

Microbiome-Targeted Polymeric Nanotherapeutics for Systemic Disease Management

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Abstract

Microbiome-targeted polymeric nanotherapeutics have emerged as a promising precision medicine approach for the management of gastrointestinal and systemic diseases by modulating interactions between the host, microbiota, and therapeutic agents. Dysbiosis can influence immune, metabolic, inflammatory, and neurobiological pathways and is associated with disease progression across multiple organ systems. Conventional microbiome-directed interventions often face limitations related to poor stability, enzymatic degradation, inadequate mucosal residence, and inconsistent therapeutic exposure. Polymeric nanocarriers provide opportunities to overcome these barriers through improved drug protection, tunable biodegradation, enhanced drug loading, and spatiotemporally controlled release. This review highlights the role of natural and synthetic polymeric systems in microbiome-targeted delivery, with emphasis on mucoadhesive, mucus-penetrating, pH-responsive, redox-responsive, enzyme-responsive, and actively targeted nanocarriers. Microbial metabolites, gastrointestinal pH, reactive oxygen species, and disease-associated bacterial enzymes are discussed as potential biological cues for site-specific therapeutic activation. The application of microbiome-targeted nanomedicine is further explored in cancer, inflammatory, metabolic, and immune-mediated disorders. Particular attention is given to host–microbiome interactions, biocompatibility, toxicological considerations, inter-individual microbiome variability, and translational challenges associated with manufacturing and regulatory requirements. Emerging strategies integrating artificial intelligence, metagenomics, multi-omics, and adaptive nanocarrier design may facilitate personalized therapeutic approaches and improve treatment precision.

Keywords: Microbiome-targeted therapy; Polymeric nanotherapeutics; Nanocarriers; Precision medicine; Targeted drug delivery.

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INTRODUCTION

Microbiome-targeted polymeric nanotherapeutics represent a precision medicine strategy to manage systemic disease by reprogramming the host–microbiome ecosystem and thereby modulating downstream immune, metabolic, and neuroinflammatory cascades; in this context, dysbiosis is mechanistically linked to both local gastrointestinal pathology and broader systemic manifestations, including chronic inflammation and disease progression across organ systems, as supported by recent reviews emphasizing the centrality of dysregulated microbiomes in chronic inflammatory disorders and systemic outcomes (Albadari et al., 2024). However, conventional microbiome-directed interventions (e.g.,

unformulated pre/probiotics, fecal microbiota transplantation) face major translational constraints due to structural and biological barriers: epithelial and mucosal interfaces impose limited residence time and selective uptake, enzymatic degradation reduces effective payload availability, and dynamic luminal shear forces hinder stable colonization or sustained therapeutic exposure, collectively contributing to inconsistent outcomes and incomplete disease control (Azwar et al., 2021). These limitations also align with the broader drug-delivery problem that microbiome-targeting agents must remain functional in harsh gastrointestinal conditions while still reaching intended inflamed niches; self-assembled and engineered nanoparticle

systems are therefore highlighted as capable of surviving gastric conditions and improving localization to inflamed regions using active and/or passive targeting, which reduces off-target toxicity relative to less controlled approaches (Broesder et al., 2020). Within this evolving landscape, polymeric nanotherapeutics are increasingly favored over metallic or lipidic nanocarriers because polymer chemistry enables rational tailoring of biodegradation kinetics, structural stability, and drug-loading capacity, while also supporting spatiotemporal release and route-dependent performance; biodegradable polymeric nanoparticles can improve stability and activity of insoluble actives, protect therapeutic payloads from degradation, and potentially reduce dose frequency, thereby mitigating systemic adverse effects (Bukowski et al., 2020). At a mechanistic level, microbiome-targeted polymer architectures can be designed for mucosal adhesion or mucus penetration, offering strategies to navigate the mucus barrier and enhance contact with microbial communities and/or mucosa-associated immune compartments; for example, mucoadhesive polymers (such as chitosan derivatives) are discussed for stomach targeting, whereas mucus-penetrating functionalization (e.g., polyethylene glycol) can support small-intestinal delivery, and parenteral formulations are engineered to address rapid clearance and enhanced bioavailability (Cervantes et al., 2024). Importantly, microbiome-responsive or microbiome-mediated release concepts extend polymeric platforms beyond simple drug transport to functional modulation of dysbiosis: the therapeutic payload may include immunomodulatory agents, antimicrobial modulators with selectivity, or microbiome-derived metabolites (such as short-chain fatty acids and bile-acid derivatives) that act as systemic regulators, with engineered probiotics and bacteriophage-based modalities further enabling sensing of disease states and targeted secretion of therapeutic molecules (Chuang et al., 2024). For systemic disease management, the translational rationale is that microbial metabolites and host-immune signaling can propagate from the gut to distant organs via circulation and immune axis effects, meaning that improving microbial homeostasis and suppressing harmful taxa can influence metabolic dysfunction, inflammatory tone, and neurodegenerative susceptibility (Guo et al., 2022).

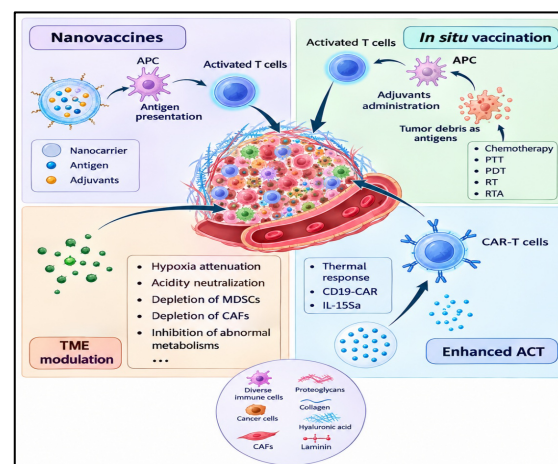


Figure 1: Nanotechnology-Based Strategies for Cancer Immunotherapy and Tumor Microenvironment Modulation
Pathophysiological Targets and Microbiome Signaling Cascades

Pathophysiological microbiome signaling cascades are driven by luminal metabolites and microbial effectors that reprogram mucosal immune tone and enable systemic immune activation, with downstream relevance to inflammation and cancer susceptibility (He et al., 2025). Microbial metabolite classes act as therapeutic intermediates by engaging host signaling targets: short-chain fatty acids (SCFAs) participate in immune regulation and epithelial homeostasis, while secondary bile acids and trimethylamine N-oxide (TMAO) function as microbiota-derived signaling metabolites that alter host metabolic responses through their receptor-mediated actions; lipopolysaccharides (LPS) act as potent pro-inflammatory stimuli that can amplify cytokine networks and establish a chronic inflammatory microenvironment (Kridis et al., 2019). Mechanistically, mucosal barrier permeability is compromised when tight junction architecture is disrupted, with reduced expression or functional impairment of ZO-1 and occludin (Occludin) weakening paracellular sealing; this promotes mucosal access of microbial components and metabolites, facilitating systemic translocation events that trigger systemic immune activation through innate immune pattern recognition signaling (Pienidz et al., 2024). At the organismal level, these events reflect “trans-kingdom” signaling in which microbiota-derived biotransformation products provide molecular cues to host tissues, and systems-level insights link dysbiosis with diseases including inflammatory bowel disorders and multiple cancer types via altered immunity, energy, and metabolic pathways. For nanomedicine-based targeting, microenvironment-specific biomarkers can be exploited as spatially resolved cues across the gastrointestinal tract (Puccini et al., 2018). First, gastrointestinal pH gradients (approximately pH

1.2 to 7.4) govern nanoparticle solubility, surface charge switching, and carrier disassembly kinetics, thereby enabling site-selective drug release across different intestinal segments. Second, inflamed microenvironments exhibit altered redox potential and reactive oxygen species (ROS) overproduction, which can promote oxidative stress, affect epithelial barrier stability, and create a chemically distinct target window for redox-responsive materials that undergo ROS-triggered transformations (Sahin et al., 2019). Third, bacterial enzyme overexpression provides substrate-level targeting opportunities: azoreductases, glucosidases, and nitroreductases can be upregulated in dysbiotic states, generating metabolite intermediates or cleavage products that activate prodrugs, enhance retention, or concentrate therapeutics at diseased foci (Zhang et al., 2025). Together, these metabolite-driven and barrier-mediated cascades define a pathophysiology-informed “targetome and signalome” framework, supporting biomarker-guided nanotargeting strategies that align carrier activation with the biochemical geography of disease pH for anatomical specificity, ROS/redox for inflammatory state specificity, and microbial enzyme expression for functional specificity while also rationalizing why microbiota-derived signaling molecules (including SCFAs, bile acids, TMAO, and LPS) are increasingly viewed as causal mediators and diagnostic/prognostic biomarker candidates in host–microbe cross-talk (Qiu et al., 2025).

Table 1: Natural and biopolymer-based materials employed in nanocarrier systems for targeted and functional drug delivery.

Pol ymer	Natur al Source	Nano carrier / Delivery System	Target ing or Functional Approach	Biocom patibility Profile	Referenc es
Chitosan	Derived from chitin, primarily obtained from crustacean shells	Nanoparticles, micelles, hydrogels	pH-responsive delivery and enhanced accumulation through the EPR effect	High; biodegradable and generally non-toxic	(Jain et al., 2024)
Inulin	Naturally present in	Nanoparticles, micell	Ligand /receptor-assiste	High; biodegradable with	(Wang et al., 2023)

	chicory and Jerusalem artichoke	es, hydrogels	d targeting, including folate-mediated approaches	good biological tolerance	)
Fucoidan	Sulfated polysaccharide obtained mainly from brown seaweeds	Nanoparticles and hydrogel systems	Promotes apoptotic pathways and modulates immune responses	Moderate to high; bioactive and immunomodulatory characteristics	(Arafat et al., 2024)
Guar gum	Seed endosperm of <i>Cyamopsis tetragonoloba</i>	Microspheres and nanoparticles	pH-responsive release and mucoadhesive interaction	High; biodegradable and generally well tolerated	(Mao et al., 2024)
Gelatin	Protein derived from animal collagen	Nanoparticles and hydrogels	Thermally responsive systems with inherent biocompatibility	High; biodegradable and biocompatible	(Jain et al., 2024)
Pectin	Commonly extracted from citrus fruits	Nanoparticles and hydrogels	pH-dependent drug release and mucoadhesion	High; biodegradable and generally non-toxic	(Zhang et al., 2024)
Xanthan gum	Microbial polysaccharide produced	Nanoparticles and hydrogels	pH-sensitive behavior and mucoadhesive	High; biodegradable and well tolerated	(Wu et al., 2021)

	by <i>Xanthomonas campestris</i>		e drug delivery		
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Polymeric Nanomaterial Platforms: Classification and Synthesis

Natural and Biopolymer Constructs

Chitosan, alginate, pectin, hyaluronic acid, and dextran form biopolymeric matrices that support native target recognition, mucoadhesion, and enzymatic responsiveness within nanomedicine systems (Hirko et al., 2022). Chitosan provides cationic surface charge enabling electrostatic binding to anionic mucins and cell membranes, promoting mucoadhesion and enhanced residence time at mucosal interfaces. Alginate hydrogels exhibit ionically crosslinked networks that respond to divalent cation concentrations, facilitating environmentally sensitive payload release and tissue-compatible scaffolding (Ramirez et al., 2020). Pectin offers gelling behavior dependent on pH and calcium ions, enabling stimulus-tuned cargo stabilization. Hyaluronic acid provides receptor-mediated targeting via CD44 and other glycoprotein clusters, supporting selective uptake in certain cancerous or inflamed tissues. Dextran contributes versatile functionalization routes and hydrocolloid properties for stealth delivery and controlled release. Collectively, these polysaccharide and polycationic constructs enable native-like targeting, surface modification, and enzyme-triggered disassembly, underpinning biocompatible nanocarriers with biologically attuned degradation pathways (McKee et al., 2021).

Synthetic and Biodegradable Polymers

Poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), poly (ethylene glycol) (PEG), and polyphosphazenes provide tunable molecular weight, polydispersity, and metabolic clearance profiles that govern pharmacokinetics and safety (Bernardo et al., 2023). PLGA and PCL yield hydrolytically degradable backbones allowing sustained drug release and programmable erosion. PEG imparts hydrophilicity and stealth characteristics reducing opsonization and prolonging systemic circulation. Polyphosphazenes introduce inorganic–organic hybrid backbones with facile side-chain diversification, enabling precise control of hydrophilicity, degradability, and biointeraction. By adjusting monomer ratios, end-group chemistry, and molecular weight, researchers tailor release kinetics, mechanical properties, and biodegradation products to match therapeutic windows while minimizing accumulation and toxicity (Laborda-Illanes et al., 2020).

Stimuli-Responsive “Smart” Polymers

pH-Sensitive systems like poly (methacrylic acid-co-methyl methacrylate) (Eudragit polymers)

exploit protonation state changes to trigger cargo release in acidic environments such as endosomes or tumor microenvironments. ROS/Redox-Responsive polymers, including poly (thioether ketal) and boronic ester-functionalized polymers, respond to oxidative stress or reductive intracellular milieus, enabling selective disassembly and payload liberation within diseased tissues (Flores et al., 2012). Enzyme-Cleavable architectures employing azo-crosslinked polymers and colonic microflora-responsive polysaccharides enable site-specific degradation in response to gut microbiota enzymes or other enzymatic cues, enhancing intestinal delivery and minimizing systemic exposure. These smart polymers provide programmable sensitivity to microenvironmental cues, enabling targeted dosing and reduced off-target effects (Parida & Sharma et al., 2019).

Architectures and Nanostructural Variants

Polymer-drug conjugates covalently tether therapeutic molecules to polymeric backbones, enabling improved solubility, targeting, and controlled release via bond cleavage. Polymeric micelles, with a hydrophobic core and hydrophilic corona, enhance solubilization of poorly water-soluble drugs and permit core-dominated release (Wei et al., 2024). Nanogels and hydrogels offer highly swollen, crosslinked networks for rapid or stimuli-triggered swelling and cargo diffusion control. Dendrimers provide highly defined, monodisperse, highly branched architectures enabling multivalent surface functionalization and precise loading capacity. Bacterial membrane-coated polymeric nanoparticles combine natural membranes with synthetic cores to impart inherent immune evasion and pathogen-derived targeting features. These diverse architectures expand the design space for optimized biodistribution, targeting accuracy, payload protection, and responsive release across cancer nanotherapy and systemic delivery contexts (Kovács et al., 2019).

Spatiotemporal Targeting Mechanisms

Spatiotemporal targeting mechanisms integrate passive, active, and environment-responsive strategies to achieve precise, time- and location-specific drug delivery across complex biological barriers (Luu et al., 2018). In passive targeting, surface charge tuning and PEGylation or zwitterionic polymer functionalization are employed to minimize nonspecific adhesion and to enable diffusion through mucus and dense extracellular matrices, thereby enhancing penetration of mucosal surfaces while reducing immunogenic recognition; such surface engineering modulates nanoparticle–mucus interactions, governs steric stabilization, and tunes nanoparticle mobility to align with the viscoelastic properties of the target mucosa (Park et al., 2021). Active cell- and bacteria-specific targeting leverages lectin- and carbohydrate-functionalized nanocarriers to

recognize distinctive bacterial cell-wall motifs, and utilizes antibody- or peptide-conjugated nanoparticles that bind dysbiotic epithelial markers, yielding selective uptake by pathogenic or dysregulated cells while spare normal tissues; this dual targeting improves specificity, minimizes off-target cytotoxicity, and can disrupt microbial biofilms or recolonization patterns (Bernardo et al., 2023). Microenvironment-triggered payload release relies on dual- and multi-responsive logic-gate polymer matrices that respond to combinations of pH, redox potential, enzymatic milieu, or ionic strength to release payloads only at designated anatomical sites or disease microenvironments; such gating enables synchronized, on-demand therapy, reduces systemic exposure, and supports complex therapeutic regimens, including sequential or combinatorial delivery (Chung et al., 2020). Together, these mechanisms enable spatiotemporal control over therapeutic distribution, with passive mucus navigation complemented by targeted cellular recognition and conditioned release, forming a cohesive framework for advanced nanomedicine in cancer therapy, infection control, and mucosal drug delivery (Jayawardena et al., 2017).

Table 2: Selected Patented Nanocarriers for Mucosal Drug and Gene Delivery

Nano carrier	Patent / Invention	Drug / Cargo	Patent No.	Assignee	Reference
Mucus-penetrating nanoparticles	Enhanced mucosal drug delivery	Loteprednol etabonate	CA2871748	Alcon Inc.; Kala Pharmaceuticals	(Zhang et al., 2015)
Hypotonic nanoparticles	Improved mucus transport	Doxorubicin	US9629813B2	Johns Hopkins University	(Sun et al., 2021)
Liposomal mucus-penetrating nanoparticles	Rapid mucus barrier traversal	CES T agent ; Doxorubicin	WO2013166498A1	Johns Hopkins University	(Naserifar et al., 2020)
PEI-based cationic nanoparticles	Mucus-permeable gene delivery	Nucleic acid	US9327037B2	Johns Hopkins University	(Priyam et al., 2018)

Cationic micro particles	Mucus-translocating drug/gene carriers	DNA	US20180344656A1	Johns Hopkins University School of Medicine	(Lee et al., 2020)
Biodegradable nanoparticles	Enhanced mucosal penetration	Not specified	EP2790733B1	Johns Hopkins University	(Li et al., 2019)
Polymeric nanoparticles	Improved mucus penetration	Doxorubicin	KR101811917B1	Not specified	(Teng et al., 2018)
Peptide conjugates	PEGylated integrin-targeting peptides	Integrin peptide	US11485758B2	University of California	(Sun et al., 2021)
PEG-vitamin E conjugate	Reduced mucosal adhesion	Vitamin E	US20200078304A1	Johns Hopkins University	(Chung et al., 2020)

Systemic Disease Management via Microbiome Modulation

Systemic disease management via microbiome modulation represents a paradigm shift in precision medicine, leveraging the gut microbiota as a master regulator of immune homeostasis, metabolic equilibrium, and neuroendocrine signaling to attenuate pathogenesis across diverse organ systems (Schneider et al., 2017). In gastrointestinal and systemic autoimmune diseases including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) dysbiosis characterized by diminished microbial diversity, depletion of short-chain fatty acid (SCFA)-producing taxa (e.g., *Faecalibacterium prausnitzii*), and expansion of pro-inflammatory species (e.g., *Prevotella copri* in RA; *Ruminococcus gnavus* in SLE) drives intestinal barrier disruption, molecular mimicry, and systemic autoreactivity via the gut–joint and gut–immune axes (Maisel et al., 2016). Therapeutic strategies such as synbiotics, fecal microbiota transplantation (FMT), and targeted prebiotics restore eubiosis, enhance regulatory T-cell (Treg)

differentiation, suppress Th17 polarization, and reduce circulating inflammatory markers (CRP, TNF- α , IL-6), with strongest clinical evidence in IBD and RA, though SLE responses remain heterogeneous due to strain-specific effects and host genetic variability. In metabolic and hepatobiliary disorders, the gut–liver–pancreas axis serves as a critical interface wherein microbiome remodeling through fermentable fiber augmentation, GLP-1 receptor agonists, metabolic surgery, or fermented foods attenuates hepatic steatosis, insulin resistance, and adipose inflammation in metabolic dysfunction-associated steatotic liver disease (MASLD), type 2 diabetes (T2DM), and obesity by enhancing butyrogenesis, reducing endotoxemia, modulating bile-acid signaling via FXR/TGR5 receptors, and improving gut barrier integrity to limit portal translocation of lipopolysaccharide (LPS) (Khutoryanskiy et al., 2018). For cardiovascular and renal pathologies, microbiome-targeted interventions inhibit microbial conversion of dietary choline and carnitine into trimethylamine (TMA), subsequently reducing hepatic flavin monooxygenase 3 (FMO3)-mediated oxidation to trimethylamine N-oxide (TMAO) a potent uremic toxin and cardiovascular risk factor while also attenuating accumulation of protein-bound toxins like indoxyl sulfate (IS) and p-cresyl sulfate (PCS) in chronic kidney disease (CKD) through Mediterranean diet adherence, prebiotic supplementation, or adsorbent therapies, thereby mitigating endothelial dysfunction, oxidative stress, and vascular remodeling within the gut–kidney–heart axis (Parlato et al., 2019). In neurological disorders governed by the gut–brain axis, polymeric nanocarriers engineered for gut-restricted or brain-penetrating delivery enable precise modulation of neuroinflammation in Parkinson’s disease, Alzheimer’s disease, and ischemic stroke by transporting anti-inflammatory biologics, SCFAs, or microbial metabolites across the blood–brain barrier or by locally suppressing gut-derived pro-inflammatory cytokines (IL-1 β , IL-17) that activate microglia and exacerbate neuronal damage, thus interrupting bidirectional neuro-immune crosstalk (Deirram et al., 2019). Finally, in immuno-oncology, intratumoral and gut microbiome engineering enhances immune checkpoint inhibitor (ICI) efficacy by enriching for immunostimulatory taxa (e.g., *Akkermansia muciniphila*, *Bifidobacterium spp.*) that promote dendritic cell maturation, CD8⁺ T-cell infiltration, and interferon- γ production within the tumor microenvironment, while FMT or defined consortia reverse ICI resistance in refractory melanoma and non-small cell lung cancer patients, underscoring the microbiome’s role as a dynamic biomarker and therapeutic lever for maximizing antitumor immunity across malignancies (Guo et al., 2023).

Biocompatibility, Toxicology, and Host–Microbiome Interactions

The biocompatibility, toxicology, and host–microbiome interaction profiles of polymeric nanotherapeutics are governed by an intricate triad of physicochemical degradation kinetics, off-target ecological perturbations of commensal flora, and immunological recognition events that collectively determine systemic safety and therapeutic index (Liu et al., 2015). Polymer biodegradation kinetics dictate the temporal release of monomeric and oligomeric residues whose molecular weight, hydrophobicity, and charge govern clearance pathways: low-molecular-weight fragments (<30–40 kDa) predominantly undergo renal filtration via glomerular sieving, whereas higher-molecular-weight or hydrophobically modified polymers evade renal elimination and accumulate in hepatic Kupffer cells and sinusoidal endothelium, where they may induce lysosomal overload, cytoplasmic vacuolation, and chronic inflammatory signaling; for instance, poly(ethylene glycol) (PEG) chains exceeding 30 kDa exhibit prolonged circulation half-lives and progressive hepatic sequestration due to insufficient oxidative degradation, while non-degradable cationic polymers such as high-generation polyamidoamine (PAMAM) dendrimers or branched polyethylenimine (PEI) resist enzymatic hydrolysis and persist in reticuloendothelial organs for weeks to months, triggering fibrotic remodeling and granulomatous responses (Suk et al., 2009). Concurrently, polymer degradation products or co-delivered antimicrobial payloads can exert non-target effects on commensal microflora by disrupting microbial membrane integrity, inhibiting essential metabolic enzymes, or altering luminal pH and redox potential, thereby inducing dysbiosis characterized by reduced alpha diversity, expansion of pathobionts such as Enterobacteriaceae, and depletion of short-chain fatty acid-producing taxa like *Faecalibacterium prausnitzii*, which may compromise gut barrier function and potentiate systemic endotoxemia; although direct evidence for polymer-induced dysbiosis remains emergent, studies on polylactic acid (PLA) oligomers reveal dose-dependent accumulation in gastrointestinal tissues and altered microbial metabolite profiles, suggesting that even ostensibly biocompatible polyesters may perturb microbial ecology upon chronic exposure (Bandi et al., 2020). Immunogenicity and complement activation represent a third critical axis of host response, wherein synthetic polymers despite historical classification as “inert” can elicit adaptive and innate immune reactions through haptenization, pattern-recognition receptor engagement, or direct complement cascade initiation; notably, PEGylated therapeutics have been implicated in the generation of anti-PEG IgM and IgG antibodies, which facilitate accelerated

blood clearance upon repeated dosing and activate the classical complement pathway to precipitate complement activation-related pseudoallergy (CARPA), manifesting clinically as acute infusion reactions ranging from urticaria and bronchospasm to life-threatening anaphylaxis, as evidenced by porcine models demonstrating lethal anaphylactic shock upon re-challenge with PEGylated liposomes concomitant with surges in pulmonary arterial pressure and terminal complement complex sC5b-9 (Fang et al., 2017). Mechanistically, anti-PEG antibodies recognize both backbone and end-group epitopes, with higher avidity observed toward structurally complex PEGylated liposomes, and their binding triggers opsonization, phagocytic uptake by macrophages, and release of anaphylatoxins C3a and C5a, which recruit mast cells and basophils to amplify hypersensitivity; furthermore, pre-existing anti-PEG seropositivity documented in PEG-naïve populations due to environmental exposure via cosmetics, laxatives, or food additives confers heightened risk for reduced drug efficacy and adverse events, underscoring the necessity for pre-screening and alternative polymer architectures such as poly(2-oxazoline)s or zwitterionic polymers that evade immune recognition (Kudgus et al., 2014).

Challenges, Emerging Technologies, and Future Perspectives

The convergence of artificial intelligence (AI), machine learning (ML), and patient-specific microbiome analytics represents a paradigm shift in the rational design and clinical translation of polymer-based nanotherapeutics, addressing long-standing challenges in encapsulation efficiency, gastrointestinal (GI) stability, targeted binding, and inter-patient variability in drug release kinetics (Poddubnyy et al., 2025). In silico screening powered by ML algorithms enables high-throughput virtual evaluation of polymer libraries for optimal physicochemical attributes including hydrophobicity, charge density, molecular weight distribution, and degradation profiles that govern encapsulation capacity, gut transit resilience, and receptor-mediated targeting specificity (Scher et al., 2025). These computational models integrate quantitative structure–activity relationship (QSAR) frameworks, molecular dynamics simulations, and deep learning architectures trained on experimental datasets to predict polymer–drug compatibility, stability under acidic gastric conditions, enzymatic resistance in the small intestine, and affinity for overexpressed biomarkers at disease sites such as tumor microenvironments or inflamed colonic mucosa (Wang et al., 2022). By reducing reliance on empirical trial-and-error synthesis, AI-driven polymer design accelerates lead optimization, minimizes resource-intensive wet-lab screening, and facilitates the identification of “design rules” linking backbone chemistry (e.g., polysaccharides,

polyesters, polyethers) to pathological contexts (e.g., oxidative stress in tumors, protease-rich synovial fluid in arthritis, pH gradients in IBD). Nevertheless, translational bottlenecks persist, including inadequate characterization of nanoscale heterogeneity, scalability of GMP-compliant manufacturing, and regulatory misalignment between nanomaterial complexity and current quality-by-design (QbD) expectations (Thompson et al., 2023). Emerging technologies in personalized microbiome nanotherapeutics further refine this landscape by leveraging metagenomic sequencing and multi-omics integration to stratify patients based on microbial enzyme abundance (e.g., β -glucuronidases, azoreductases, glycosidases) that govern polymer degradation triggers in colon-targeted delivery systems. Inter-individual variations in microbiota composition driven by diet, age, antibiotic exposure, and disease state can lead to premature or delayed drug release, compromising therapeutic windows and increasing off-target toxicity risks (Ruff et al., 2020). To mitigate this, next-generation platforms incorporate dual-trigger mechanisms (e.g., pH-responsive outer coatings combined with microbiota-cleavable linkers) and adaptive polymer architectures whose cross-link density, substitution patterns, and layer thickness are tuned to broaden the “activation window” and reduce dependence on a single microbial phenotype (Salem et al., 2019). AI-enhanced toxicology platforms simulate host–microbiome–nanocarrier interactions, predicting metabolic disruptions and adverse events prior to human trials, thereby enabling dynamic formulation adjustments aligned with individual microbial landscapes. Such patient-specific customization not only enhances bioavailability and therapeutic index but also supports the development of “tribiotic” strategies wherein nanocarriers, probiotics, and prebiotics are co-engineered to modulate microbial metabolism for synergistic efficacy (Wang et al., 2022).

CONCLUSION

Microbiome-targeted polymeric nanotherapeutics represent an emerging approach for integrating advanced drug delivery with microbiome modulation and systemic disease management. The reviewed evidence highlights that dysbiosis can influence gastrointestinal, immune, metabolic, inflammatory, and neurobiological pathways, supporting the therapeutic relevance of restoring or selectively modifying microbial homeostasis. Polymeric nanocarriers provide important advantages through tunable biodegradation, improved drug stability and loading, enhanced mucosal interaction, and controlled spatial and temporal drug release. Mucoadhesive, mucus-penetrating, pH-responsive, redox-responsive, enzyme-responsive, and actively targeted systems offer multiple strategies for overcoming

gastrointestinal barriers and achieving site-specific therapeutic action. Furthermore, microbiome-responsive delivery, engineered probiotics, bacteriophage-based approaches, and microbial metabolite-based strategies may extend nanotherapeutics beyond conventional drug transport toward functional regulation of host–microbiome interactions. Despite these advances, translation into clinical applications remains challenging. Inter-individual microbiome variability, premature or delayed payload release, potential disruption of beneficial microbial communities, polymer-related toxicity, immunogenicity, manufacturing scalability, and regulatory requirements require careful consideration. The integration of artificial intelligence, machine learning, metagenomics, multi-omics, and adaptive nanocarrier architectures may help address these limitations by enabling more precise and personalized therapeutic design. Future development should therefore emphasize biocompatibility, long-term microbiome safety, reproducible manufacturing, and clinically relevant validation.

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