, NK-cell, and myeloid-cell responses in experimental cancer models, with effects varying by intervention and biological context (33, 72). These changes have accompanied improved responses to selected anticancer treatments, but increased diversity or altered taxonomic abundance does not, by itself, establish restoration of a healthy microbial state. Although this review focuses on breast cancer, related observations in other solid tumors provide mechanistic context for microbiota-directed interventions. Their relevance to breast cancer should nevertheless be established independently rather than extrapolated across tumor types.

The ecological consequences of microbiota modulation require careful consideration. Increased microbial diversity or enrichment of selected taxa should not automatically be interpreted as restoration of a healthy microbiome, because microbial functions and host effects depend on community composition, metabolic activity, and biological context. Broad microbial depletion may eliminate beneficial organisms, alter metabolite production, and promote antimicrobial resistance or opportunistic colonization. Conversely, selective microbial targeting may preserve beneficial microbial functions, although this advantage remains to be demonstrated for most microbiome-modulating nanoplatforms. Future studies should therefore assess microbial functional capacity, ecological stability, and recovery following treatment rather than relying exclusively on changes in relative taxonomic abundance.

4. Nanocarriers for Microbiota Modulation in Breast Cancer

Experimental evidence that tumor-resident bacteria can promote metastatic colonization has motivated microbiota-directed therapeutic strategies in breast cancer (29, 56). Nevertheless, traditional treatment methods that rely on broad-spectrum antibiotics remain constrained by their lack of specificity. Unnecessary use of these antibiotics destroys both harmful and harmless microorganisms, disrupts the bacterial flora, weakens the immune system, and increases resistance risk (75, 76). Repeated antibiotic exposure can produce individualized and incompletely reversible changes in the human gut microbiota (77). Nanocarrier-based approaches may offer greater spatial control over antimicrobial or microbiota-modulating interventions than systemic microbial depletion (23). Tumor-directed antimicrobial delivery may reduce exposure of non-target microbial communities compared with conventional systemic antibiotic administration. In a preclinical breast cancer model, liposomal mupirocin demonstrated activity against intratumoral *F. nucleatum* without an immediate detectable effect on the

gut microbiome (78). Whether this selectivity persists during repeated treatment or preserves microbiome function in patients remains to be established.

Another experimental strategy integrates bacteria-assisted tumor targeting with nanoparticle-mediated chemotherapy. In breast cancer models, *Bifidobacterium infantis*-nanoparticle biohybrids preferentially accumulated in hypoxic tumor regions, enhanced doxorubicin delivery, and improved therapeutic outcomes (79). For example, nanoplatforms that integrate microbial targeting and ferroptosis induction can simultaneously disrupt bacterial survival and induce oxidative stress-mediated cancer cell death (23, 41). Similarly, microbiota-targeted systems can enhance immunotherapy by alleviating bacterial-induced immunosuppression and promoting immune cell activation (33). Some preclinical nanocarriers alter both intratumoral and intestinal microbial communities, raising the possibility of coordinated local and systemic effects. This dual activity may be advantageous, but it also complicates attribution of therapeutic benefit to a specific microbial compartment.

4.1 Liposomal Nanocarriers

Liposomes are clinically established anticancer drug-delivery platforms, as demonstrated by randomized trials of pegylated liposomal doxorubicin in breast cancer (80). Their application to microbiota-directed treatment remains experimental, although preclinical studies have demonstrated the feasibility of liposomal antibiotic delivery against tumor-associated bacteria (66, 78). Their lipid bilayer structure and tunable surface properties enable the encapsulation and targeted delivery of antibiotics and other bioactive agents, providing opportunities to modulate tumor-associated microbial populations (81, 82). However, preferential tumor accumulation does not necessarily confer bacterial selectivity. Although microbiota-directed nanoplatforms have demonstrated targeted intratumoral bacterial depletion and enhanced antitumor responses in preclinical breast cancer models, their ability to preserve beneficial microbial communities during repeated treatment remains to be established (23, 83).

Controlled release and surface functionalization may improve local drug exposure and support microbiota-directed therapeutic strategies, although their contribution to treatment efficacy must be distinguished from improvements in drug pharmacokinetics and direct tumor-cell cytotoxicity (36, 84). An ergosterol-containing, folate-targeted liposomal nanoplatform (DD@FEL) has been developed to simultaneously target tumor cells and the intratumoral microbiota in triple-negative breast cancer (TNBC). The platform co-delivers doxycycline and doxorubicin (DOX), combining microbiota-directed antibacterial activity with DOX-mediated tumor-cell cytotoxicity. The replacement of conventional liposomal cholesterol with ergosterol introduces an additional bioactive component with reported antitumor activity. This study focused on the intratumoral microbiota and did not assess effects on the gut microbial community.

In 4T1 cells, DD@FEL showed enhanced cellular uptake associated with folate-receptor targeting and produced greater cytotoxicity and apoptosis, along with reduced proliferation and migration, compared with the corresponding single-treatment controls (85). DD@FEL also reduced the abundance of tumor-associated *S. xylosus* and *L. animalis* in the reported model, consistent with antibacterial activity against the microbial compartment examined. In the reported in vivo model, DD@FEL reduced primary tumor growth and lung metastatic burden, with reported inhibition rates of 81.6% and 80.6%, respectively (85). No major toxicity was detected using the parameters examined; however, these short-term measurements do not establish systemic or long-term safety (Figure 1).

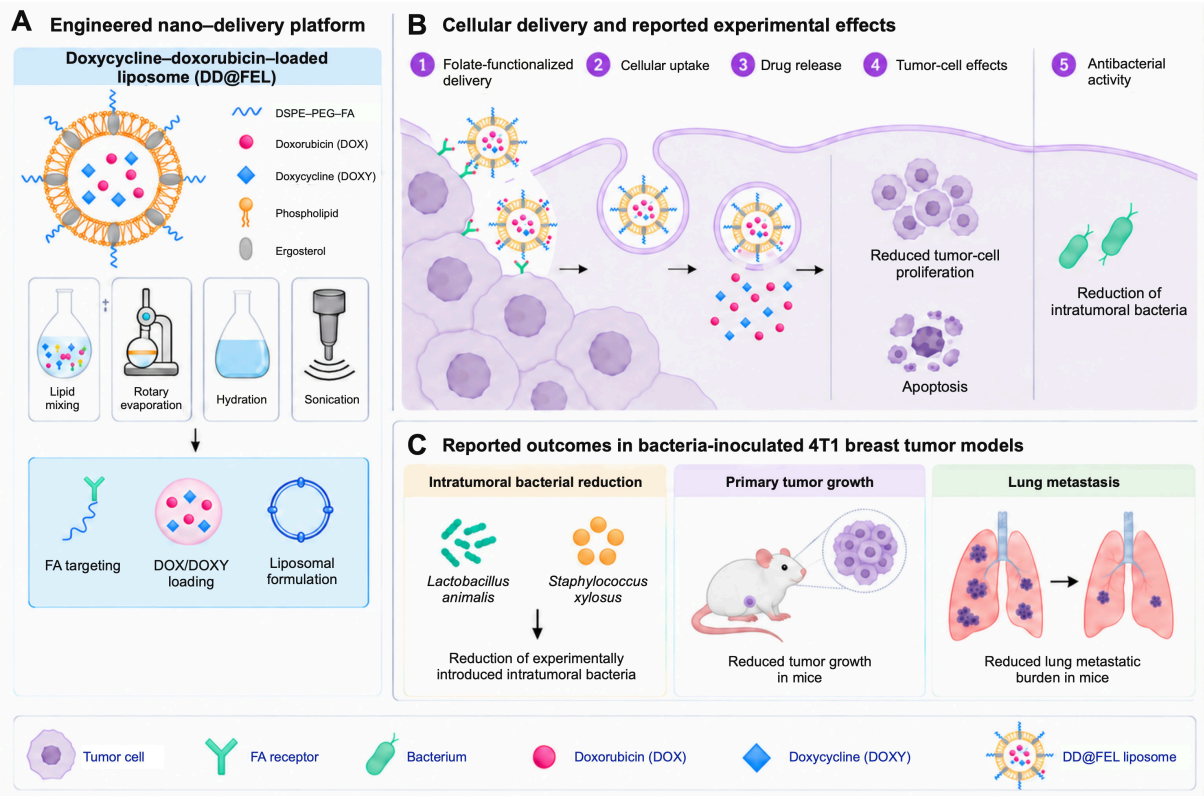


Figure 1. DD@FEL liposomes for combined antibacterial and anticancer treatment in breast cancer models. *(A) Schematic formulation containing doxycycline (DOXY), doxorubicin (DOX), phospholipids, ergosterol, and folate-functionalized lipid components. (B) Conceptual representation of cellular targeting, uptake, drug release, antibacterial activity, and tumor-cell injury. (C) Summary of reported preclinical effects on tumor-associated bacteria, tumor growth, and metastatic burden (85). The schematic does not establish an independent causal contribution for every illustrated pathway. The authors prepared the illustration with assistance from generative artificial intelligence and then reviewed and edited it for scientific accuracy.* ***Abbreviations:*** *DOX, doxorubicin; DOXY, doxycycline; FA, folic acid; DSPE–PEG–FA, folate-conjugated distearoylphosphatidylethanolamine–polyethylene glycol.*

Tumor-associated *F. nucleatum* has been implicated in breast cancer chemoresistance through Gal-GalNAc-mediated tumor colonization and activation of autophagy and epithelial–mesenchymal transition (EMT) programs. To counter this microbiota-associated resistance, *F. nucleatum*-mimicking nanovehicles (LipoFM) were engineered by incorporating bacterial membrane components into antibiotic-loaded liposomes, enabling preferential tumor targeting and localized antibacterial activity. Colistin-loaded LipoFM selectively reduced intratumoral *F. nucleatum* and restored chemotherapy responsiveness in experimental breast cancer models (86). Doxycycline-loaded LipoFM was developed to target additional tumor-associated bacteria. Combined with conventional chemotherapy, it reduced lung metastasis and produced complete regression of established tumors in some mice (86). However, deliberately colonized or bacteria-rich experimental models may amplify microbial contributions relative to naturally occurring human breast cancers. The prevalence, abundance, and functional importance of *F. nucleatum* in unselected breast tumors therefore remain important determinants of clinical applicability.

Depletion of the gut microbiota with antibiotics (ABX) has been shown to alter host interactions with nanotherapeutics and increase the intratumoral accumulation of liposomal doxorubicin (LipoDox). Microbiota depletion following ABX treatment was confirmed by RT-qPCR and 16S rRNA sequencing and was accompanied by increased tumor vascular permeability and enhanced nanoparticle penetration. These changes were associated with greater antitumor activity and improved survival following

LipoDox treatment. Notably, the intratumoral microbiota remained largely unchanged, supporting a predominantly gut microbiota-associated effect on host physiology and nanoparticle delivery rather than direct remodeling of the tumor-associated microbial community (65) (Figure 2).

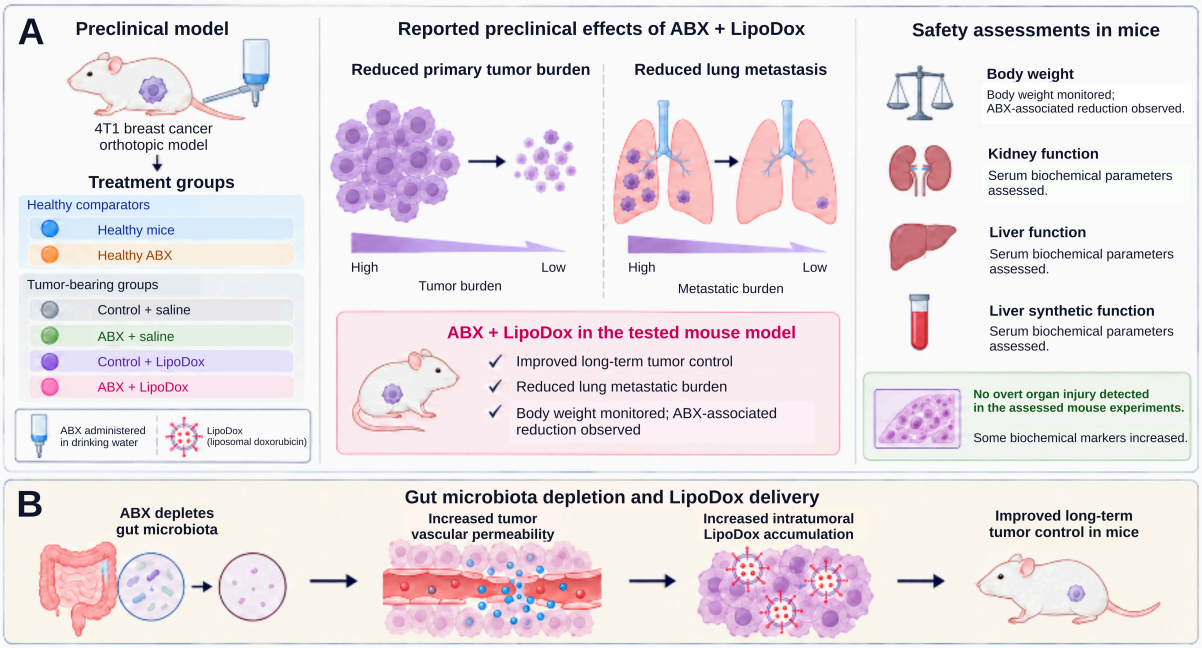


Figure 2. Gut microbiota depletion and liposomal doxorubicin treatment in a preclinical breast cancer model. *(A) Summary of experimental groups and reported findings in mice bearing orthotopic 4T1 breast tumors. Antibiotics (ABX) were administered in drinking water, and liposomal doxorubicin (LipoDox) was administered intravenously. Combined treatment improved long-term tumor control and reduced lung metastatic burden. Safety assessments included body weight, serum biochemical parameters, and organ histology. ABX-treated mice showed lower body weight, and some biochemical markers increased; no overt organ injury was detected in the assessed experiments. These findings do not rule out toxicity. (B) Schematic linking ABX-mediated gut microbiota depletion with increased tumor vascular permeability, greater intratumoral LipoDox accumulation, and improved long-term tumor control. The specific microbial taxa and molecular mechanisms underlying the permeability changes remain unresolved (65). The authors prepared the illustration with assistance from generative artificial intelligence and then reviewed and edited it for scientific accuracy.* ***Abbreviations:*** *ABX, antibiotic treatment; LipoDox, liposomal doxorubicin; 4T1, murine mammary carcinoma cell line.*

Nano-mupirocin is a nanoliposomal formulation of the antibiotic mupirocin designed to enable systemic administration and improve drug exposure beyond that achievable with conventional topical formulations (78). The formulation has been investigated for selective targeting of tumor-associated bacteria while limiting perturbation of the gut microbiota. Nanoparticle encapsulation improved mupirocin's pharmacokinetic profile, resulting in prolonged systemic exposure, increased plasma concentrations, and sustained drug release.

Following tumor accumulation, Nano-mupirocin exerted antibacterial activity against tumor-associated *F. nucleatum* and substantially reduced intratumoral bacterial burden. Microbiome profiling showed no significant changes in the assessed gut microbial diversity following treatment, in contrast to the broader microbiota alterations associated with conventional antibiotic exposure (78). A complementary approach targets bacterial mechanisms of chemotherapy resistance rather than relying exclusively on bacterial depletion. Xi et al. developed carbon nanozymes to counteract intratumoral bacteria-mediated gemcitabine resistance by inhibiting bacterial cytidine deaminase activity. In experimental tumor models, this strategy enhanced gemcitabine-associated antitumor activity, illustrating the potential of nanomaterials to interfere with microbial drug metabolism (87). However, these findings were not established in breast cancer and should be considered mechanistic evidence from other tumor models

rather than direct validation of microbiome-targeted nanotherapy in breast cancer. Separately, nano-mupirocin liposomes retained in vitro activity against several multidrug-resistant bacterial strains and maintained plasma antibiotic concentrations above relevant minimum inhibitory concentrations for more than 24 hours in rats, supporting their potential for systemic antibacterial delivery (88).

4.2 Lipid-Based Nanoparticles

Lipid-based drug-delivery systems encompass solid lipid nanoparticles, nanostructured lipid carriers, and lipid–polymer hybrid nanoparticles, which can improve the stability, encapsulation, and controlled release of selected bioactive compounds (89–91). Lipid composition, surface charge, and functionalization can influence membrane interactions and cargo delivery (36, 92–94). These properties may support microbiota-directed applications, but formulation-specific evidence is needed to demonstrate microbial selectivity, physiological stability, and therapeutic benefit. Lipid-based delivery alone does not establish control of microbial communities or improved microbiome-mediated treatment outcomes (23, 44).

An RGD-functionalized solid lipid nanoparticle platform produced using microfluidic technology (MF-SLNs) has been developed for oral doxorubicin delivery. In addition to enhancing antitumor activity, MF-SLN treatment was associated with substantial changes in gut microbial composition, as assessed by 16S rRNA sequencing. These changes included increased relative abundance of genera such as *Faecalibacterium* and *Bacillus* and reduced abundance of *Staphylococcus*, *Enterococcus*, and *Shigella* compared with conventional doxorubicin treatment. The resulting microbial profile was consistent with attenuation of chemotherapy-associated dysbiosis, although the functional contribution of individual taxa to treatment response remains to be established. In vivo, these microbiota changes accompanied greater tumor suppression, improved survival, and reduced treatment-associated toxicity. The parallel changes in microbial composition and treatment response establish an association but do not determine whether microbiota remodeling mediated the therapeutic benefit or occurred secondarily to altered drug exposure (95).

4.3 Inorganic and Hybrid Nanoparticles

Inorganic and hybrid nanoparticles provide a structurally unique platform for microbiota-based breast cancer approaches because they can combine nanocatalytic, physicochemical, and bioresponsive functionalities (23, 78). Unlike purely lipid-based approaches, inorganic nanomaterials offer opportunities for both bacterial disruption and tumor targeting by generating reactive oxygen species, releasing ions, and enabling externally induced stimulation (96, 97). Selected inorganic and hybrid platforms combine antibacterial activity with oxidative tumor-cell injury, including ferroptosis; effects on microbial metabolites require platform-specific mechanistic evidence (41).

Hybrid nanoplatforms combining inorganic and lipid-based components can integrate targeted delivery with immunomodulatory functions. For example, liposome-coated gold nanocages carrying tumor antigens and immune adjuvants enhanced dendritic-cell activation and antitumor immune responses in preclinical melanoma models (98). Other inorganic–organic hybrid systems may provide complementary tumor-targeting and therapeutic functions (99). A pH-responsive nanoplatform (PEPCA@SPA/Fe^{3+} NPs) has been developed to integrate intratumoral microbiota modulation with ferroptosis-based therapy and antitumor immune activation. In preclinical breast cancer models, treatment remodeled the intratumoral microbial community, altering overall microbial diversity and taxonomic composition, including reduced Proteobacteria abundance and changes in genera such as *Lactobacillus* and *Akkermansia*. Treatment-associated microbiota changes accompanied ferroptotic

tumor-cell injury; combination with anti-CD47 treatment additionally enhanced antitumor immune responses in the tested models (Figure 3) (100).

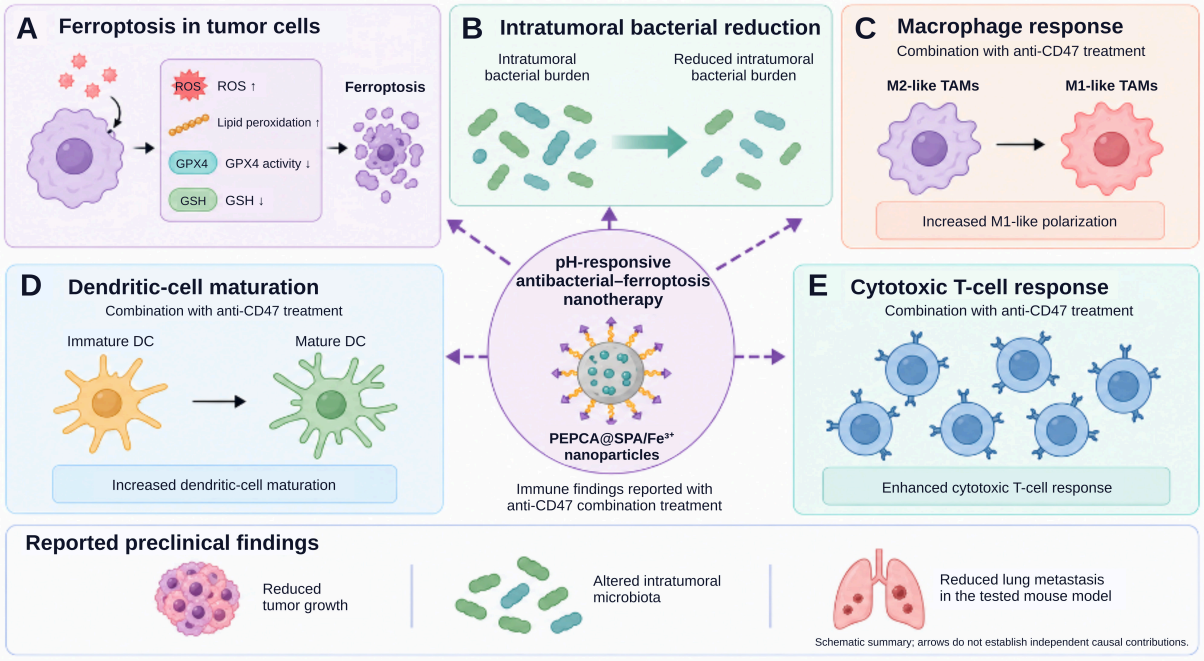


Figure 3. pH-responsive antibacterial–ferroptosis nanotherapy in preclinical breast cancer models. Schematic summary of PEPCA@SPA/Fe³⁺ nanoparticles and reported treatment-associated findings. *(A) Ferroptotic tumor-cell injury involving increased reactive oxygen species and lipid peroxidation, glutathione depletion, and reduced GPX4 activity. (B) Reduction of intratumoral bacterial burden. (C–E) Immune findings reported with anti-CD47 combination treatment include increased M1-like macrophage polarization, dendritic-cell maturation, and enhanced cytotoxic T-cell responses. The lower panel summarizes reduced tumor growth, altered intratumoral microbiota, and reduced lung metastasis in the tested mouse model (100). Arrows organize the reported findings without establishing the independent causal contribution of each pathway. The authors prepared the illustration with assistance from generative artificial intelligence and then reviewed and edited it for scientific accuracy.* ***Abbreviations:*** *DC, dendritic cell; GPX4, glutathione peroxidase 4; GSH, glutathione; ROS, reactive oxygen species; SPA, sparfloxacin; TAMs, tumor-associated macrophages; PEPCA, polyethylene glycol–poly(cinnamyl aldehyde).*

Nanoplatform treatment suppressed primary tumor growth and reduced lung metastasis; however, these experiments do not isolate the contribution of bacterial reduction from direct ferroptotic injury or accompanying immune effects (100). Mechanistically, the nanoparticles showed potent antibacterial activity against *E. coli*, *Pseudomonas aeruginosa*, and *F. nucleatum* while inducing ferroptosis by disrupting the GSH/GPX4 axis, increasing ROS, and promoting lipid peroxidation. Furthermore, microbiota elimination synergized with α-CD47 immune checkpoint blockade to enhance antitumor immunity by promoting dendritic cell maturation, M1 macrophage polarization, increased $CD8^+$ T-cell infiltration, and reduction of regulatory T cells (100). A multifunctional amorphous nanoassembly (DFTV) has been developed to simultaneously target intratumoral Gram-positive (G^+) bacteria and breast tumor cells. The platform reduced intratumoral bacterial burden and was associated with attenuated inflammatory signaling and disrupted cytoskeletal remodeling linked to tumor-cell motility, thereby addressing limitations of conventional antibiotic delivery within tumors. In preclinical models, DFTV treatment inhibited tumor growth, metastatic progression, and postoperative recurrence. Mechanistically, DFTV promoted iron-dependent lipid peroxidation and ferroptotic tumor-cell death, enhanced by laser irradiation, while also contributing to antibacterial activity and remodeling of the tumor immune microenvironment (Figure 4) (101).

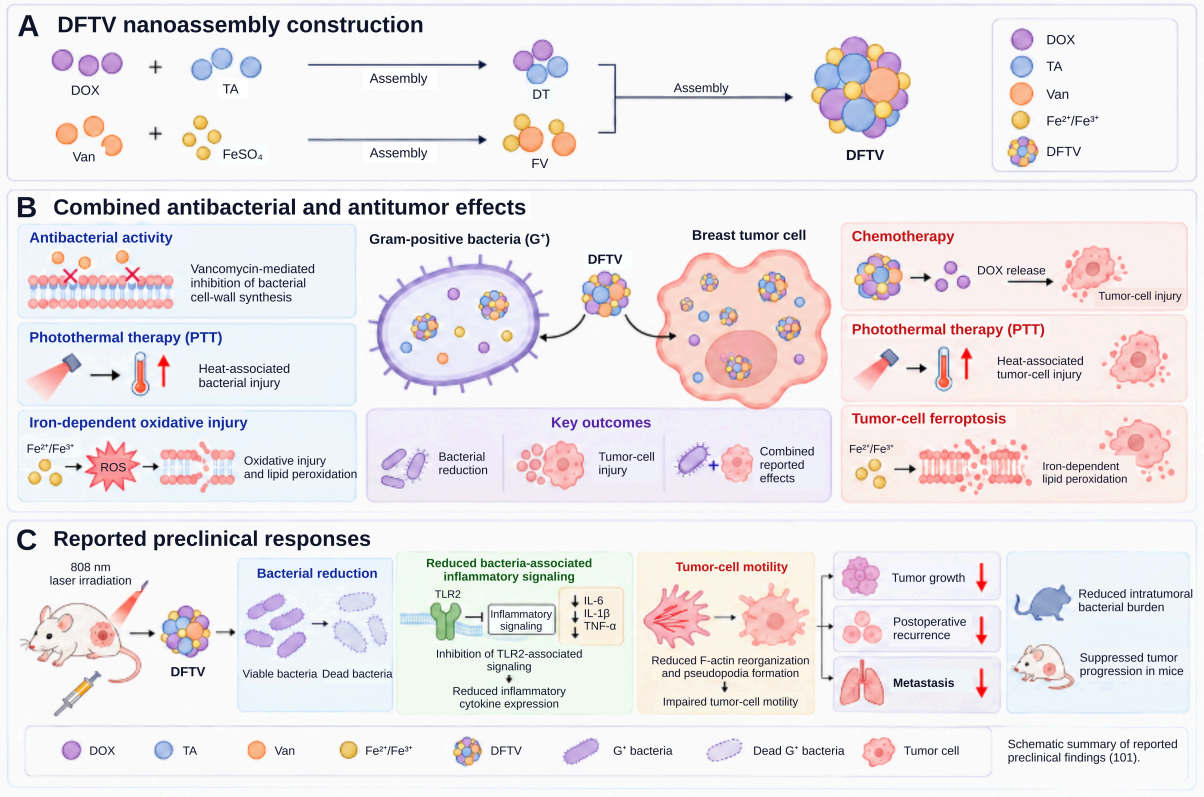


Figure 4. DFTV nanoassembly for combined antibacterial and antitumor treatment in preclinical breast cancer models. *(A) Schematic construction of DFTV from doxorubicin (DOX), tannic acid (TA), ferrous sulfate and vancomycin (Van), through intermediate DOX–TA (DT) and iron–vancomycin (FV) assemblies. (B) Summary of antibacterial and tumor-cell effects, including vancomycin-mediated inhibition of bacterial cell-wall synthesis, photothermal injury, iron-dependent oxidative injury and lipid peroxidation, DOX-associated tumor-cell injury, and tumor-cell ferroptosis. (C) Reported preclinical responses following DFTV treatment and 808-nm irradiation: reduced intratumoral bacterial burden, inhibition of TLR2-associated inflammatory signaling with decreased IL-6, IL-1β and TNF-α expression, and reduced F-actin reorganization and pseudopodia formation. These responses accompanied suppression of tumor growth, postoperative recurrence, and metastasis in the tested models (101). The schematic summarizes reported findings without establishing the independent contribution of every illustrated pathway. The authors prepared the illustration with assistance from generative artificial intelligence and then reviewed and edited it for scientific accuracy.* ***Abbreviations:*** *G^+, Gram-positive bacteria; PTT, photothermal therapy; ROS, reactive oxygen species; TLR2, Toll-like receptor 2; IL, interleukin; TNF-α, tumor necrosis factor alpha.*

A multifunctional ultrasound (US)-activatable piezoelectric nanoplatform (HN-T/BT@Lip) has been developed for triple-negative breast cancer (TNBC) by integrating ferroptosis induction with modulation of intratumoral microbial metabolism. The platform incorporates toyocamycin-loaded $CaCO_3$–carboxymethyl chitosan hybrid nanoparticles and barium titanate within folate-modified liposomes, enabling targeted delivery and US-responsive activation. Upon US stimulation, the nanoplatform generates localized electric fields, promotes Ca^{2+} influx, and increases reactive oxygen species (ROS) production. Treatment was also associated with remodeling of the intratumoral microbiota and its metabolic profile, with trimethylamine N-oxide (TMAO) identified as a key metabolite linked to the therapeutic response. Mechanistically, TMAO was implicated in potentiating ferroptotic cell death by enhancing lipid peroxidation and suppressing antioxidant defenses involving the Nrf2–GSH/GPX4 axis, thereby providing a potential mechanistic link between microbiota-derived metabolism and ferroptosis-based therapy (102).

Although these findings suggest a mechanistic relationship between microbiota-associated metabolic remodeling and ferroptosis, the contribution of TMAO should be distinguished from the direct effects

of ultrasound activation, reactive oxygen species generation, and the therapeutic cargo. Establishing metabolite-dependent efficacy requires experiments that independently manipulate TMAO availability and assess whether metabolite supplementation or inhibition alters lipid peroxidation, ferroptosis, and tumor control. Such studies should also determine whether the relevant metabolic changes originate from intratumoral microorganisms, intestinal microbiota, or host metabolism. External laser activation can provide spatial control over selected photothermal nanoplatforms, potentially limiting treatment to the irradiated region (23, 103). In experimental breast cancer cell models harboring intracellular bacteria, near-infrared-activated silver nanoparticles demonstrated photothermal cytotoxicity and reduced intracellular bacterial burden (104). However, the extent of microbiota modulation depends on the platform and experimental context, and localized activation does not necessarily translate into reduced systemic toxicity. Camptothecin-loaded nanoparticles (PCRHNs) have been developed to mitigate treatment-associated alterations in the gut microbiota while enhancing anticancer activity. In the reported preclinical model, high-dose free camptothecin (CPT) induced gut microbial dysbiosis, including increased abundance of potentially pathogenic *Escherichia* and *Shigella*, whereas PCRHN treatment combined with laser irradiation preserved microbial richness and diversity and increased the abundance of potentially beneficial species, including *Lactobacillus reuteri*. Mechanistically, the photothermal activity of PCRHNs enhanced catalase-like activity and oxygen generation, thereby altering the intestinal microenvironment in a manner proposed to favor the growth of facultative anaerobic probiotic bacteria (105).

DNA aptamers provide programmable molecular recognition and can be incorporated into nanocarriers to improve binding to selected cellular or microbial targets (106). However, their in vivo performance depends on target accessibility, nuclease stability, pharmacokinetics, and retention of binding specificity in complex biological environments. Researchers developed a DNA tetrahedron-based nanodelivery system functionalized with a bacteria-targeting aptamer (TA@B) for targeted berberine delivery. The nanostructure exhibited high drug-loading capacity and selective binding to intratumoral bacteria, integrating antibacterial, anticancer, and immunomodulatory activities. In preclinical models, TA@B suppressed tumor-cell proliferation both in vitro and in vivo and was associated with reduced TNF-α and IL-6 levels and remodeling of the immune microenvironment (107).

4.4 Metallic Nanoparticles and Bacteria-Metal Biohybrids

Metallic nanoparticles offer physicochemical properties that have been widely investigated for antimicrobial applications, including surface functionalization, catalytic activity, ion release, and the generation of reactive oxygen species (108). Their integration with engineered bacteria has enabled the development of bacteria–nanomaterial biohybrids that combine bacterial tumor-homing capabilities with nanomaterial-mediated cargo delivery and therapeutic functions (109). In cancer therapy, metallic nanomaterials can also provide photothermal, catalytic, and immunomodulatory functions that may be exploited within the tumor microenvironment (110). However, the biological behavior and therapeutic performance of these systems depend on the specific nanomaterial, bacterial strain, route of administration, and platform design. A bacteria-nanoparticle biohybrid system has been shown to function as an efficient peptide-delivery platform while concurrently modulating the tumor-associated microbiota and immune microenvironment (111). A quorum-sensing-engineered *E. coli* strain TSYPU was used as a bacterial delivery system for the scorpion venom-derived peptide (BmK AGAP). This enabled synchronized lysis and sustained intratumoral drug release. TSYPU colonized the tumor microenvironment and released AGAP, resulting in considerable inhibition of tumor growth through anti-proliferative and anti-angiogenic effects, along with TME modulation, as *E. coli* K12 induced immune activation and macrophage polarization toward the anti-tumor M1 phenotype, thereby enhancing therapeutic efficacy. To further improve delivery efficiency and stability, TSYPU was

integrated with gold nanoparticles (TSYPU@Au), which protected the bacteria from gastrointestinal degradation and enabled effective oral administration. TSYPU@Au produced greater tumor suppression than the bacterial system alone in the reported experimental models (111), although the safety and controllability of orally administered live engineered bacteria–nanoparticle hybrids remain major translational considerations.

4.5 Biomimetic and Biohybrid Nanocarriers

Biomimetic platforms and nano–bacterial biohybrids use biological components or live bacteria with nanomaterials for targeted drug delivery and microbiota modulation (109, 112). The nano–bacterial biohybrid LYC@Bac combines IL-15-expressing engineered Escherichia coli with pH-responsive lysozyme nanoparticles targeting F. nucleatum. Treatment reduced F. nucleatum colonization and altered microbial composition, including increased Escherichia abundance detected by 16S rRNA sequencing. These changes accompanied reduced immunosuppression and enhanced antitumor immune activity. Bacterial clearance and pathogen-associated molecular pattern (PAMP) release promoted dendritic-cell activation, while bacteria-derived IL-15 enhanced NK-cell activity through mTOR signaling, suggesting a reinforcing interaction between microbial clearance and immune activation (113).

The biomimetic nanoplatform DPI@HMV-RS17 targets F. nucleatum-colonized triple-negative breast cancer (TNBC). It integrates doxorubicin (DOX), IR820, polymetformin, and RS17-functionalized hybrid membrane vesicles for combined chemotherapy, phototherapy, and immunomodulation. In preclinical models, treatment achieved a reported 99.86% reduction in intratumoral F. nucleatum abundance and was associated with reduced bacteria-associated chemoresistance and immunosuppression. Experiments using infected 4T1 cells and colonized 4T1 tumor-bearing mice demonstrated antitumor activity, including suppression of primary tumor growth, lung metastasis, and recurrence in mice (114) (Figure 5).

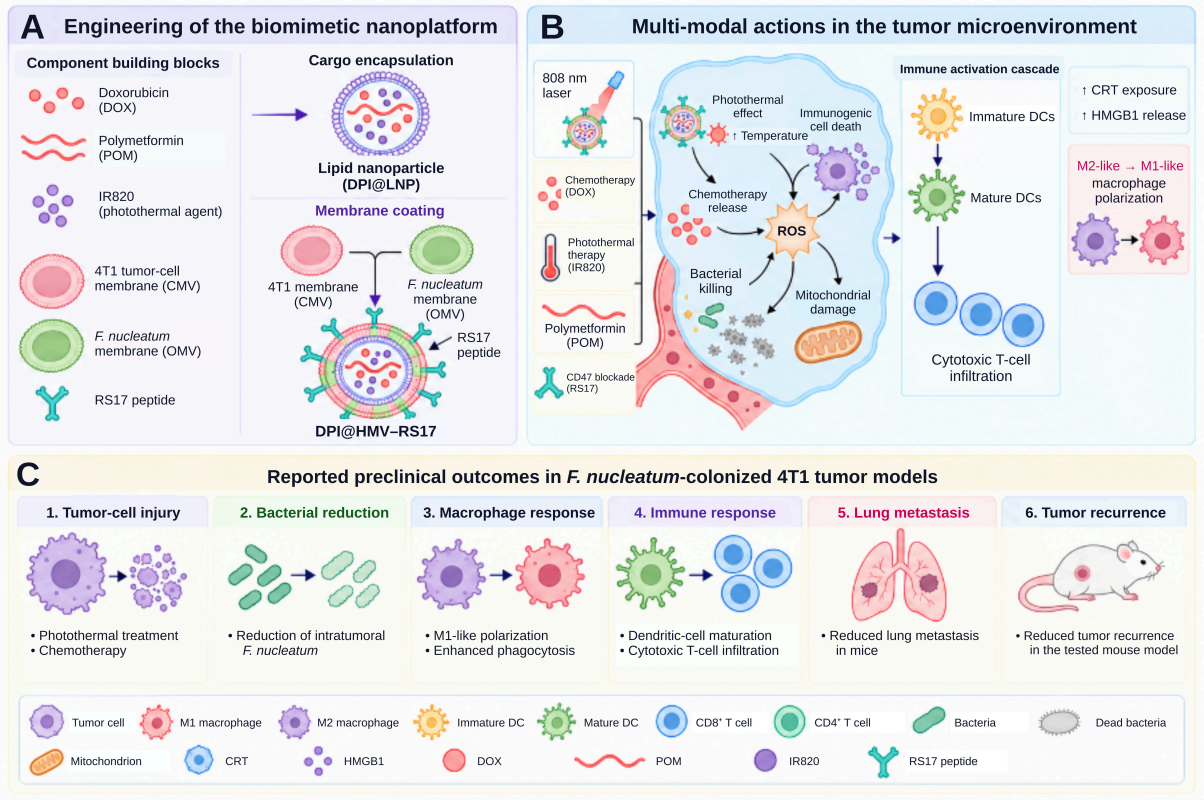


Figure 5. DPI@HMV–RS17 for combined microbial targeting and antitumor treatment. *(A) Simplified construction of lipid nanoparticles carrying doxorubicin, polymetformin, and IR820, coated with hybrid F. nucleatum/4T1 cell-membrane vesicles and functionalized with RS17. (B) Reported treatment-associated mechanisms include bacterial reduction, tumor-cell injury, immunogenic cell death, and CD47–SIRPα-associated macrophage responses. (C) Summary of preclinical tumor-control outcomes in F. nucleatum-colonized breast cancer models (114). Arrows summarize the proposed integration of these effects rather than independent proof of every causal connection. The authors prepared the illustration with assistance from generative artificial intelligence and then reviewed and edited it for scientific accuracy.* ***Abbreviations:*** *DOX, doxorubicin; POM, polymetformin; HMV, hybrid membrane vesicle; DC, dendritic cell; ROS, reactive oxygen species; RS17, CD47-binding peptide; IR820, near-infrared cyanine dye; CRT, calreticulin; HMGB1, high-mobility group box 1.*

These antitumor effects were accompanied by remodeling of the immune microenvironment, including enhanced dendritic-cell maturation, increased cytotoxic T-cell infiltration, and macrophage polarization toward an M1-like phenotype through inhibition of CD47–SIRPα signaling (114). The magnitude of bacterial depletion and tumor control in this model is notable, but both outcomes were obtained in *F. nucleatum*-colonized experimental systems. To establish broader relevance, comparable targeting in tumors with naturally occurring, lower-biomass, heterogeneous microbial communities is needed. Various studies elucidate the role of intratumoral microbiota, particularly *F. nucleatum*, in driving immunosuppression and limiting the efficacy of immune checkpoint blockade (ICB) therapy in breast cancer (48). *F. nucleatum* has been implicated in an immunosuppressive tumor microenvironment characterized by increased infiltration of myeloid-derived suppressor cells (MDSCs) and M2-like macrophages, along with reduced $CD8^+$ T-cell activity and resistance to anti-PD-L1 therapy (115).

Biomimetic nanovehicles have been investigated for targeted depletion of intratumoral *F. nucleatum* in breast cancer. In preclinical models, selective bacterial depletion was combined with PD-L1 blockade to enhance antitumor activity, providing a microbiota-directed strategy for simultaneously targeting tumor-associated bacteria and immunosuppression (83). Nevertheless, the relative contribution of bacterial depletion to therapeutic efficacy should be distinguished from the independent effects of immune checkpoint blockade. An alternative biohybrid strategy integrates intratumoral bacterial elimination with activation of innate immune signaling. Zhou et al. developed nanodrug–bacteria biohybrids designed to eliminate intratumoral bacteria while activating the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) pathway. In preclinical tumor models, the platform combined antibacterial activity with immune stimulation, providing a distinct approach to enhancing cancer immunotherapy (116). Unlike approaches combining bacterial depletion with immune checkpoint blockade, this system couples bacterial targeting to cGAS–STING activation. Nevertheless, the relative contributions of bacterial elimination, biohybrid-associated immunostimulation, and other therapeutic components require careful interpretation when evaluating microbiota-dependent antitumor efficacy.

A cold tumor microenvironment is characterized by low immune-cell infiltration, reduced antigen presentation, and minimal inflammatory signaling, making tumors less responsive to immunotherapy (117). This immunosuppressive state limits effective antitumor immune activation and represents a major challenge in cancer treatment (118). Microbiota-targeted outer membrane vesicle (OMV)-coated nanoparticles (OMV@Fe-ZIF-90@M) have been developed to remodel the intratumoral microbiota and enhance antitumor immunity in triple-negative breast cancer (TNBC). The platform exploits homologous bacterial targeting and Fap2-Gal-GalNAc interactions to selectively target *F. nucleatum*, achieving a reported 99.7% reduction in bacterial burden. Beyond bacterial depletion, treatment was designed to convert microbiota-associated signals into immunostimulatory cues: disruption of *F. nucleatum* releases pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide (LPS), which act together with immunostimulatory OMV components to promote dendritic-cell maturation and antigen presentation. In preclinical models, these effects were accompanied by increased

TNF-α and IFN-γ, reduced IL-6 and IL-10, and enhanced infiltration of $CD4^+$ and $CD8^+$ T cells, consistent with remodeling of the immunosuppressive tumor microenvironment toward a more immune-active state (119).

Collectively, these studies support the experimental feasibility of integrating microbiota modulation with immune activation in breast cancer models. However, increased immune-cell infiltration, cytokine production, or improved responses to immune checkpoint blockade do not independently establish microbiota-mediated immune restoration, particularly when nanoplatforms contain immunostimulatory components or cytotoxic agents that can induce immunogenic cell death. Furthermore, clinical evidence supporting microbiome-based immunotherapy modulation in other malignancies should not be directly extrapolated to breast cancer. Future studies should determine whether microbial depletion or remodeling contributes independently to immune checkpoint blockade efficacy using platform-matched controls, microbial recolonization, and clinically representative breast cancer models.

4.6 Natural Nanocarriers

Naturally derived nanocarriers, including plant-derived extracellular vesicle-like particles, have emerged as experimental delivery systems that can affect both tumor cells and host microbial communities (120–123). Their biological composition may confer distinct uptake and biodistribution properties, but evidence that their natural origin provides a specific advantage for microbiome modulation remains limited (120). For example, plant-based exosome-like nanoparticles and vesicles loaded with bioactive molecules can simultaneously exert direct cytotoxicity against cancer cells and alter gut microbial composition and diversity, with potentially beneficial effects that require functional validation (121). Plant-derived extracellular vesicles have demonstrated the potential to modulate gut microbiota and reshape the tumor immune microenvironment. In preclinical triple-negative breast cancer models, *Platycodon grandiflorum*-derived extracellular vesicles altered gut microbial composition, promoted M1-like macrophage polarization and cytotoxic T-cell infiltration, and suppressed tumor growth (122). Likewise, researchers have developed nano formulations based on natural compounds to enable controlled release and distribution throughout the body, thereby modulating the microbiota in the intestine and tumor tissues (123).

Natural nanocarriers can influence microbial composition, microbial metabolites, and host immune responses while also directly affecting tumor cells. These overlapping activities make mechanistic attribution difficult, and short-term tolerability in preclinical models should not be interpreted as evidence of no toxicity. Tea flower-derived exosome-like nanoparticles (TFENs), containing bioactive constituents including polyphenols, flavonoids, proteins, and lipids, have been investigated as a plant-derived nanoplatform for breast cancer therapy. TFENs were efficiently internalized by breast cancer cells and induced reactive oxygen species (ROS) accumulation, mitochondrial dysfunction, cell-cycle arrest, and apoptosis, with G2-phase arrest observed in MCF-7 cells and S/G2-phase arrest in 4T1 cells. In preclinical models, both intravenous and oral administration suppressed primary tumor growth and lung metastasis, with preferential nanoparticle accumulation at tumor and metastatic sites. Notably, oral administration produced substantial antitumor activity despite lower pulmonary accumulation and was associated with gut microbiota remodeling and enhanced systemic antitumor immune responses. TFEN activity therefore coincided with both ROS-mediated tumor-cell injury and microbiota-associated immune changes (121); the available experiments do not establish the relative contribution of these mechanisms to tumor control.

Tea leaf-derived exosome-like nanotherapeutics (TLNTs) have also been investigated for breast cancer treatment, with direct anticancer activity accompanied by changes in gut microbial composition and

immune responses (124). The TLNTs were efficiently internalized by 4T1 breast cancer cells, resulting in a 2.5-fold increase in ROS levels, mitochondrial dysfunction, cell cycle arrest at the G0/G1 and S phases, and apoptosis. Notably, TLNT treatment altered gut microbial composition and increased microbial diversity, accompanied by a higher Bacteroidetes/Firmicutes ratio, enrichment of *Alloprevotella*, and reduced abundance of *Alistipes*, *Oscillibacter*, and *Desulfovibrio*. Although these changes coincided with enhanced antitumor immune activity, their functional significance and contribution to tumor suppression require further validation (124). More broadly, microbiota–cancer interactions involve interconnected metabolic, inflammatory, and immune pathways that vary with microbial composition, anatomical location, and host context (125). Accordingly, microbiota changes observed following nanocarrier treatment require functional validation before they can be considered responsible for improved antitumor activity.

FerriNano provides a preclinical example of a nanoplatform combining tumor-directed ferroptotic stress with modulation of intestinal and intratumoral microbiota. Following systemic administration, a fraction of the formulation underwent hepatobiliary excretion and reached the intestinal compartment, where treatment was associated with changes in microbial diversity, community composition, and metabolite profiles. These changes included reduced abundance of potentially pathogenic genera, such as *Streptococcus* and *Staphylococcus*, and enrichment of *Bifidobacterium* and *Blautia*, accompanied by reduced tumor progression. Metabolomic analysis also identified increased prostaglandin E3 levels, suggesting a possible association between microbiota remodeling, metabolic changes, and antitumor responses; however, its microbial origin and independent functional contribution require confirmation. FerriNano additionally reduced intratumoral bacterial burden, suggesting activity in both intestinal and tumor-associated microbial compartments.

Importantly, antibiotic-mediated microbiota depletion attenuated therapeutic efficacy, supporting a microbiota-dependent component of the response. Nevertheless, because antibiotics can independently alter host metabolism and immunity, these findings do not establish which microbial taxa or metabolites mediate tumor suppression. Studies using defined microbial communities, metabolite-depletion and rescue experiments, and compartment-specific microbial manipulation are needed to resolve these causal relationships (126) (Figure 6).

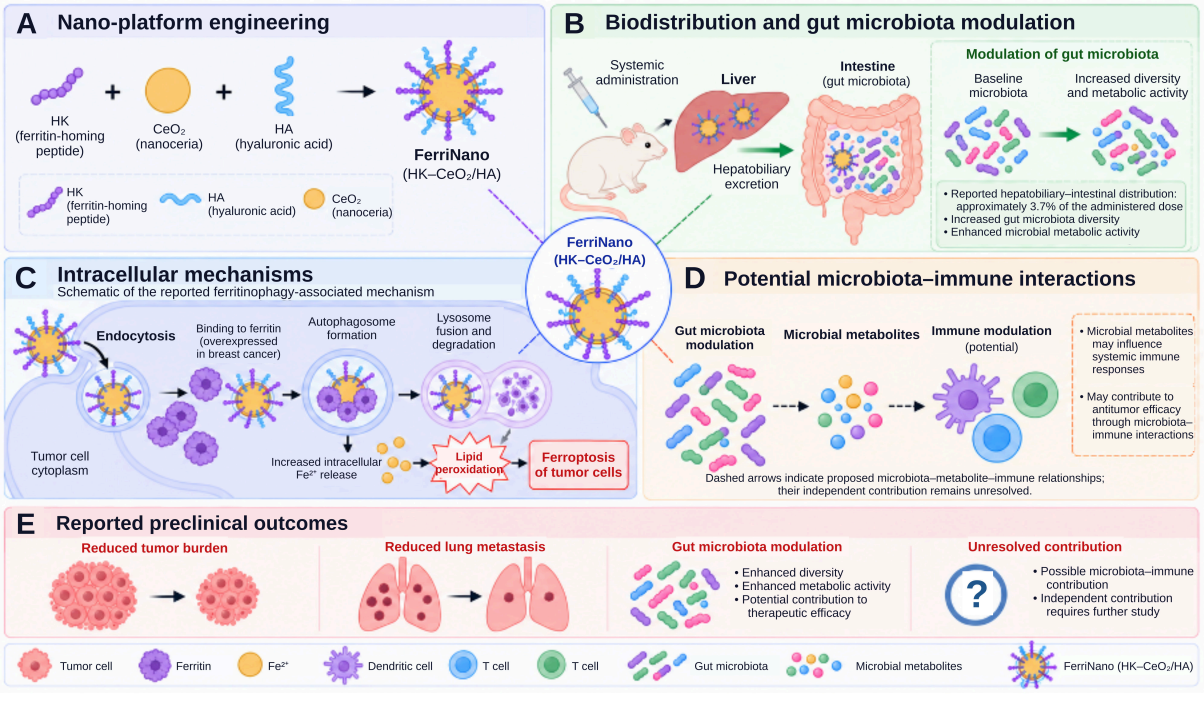


Figure 6. FerriNano-mediated ferritin degradation and microbiota-associated effects. *(A) HK-functionalized nanoceria coated with hyaluronic acid. (B) Tumor targeting and hepatobiliary distribution. (C) Ferritin binding and autophagic–lysosomal degradation, linked to ferroptotic tumor-cell injury. (D) Proposed microbiota–metabolite–immune interactions. (E) Reported preclinical antitumor and antimetastatic outcomes (126). Dashed arrows indicate proposed relationships whose independent contributions remain unresolved. The authors prepared the illustration with assistance from generative artificial intelligence and then reviewed and edited it for scientific accuracy.* ***Abbreviations:*** *HK, ferritin-homing peptide; CeO_2, cerium dioxide; HA, hyaluronic acid; Fe^{2+}, ferrous iron.*

PEGylated antibiotic nanoparticles (MTI-PEG) have been developed to selectively target intratumoral bacteria, including *F. nucleatum*, while limiting perturbation of the intestinal microbiota. In preclinical models, MTI-PEG preferentially accumulated in tumors and markedly reduced intratumoral bacterial burden. Bacterial depletion attenuated microbiota-driven mechanisms implicated in therapeutic resistance, including TLR4-MYD88-associated autophagy, TIGIT-associated suppression of NK-cell activity, and PI3K-AKT-mTOR signaling. Accordingly, MTI-PEG enhanced responses to multiple therapeutic modalities, including oxaliplatin, NK-cell-based therapy, and trastuzumab, while producing comparatively limited alterations in intestinal microbial composition and reducing treatment-associated toxicity.

These findings suggest that selectively targeting intratumoral bacteria may mitigate microbiota-associated therapeutic resistance while producing fewer detectable changes in intestinal microbial composition than less selective antimicrobial approaches; however, intestinal microbial function and long-term ecological stability remain to be established (127). Zhang et al. developed a programmed nanocloak incorporating commensal bacteria-derived nanovesicles to enhance antitumor immune responses. In experimental tumor models, this strategy suppressed tumor growth and metastatic progression, demonstrating the potential of engineered bacterial vesicles as immunotherapeutic components (128).

The potential value of selective bacterial targeting is further supported by evidence that intratumoral bacterial species beyond *F. nucleatum* can influence breast cancer progression. Gerbec et al. identified intratumoral bacteria capable of enhancing breast tumor metastasis in experimental models (129). These findings underscore the importance of identifying functionally relevant bacterial targets rather than assuming that a single antimicrobial strategy will be appropriate across heterogeneous breast tumors. Across these studies, microbiota modulation accompanies antitumor activity through substantially different delivery systems and mechanisms. Table 1 summarizes representative platforms, emphasizing that most evidence comes from model-specific preclinical studies rather than comparative or clinical evaluations.

Table 1: Summary of Microbiota-Modulating Nanoplatforms in Breast Cancer Treatment.

Nanoplatform	Microbiota target/modulation	Therapeutic strategy	Reported preclinical outcome	Ref
DD@FEL	Decrease tumor-associated bacteria	Antibacterial activity + DOX chemotherapy	Reduced primary tumor growth and metastasis	(85)
Colistin-LipoFM / Doxy-LipoFM	*F. nucleatum* / broader intratumoral microbiota	Targeted bacterial depletion combined with chemotherapy	Improved chemotherapy responsiveness; reduced lung metastasis and complete tumor regression in some mice with Doxy-LipoFM combination	(86)
MF-SLNs	Gut microbiota remodeling	DOX delivery + attenuation of dysbiosis	Improved tumor suppression and reduced toxicity	(95)
PEPCA@SPA/Fe^{3+}	Intratumoral microbiota remodeling	Ferroptosis + immune remodeling	Reduced tumor progression/metastasis	(100)

HN-T/BT@Lip	Microbiota metabolic remodeling/TMAO	Ultrasound activation + ferroptosis	TMAO-associated potentiation of ferroptosis	(102)
DPI@HMV-RS17	Intratumoral *F. nucleatum*	Targeted bacterial eradication, chemotherapy and immune microenvironment reprogramming	Reduced tumor growth and metastasis; enhanced dendritic-cell maturation, CD8+ T-cell infiltration and M1-like macrophage polarization	(114)
OMV@Fe-ZIF-90@M	Decrease *F. nucleatum*	Microbial targeting + immune activation	Increased antitumor immune activity	(119)
TFENs	Gut microbiota remodeling	ROS-mediated tumor injury + systemic immune modulation	Reduced tumor growth and metastasis	(121)
FerriNano	Gut + intratumoral microbiota remodeling	Ferritinophagy/ferroptosis + microbiota modulation	Microbiota-dependent antitumor activity	(126)
MTI-PEG	Decrease *F. nucleatum*	Selective antibacterial targeting + therapy sensitization	Enhanced responses to multiple therapeutic modalities	(127)

Abbreviations: DD@FEL, doxycycline and doxorubicin co-loaded in a folate-functionalized, ergosterol-based liposome. Colistin-LipoFM, colistin-loaded liposomes fused with Fusobacterium nucleatum cytoplasmic membrane. Doxy-LipoFM, doxycycline-loaded liposomes fused with F. nucleatum cytoplasmic membrane. MF-SLNs, microfluidics-prepared, RGD-modified solid lipid nanoparticles. PEPCA@SPA/Fe^{3+}, sparfloxacin–ferric ion nanoparticles encapsulated in a polyethylene glycol–poly (cinnamyl aldehyde) copolymer. HN-T/BT@Lip, folate-modified liposomes co-encapsulating toyocamycin-loaded calcium carbonate–carboxymethyl chitosan hybrid nanoparticles and barium titanate. DPI@HMV-RS17, lipid nanoparticles co-loaded with doxorubicin, polymetformin, and IR820, functionalized with F. nucleatum–4T1 hybrid cell membrane vesicles and decorated with the RS17 peptide. OMV@Fe-ZIF-90@M, F. nucleatum outer membrane vesicle-coated, metronidazole-loaded iron-containing zeolitic imidazolate framework-90. TFENs, tea flower-derived exosome-like nanovesicles. FerriNano, ferritin nanochaperone composed of ferritin-homing peptide-functionalized nanoceria coated with hyaluronic acid. MTI-PEG, polyethylene glycol-conjugated metronidazole. $CD8^+$, cluster of differentiation 8-positive. DOX, doxorubicin. F. nucleatum, Fusobacterium nucleatum. RGD, arginine–glycine–aspartic acid. ROS, reactive oxygen species. TMAO, trimethylamine N-oxide.

4.7 Comparative Therapeutic Value of Microbiome-Modulating Nanoplatforms

The therapeutic relevance of microbiome-modulating nanoplatforms should be assessed against existing treatment strategies, not solely based on their multifunctional design or superior efficacy relative to untreated controls. Conventional antibiotics offer established antibacterial activity but may disrupt beneficial microbial communities and promote antimicrobial resistance. Tumor-directed antibiotic nanocarriers may provide greater spatial control and reduce systemic exposure; however, preferential tumor accumulation does not necessarily confer selective bacterial targeting or preserve intestinal microbial function.

Multifunctional nanoplatforms integrate antimicrobial activity with chemotherapy, ferroptosis induction, phototherapy, or immunomodulation. Although these combinations have produced promising results in preclinical breast cancer models, their added therapeutic value must be distinguished from improvements in drug delivery and the independent anticancer activities of their constituent components. Similarly, microbiota-derived metabolite modulation and engineered bacterial biohybrids offer alternative approaches to modifying tumor–microbe interactions, but uncertainties about mechanistic specificity, biological reproducibility, microbial persistence, and safety constrain their clinical development.

The central question is therefore whether microbiome-directed engineering provides a reproducible therapeutic advantage over simpler treatment strategies. Future comparative studies should incorporate free-drug controls, conventional nanocarriers, platform-matched formulations without antimicrobial components, and microbiota-depleted or recolonized experimental models. Comparative endpoints should include tumor control, microbial selectivity, systemic toxicity, ecological stability, and the incremental contribution of microbiota modulation. These considerations are summarized in Table 2.

Table 2. Comparative Therapeutic Advantages and Unresolved Challenges of Microbiome-Modulating Strategies in Breast Cancer

Strategy	Potential advantage	Principal unresolved question
Systemic antibiotics	Established antibacterial activity and clinical accessibility	Can harmful ecological effects be avoided?
Tumor-directed antibiotic nanoparticles	Greater spatial control and potentially reduced systemic exposure	Is microbial selectivity demonstrated?
Multifunctional nanoplatforms	Simultaneous targeting of microbial and tumor-associated pathways	Does added complexity provide incremental therapeutic benefit?
Engineered bacterial biohybrids	Localized therapeutic production and responsive delivery	Can colonization, persistence and systemic safety be controlled?
Microbiota-derived metabolite modulation	Potentially more selective biological intervention	Which metabolites have reproducible causal effects?

5. Mechanistic Basis of Microbiome-Modulating Nanotherapy

Microbiome-directed nanoplatforms may influence therapeutic responses through complementary mechanisms, including modulation of intratumoral bacteria, enhanced chemotherapy delivery, and remodeling of local antitumor immunity. In preclinical triple-negative breast cancer models, a doxycycline- and doxorubicin-loaded liposomal platform demonstrated that microbiota modulation can complement chemotherapy to suppress tumor growth and metastasis (85). In contrast, bacteria-derived nanovesicle platforms, discussed in Section 4.6, exploit microbial components to stimulate antitumor immunity rather than primarily depleting tumor-associated bacteria (128). These distinct approaches illustrate why microbiota-dependent effects must be distinguished from the direct pharmacological and immunological activities of nanoplatforms.

Other experimental approaches have investigated changes in drug distribution and immune activity (65, 83, 130). Nanocarriers can increase intratumoral drug exposure and protect therapeutic cargo from premature degradation, but these pharmacological effects can themselves improve tumor control independently of microbiota modulation. Similarly, changes in dendritic cells, cytotoxic T cells, NK cells, macrophages, Tregs, and MDSCs may reflect direct nanomaterial or drug effects as well as microbial remodeling. Mechanistic studies therefore need to distinguish microbiota-dependent effects from the intrinsic pharmacological and immunological activity of the nanoplatform. For platforms involving microbial metabolites, targeted metabolomics combined with metabolite-depletion and rescue experiments will be particularly important for distinguishing causal mediators from treatment-associated metabolic changes.

Understanding these mechanisms may eventually support microbiome-informed treatment selection, although their application to personalized nanotherapy remains investigational. Substantial interpatient variability in microbiome composition complicates, rather than yet enables, microbiome-guided nanotherapy (131). Advances in 16S rRNA sequencing, metagenomic analysis, and multi-omics approaches have enabled detailed characterization of microbiome profiles, helping identify microbial markers of response and disease progression (131, 132). Combining microbial markers with nanotechnology may support patient stratification, rational use of microbiome-specific nanocarriers, and tailoring drug combinations based on individual microbiome and tumor profiles (131, 133). Whether microbiome-based stratification improves treatment selection, efficacy, or toxicity beyond established tumor and host biomarkers remains to be tested prospectively (134).

Integrating microbiome, metabolome, immunome, and other multi-omic data with machine-learning approaches could assist patient stratification and modeling of nanocarrier–microbiome–host

interactions (135). Such models will require external validation, adequate sample sizes, standardized input data, and prospective demonstration that their predictions improve therapeutic decision-making.

Despite promising preclinical results, many obstacles remain before microbiome-regulating nanotechnologies can be implemented in clinical practice. Key prerequisites for successful implementation include standardizing microbiome analysis tools, validating microbial biomarkers with high predictive value, and conducting well-planned clinical trials (136, 137). Until standardized microbial measurements, reproducible biomarkers, and prospective clinical evidence are available, microbiome-guided nanotherapy should be regarded as an experimental precision-medicine strategy rather than an established treatment paradigm.

6. Translational Barriers and Clinical Development.

The clinical translation of microbiome-regulating nanomedicine for breast cancer faces considerable biological and technological limitations. Interpatient heterogeneity in both gut and intratumoral microbiota impedes reproducibility (28). Safety remains a critical concern because disrupting the microbial ecosystem could cause chronic dysbiosis, immune imbalance, and inflammation. In addition, preclinical models of the tumor-microbiome interface have insufficient fidelity to humans (138). The lack of a standard process for evaluating the microbiome, nanoparticles, and pharmacokinetics-microbiome interactions reduces comparability and slows regulatory progress (139). Moreover, detecting and quantifying tumor-associated bacteria or metabolites in the microbiome further hinders the development of effective treatments (16). Tumor heterogeneity, including differences in vasculature and microbial niches, also affects nanoparticle delivery and retention.

A major analytical challenge is reliably characterizing low-biomass intratumoral microbiota, where microbial signals may be difficult to distinguish from contamination introduced during tissue collection, processing, DNA extraction, and sequencing (13, 15). Analytical workflows for low-biomass samples should include appropriate negative controls and assessment of reagent-derived contamination (140). Importantly, sequencing-based detection of microbial DNA does not establish bacterial viability, active colonization, or functional involvement in tumor biology (13). Differences in extraction reagents and laboratory processing can generate misleading microbial profiles, particularly in low-biomass samples (140). Accordingly, claims of intratumoral microbial persistence or functional activity should be supported by complementary spatial, microbiological, or transcriptomic evidence. Standardized microbial measurements and independently validated biomarkers are essential to distinguish biologically relevant microbial communities from technical artifacts and establish the clinical relevance of microbiome-targeted therapeutic strategies (136, 137).

Moreover, significant interindividual variability in gut and breast microbiome composition, influenced by age, diet, ethnicity, antibiotic exposure, obesity, hormonal status, and environmental factors, makes developing universally applicable microbiome-based therapeutic strategies challenging (131, 141). Although preclinical models report microbiome remodeling and improved antitumor responses, clinical evidence for microbiome-directed interventions in breast cancer remains sparse, and clinical evidence for microbiome-modulating nanomedicine remains unestablished. Fecal microbiota transplantation (FMT) carries documented pathogen-transmission risks: donor-derived drug-resistant Escherichia coli caused bloodstream infections in recipients (142). Similarly, clinical evidence from gastrointestinal conditions indicates that probiotic benefits vary across indications, strains, and formulations, limiting the generalizability of findings between preparations (143).

Furthermore, emerging microbiome-based nanomedicine approaches encounter additional challenges, including targeted delivery to specific microbial or tumor-associated sites, nanoparticle stability, long-term biosafety evaluation, scalable manufacturing, and regulatory approval. The absence of standardized regulatory frameworks and ethical guidelines for microbiome-derived therapeutics further restricts their clinical implementation (144, 145). Therefore, future studies should develop standardized analytical protocols, conduct well-designed multicenter clinical trials, and establish personalized microbiome-based strategies to support the safe and effective translation of microbiome-targeted therapies into clinical practice.

Clinical investigation of the microbiome in breast cancer remains in its early stages (Table 3). Existing studies primarily examine probiotics or microbiome profiling, whereas FMT as an immunotherapy-resensitization strategy has been investigated principally outside breast cancer. Small cohorts, heterogeneous populations, non-standardized microbiome assays, and limited efficacy endpoints restrict cross-study interpretation. Clinical evidence supporting microbiome-modulating nanomedicines in breast cancer remains unestablished, leaving a substantial translational gap between the preclinical platforms discussed here and demonstrated patient benefit.

A major limitation across the current literature is that microbiome modulation is frequently measured as a treatment-associated endpoint rather than tested as a causal determinant of therapeutic response. Many nanoplatforms simultaneously alter drug pharmacokinetics, tumor-cell viability, oxidative stress, vascular permeability, and immune activity, making it difficult to attribute improved efficacy specifically to microbial remodeling. Antibiotic-depletion experiments provide useful evidence but are themselves confounded by systemic metabolic and immunological effects.

Stronger causal inference will require platform-matched controls, gnotobiotic or defined-community models, microbial depletion followed by recolonization, and rescue experiments linking specific taxa or metabolites to therapeutic response. Without such evidence, changes in microbial abundance are described as treatment-associated rather than microbiome-mediated.

Table 3: Clinical studies of microbiome-directed interventions in breast cancer and relevant evidence from other solid tumors.

Clinical strategy	Clinical Trial ID	Disease	Intervention	Main objective	Major limitation	Ref
Fecal microbiota transplantation (FMT) + anti-PD-1	NCT03353402	Melanoma	FMT + anti-PD-1 immunotherapy	Restore immunotherapy response	Safety, donor variability, and lack of standardization	(146)
Engineering gut microbiome using probiotics	NCT03358511	Breast cancer	Primal Defense Ultra® probiotic	Evaluate probiotic supplementation on the gut microbiome, immune function	Small sample size, short intervention period, limited evidence of therapeutic efficacy	NCT03358511
Probiotic intervention	NCT04362826	Breast cancer	BIOHM probiotic versus placebo	Assess the effects of probiotics on gut and breast microbiome composition and systemic inflammation	Microbiome and inflammatory endpoints do not establish improved breast-cancer treatment outcomes.	NCT04362826

Microbiome biomarker profiling	Various observational studies. No NCT	Breast cancer	16S rRNA sequencing and microbiome analysis	Identify microbial biomarkers associated with breast cancer diagnosis, prognosis, and treatment response	Lack of standardized sampling, sequencing, and bioinformatics methods	(15)

Abbreviations: 16S rRNA, 16S ribosomal RNA. Anti-PD-1, antibody targeting programmed cell death protein 1. FMT, fecal microbiota transplantation. NCT, ClinicalTrials.gov trial registration identifier prefix.

7. Critical Perspectives and Research Priorities

Future development should prioritize establishing the clinical utility of microbiome-targeted nanotherapy rather than increasing platform complexity alone. Clinical microbiome studies have demonstrated the potential of strain-resolved microbial signatures to predict immunotherapy response, while also revealing important limitations in reproducibility across treatment regimens (147). Prospective studies in breast cancer are therefore needed to determine whether microbial biomarkers provide predictive value beyond established clinical variables and whether deliberate microbiome modulation improves treatment outcomes. Multi-omic and computational approaches may help model nanocarrier–microbiome–host interactions, but their utility will depend on standardized datasets and external validation (148, 149).

Stimuli-responsive and theranostic platforms could improve spatial or temporal control of treatment (150, 151), although additional engineering complexity must be balanced against manufacturability, reproducibility, safety, and regulatory feasibility. Another research priority is to determine whether tumor-associated bacteria can serve as reproducible targets for precision nanomedicine. Song et al. developed bacteria-targeted mesoporous silica nanoparticles and demonstrated tumor targeting in mouse models of colon, lung, and breast cancer (152). Clinical translation will require confirmation that the targeted bacterial features are reproducible, biologically relevant, and accessible in naturally occurring human breast tumors.

A further challenge is determining when microbiota modulation contributes enough to justify its inclusion in a therapeutic nanoplatform. If tumor accumulation or the anticancer cargo accounts for most of the observed benefit, adding a microbiome-directed component may increase biological and regulatory complexity while offering little clinical value. Studies should use platform-matched comparators that deliver the same anticancer cargo at comparable tumor exposure. Microbiota depletion and controlled recolonization can help determine whether the treatment response depends on specific organisms or microbial functions. Patient stratification should account for breast cancer molecular subtype, disease stage, treatment history, and baseline microbial features. Candidate microbial biomarkers should be validated in independent cohorts to establish whether they predict added benefit from microbial targeting.

These priorities place comparative therapeutic value at the center of nanoplatform development. Clinically representative tumor models, rigorous microbial controls, and standardized analytical methods can help establish which approaches warrant further study. Comparisons with conventional drug delivery should assess the magnitude and durability of any improvement in tumor control and determine whether it comes at the cost of greater toxicity or persistent disruption of commensal communities. For clinical translation, the strongest case would be a reproducible benefit in a defined patient population that is large enough to justify the additional demands of manufacturing, safety monitoring, and regulatory evaluation.

Discussion

Evidence reviewed here supports interactions among tumor-associated microbiota, gut microbial communities, host immunity, and therapeutic response in breast cancer, although the strength of evidence varies across mechanisms and experimental systems. Nanocarriers can modify these interactions while delivering cytotoxic, ferroptosis-inducing, photothermal, or immunomodulatory interventions. This versatility creates an attribution problem because the same formulation can alter microbial abundance, drug exposure, tumor-cell viability, and immune activity. To determine whether microbial changes contribute to tumor control, studies should compare formulations with matched anticancer cargo and delivery properties that differ in microbial targeting. Microbial depletion and reconstitution experiments can then help establish whether specific organisms or microbial products influence the response to treatment.

The translational significance of these findings depends on whether microbiota-associated effects observed in experimental models can be reproduced across clinically heterogeneous breast cancers. Low microbial biomass in tumor specimens complicates distinguishing resident organisms from contamination, while differences in sampling and processing can limit comparisons across studies. Gut and intratumoral microbial changes should also be measured separately because shifts in one compartment provide limited information about the other. Longitudinal sampling could help determine whether microbial changes precede tumor regression or occur after treatment alters the tumor environment. In clinical studies, baseline microbial profiles, breast cancer subtype, and prior antibiotic exposure may help explain why patients respond differently to the same intervention. Changes in microbial composition and immune markers can inform mechanistic interpretation, while comparative clinical outcomes are needed to establish therapeutic benefit.

In conclusion, microbiome-modulating nanoplatforms offer a way to integrate microbial targeting with breast cancer therapy. Preclinical studies report effects on microbial communities, drug delivery, immune responses, and tumor control, but the independent contribution of microbiota modulation remains incompletely established, and clinical validation is lacking. Progress will depend on reproducible microbial biomarkers, mechanistic studies that isolate the contribution of microbial targeting, and long-term safety assessment, including the persistence of treatment-induced changes in microbial communities. The decisive clinical question is whether adding microbial targeting to a comparable treatment regimen improves response depth or durability, reduces recurrence, or lowers treatment-related toxicity.

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Declarations

Funding Statement: The author acknowledges financial support from the Indian Council of Medical Research (ICMR), New Delhi, India, and the Central Council for Research in Unani Medicine (CCRUM), New Delhi, India, through Extramural Research Grants.

Competing Interest: The authors declare no financial or personal relationships with other individuals or organizations that could inappropriately influence or bias the content of this work. All authors have read the final version of the manuscript and confirm that there are no competing interests.

Consent for publication: All authors have approved the final version of the manuscript.

Use of Artificial Intelligence Disclosure: This article was written by human contributors. Artificial intelligence (AI)-based tools were used to improve grammar, language, and readability without altering the scientific content, data interpretation, or conclusions. Figure illustrations were prepared with assistance from generative AI and subsequently reviewed and edited by the authors, as needed, for scientific accuracy. The authors reviewed and verified the final manuscript, including all AI-assisted content, and take full responsibility for its accuracy and integrity.

Data Availability Statement: No datasets were generated or analyzed in the current study.

Ethics approval and consent to participate: Not applicable. This review reports no new studies involving human participants or animals.

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