Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

MECHANICAL ENGINEERING APPROACHES TO DECODE GUT MICROBIOME INFLUENCE ON CANCER IMMUNOTHERAPY: FROM MICROCHIPS TO PRECISION MEDICINE

Muqadas Munir[1*], Javeria Hadi[2,3]

[1]*University of Azad Jammu and Kashmir, Muzaffarabad, AJK, Pakistan*
[2]*University of Peshawar, Pakistan*
[3]*F.G Degree College for Women Peshawar Cantt, Pakistan*

[*1]muqadasmunir869@gmail.com, [2]javeriahadi1@gmail.com

DOI: https://doi.org/10.5281/zenodo.20712181

Keywords
Gut microbiome; cancer immunotherapy; microfluidics; gut-on-a-chip; 3D bioprinting; biosensors; precision medicine

Article History
Received: 11 May 2026
Accepted: 08 June 2026
Published: 16 June 2026

Corresponding Author: *
Muqadas Munir

Abstract

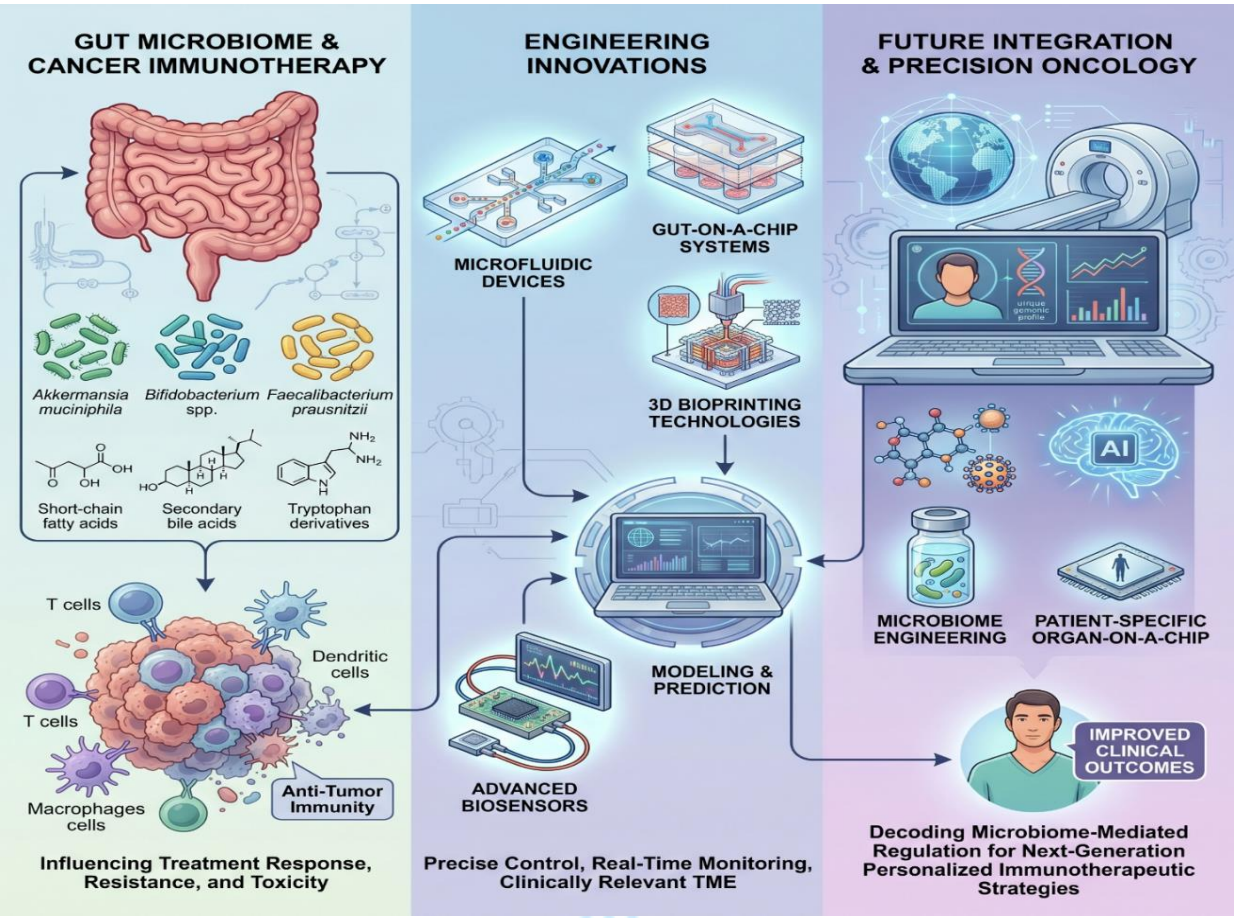
The gut microbiome has emerged as a critical determinant of cancer immunotherapy efficacy, influencing treatment response, resistance, and immune-related toxicity through complex interactions with host immune pathways. Recent evidence highlights the roles of beneficial microorganisms, including Akkermansia muciniphila, Bifidobacterium spp., and Faecalibacterium prausnitzii, as well as microbial metabolites such as short-chain fatty acids, secondary bile acids, and tryptophan derivatives, in regulating anti-tumor immunity. However, conventional cell culture systems and animal models often fail to accurately replicate the dynamic interactions among microbial communities, host tissues, immune cells, and tumors. This review examines how mechanical engineering innovations are transforming microbiome–cancer research through the development of microfluidic devices, gut-on-a-chip systems, tumor-on-a-chip platforms, three-dimensional bioprinting technologies, and advanced biosensors. These technologies enable precise control of physiological conditions, real-time monitoring of microbial and immune responses, and recreation of clinically relevant tumor microenvironments. The review further discusses their applications in modeling host–microbe communication, predicting immunotherapy responses, evaluating drug resistance, and facilitating personalized therapeutic screening. Major translational challenges, including standardization, manufacturing scalability, regulatory approval, and clinical validation, are critically assessed. The current evidence indicates that engineering-driven platforms provide powerful tools for decoding microbiome-mediated regulation of cancer immunotherapy and offer a foundation for next-generation precision oncology. Future integration of artificial intelligence, microbiome engineering, nanotechnology, and patient-specific organ-on-a-chip systems may enable highly personalized immunotherapeutic strategies and improve clinical outcomes.

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Graphical Abstract



INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide despite significant advances in diagnosis and treatment. In recent years, cancer immunotherapy has revolutionized oncology by harnessing the host immune system to recognize and eliminate malignant cells. Immune checkpoint inhibitors targeting programmed cell death protein-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have demonstrated remarkable clinical success across multiple cancer types, including melanoma, lung cancer, renal cell carcinoma, and colorectal cancer (Ghemrawi et al., 2024). However, durable therapeutic responses are observed in only a subset of patients, highlighting the need to identify biological factors that influence treatment efficacy and resistance (Li et al., 2025).

Among the factors affecting immunotherapy outcomes, the gut microbiome has emerged as a critical regulator of anti-tumor immunity. The human gastrointestinal tract harbors trillions of microorganisms, including bacteria, fungi, archaea, and viruses, which collectively contribute to immune development, metabolic homeostasis, and maintenance of intestinal barrier integrity (Lei et al., 2025). Accumulating evidence indicates that variations in microbiome composition significantly influence responses to cancer immunotherapy. Beneficial microbial taxa such as *Akkermansia muciniphila*, *Bifidobacterium* spp., and *Faecalibacterium prausnitzii* have been associated with enhanced immune checkpoint inhibitor efficacy, whereas dysbiosis and enrichment of pathogenic microorganisms may promote

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

immune suppression and therapeutic resistance (Park et al., 2026). Furthermore, microbial metabolites including short-chain fatty acids, secondary bile acids, and tryptophan-derived compounds modulate immune signaling pathways, cytokine production, and tumor microenvironment dynamics, thereby influencing clinical outcomes (Duan et al., 2025).

Despite substantial progress in microbiome research, understanding the complex interactions among gut microorganisms, host immunity, and tumor biology remains a significant challenge. Conventional in vitro cell culture systems often lack physiological complexity, while animal models frequently fail to accurately reproduce human-specific microbiome composition and immune responses (Bertorello et al., 2024). These limitations restrict mechanistic investigations and hinder the translation of microbiome discoveries into clinically actionable therapeutic strategies.

Mechanical engineering has emerged as a transformative discipline in this regard, providing advanced technologies that bridge the gap between biological complexity and experimental controllability. Innovations such as microfluidics, organ-on-a-chip systems, tumor-on-a-chip platforms, three-dimensional (3D) bioprinting, and biosensors enable precise recreation of physiological microenvironments and real-time monitoring of biological processes (An et al., 2025). These technologies allow researchers to mimic intestinal architecture, fluid flow, oxygen gradients, microbial colonization, immune cell trafficking, and tumor microenvironment characteristics with unprecedented accuracy. As a result, engineering-based platforms are increasingly being employed to investigate microbiome-mediated regulation of cancer progression and immunotherapy responses.

Recent advances in microfluidic gut-on-a-chip systems have enabled long-term co-culture of human intestinal cells and anaerobic gut microorganisms under physiologically relevant conditions, facilitating detailed analysis of host–microbe communication (Bein et al., 2018). Similarly, tumor-on-a-chip technologies provide dynamic models for studying immune infiltration, therapeutic responses, and drug resistance mechanisms, while 3D bioprinting allows the fabrication of patient-specific tumor constructs for personalized medicine applications (Signore et al., 2021).

This review critically examines the application of mechanical engineering approaches in deciphering the influence of the gut microbiome on cancer immunotherapy. Specifically, it discusses the roles of microfluidics, gut-on-a-chip systems, tumor-on-a-chip platforms, 3D bioprinting, and biosensor technologies in modeling microbiome–immune–tumor interactions. The review further evaluates current translational challenges and highlights future opportunities involving artificial intelligence, microbiome engineering, and precision medicine. By integrating perspectives from microbiology, oncology, and engineering, this review provides a comprehensive framework for understanding how advanced technological platforms can accelerate the development of personalized cancer immunotherapies.

Gut Microbiome Regulation of Cancer Immunotherapy

The gut microbiome has emerged as a critical regulator of cancer immunotherapy efficacy, influencing both treatment responsiveness and resistance through complex interactions with the host immune system. Accumulating evidence indicates that specific microbial taxa can modulate anti-tumor immunity and determine clinical outcomes in patients receiving immune checkpoint inhibitors (Araji et al., 2021). Among the beneficial microorganisms, *Akkermansia muciniphila* has attracted considerable attention because of its ability to strengthen intestinal barrier integrity, enhance antigen presentation, and promote the recruitment of cytotoxic CD8+ T cells into the tumor microenvironment. Clinical studies have demonstrated that a higher abundance of *A. muciniphila* is associated with improved responses to programmed cell death protein-1 (PD-1) blockade therapy in patients with advanced cancers (Fan et al., 2023). Similarly, members of the genus *Bifidobacterium* have been shown to enhance dendritic cell activation and stimulate anti-tumor T-cell responses, thereby

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

improving the efficacy of immune checkpoint inhibitors (Pei et al., 2024). Another beneficial commensal, *Faecalibacterium prausnitzii*, shown in Fig. 1 contributes to immune homeostasis through its anti-inflammatory properties and production of metabolites that support epithelial health and immune regulation. Increased abundance of *F. prausnitzii* has been correlated with prolonged progression-free survival and enhanced therapeutic outcomes in melanoma patients receiving immunotherapy (Guo et al., 2025).

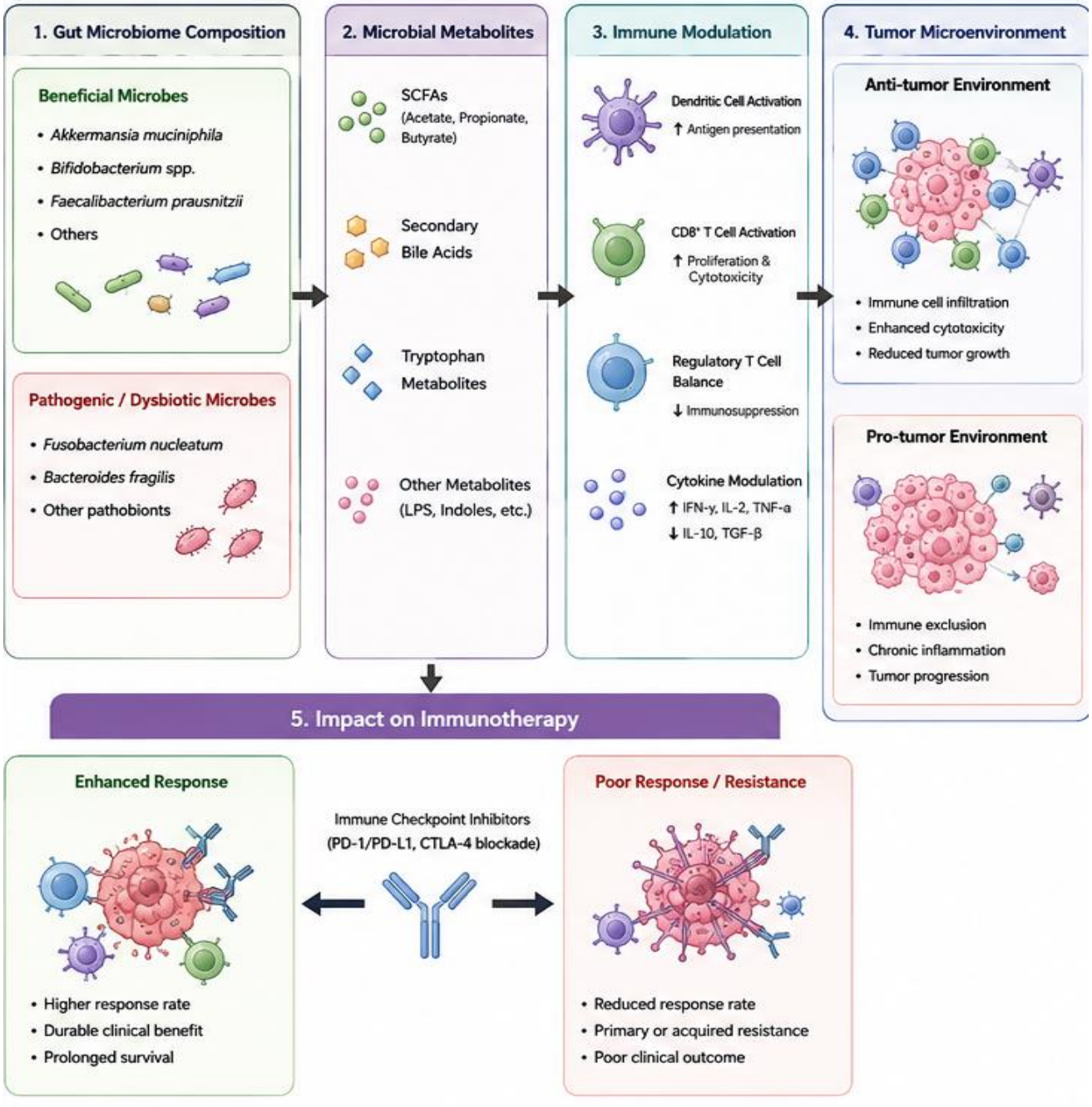


Fig. 1 Mechanistic pathways through which the gut microbiome regulates cancer immunotherapy responses.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

In contrast, certain microbial species may impair immunotherapeutic responses and promote tumor progression. *Fusobacterium nucleatum*, an opportunistic pathogen frequently enriched in colorectal tumors, has been implicated in immune evasion, chronic inflammation, and resistance to anti-cancer therapies. This microorganism can suppress natural killer cell activity, modulate tumor-associated immune responses, and facilitate an immunosuppressive microenvironment that favors tumor growth (Incognito et al., 2025). Likewise, enterotoxigenic *Bacteroides fragilis* produces the *B. fragilis* toxin (BFT), which induces inflammatory signaling pathways and promotes carcinogenic processes through activation of nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) pathways (Jasemi et al., 2025).

The immunomodulatory effects of the gut microbiome are largely mediated through a diverse repertoire of microbial metabolites that act as signaling molecules between intestinal microorganisms and the host immune system. Among these, short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are generated through bacterial fermentation of dietary fibers and play fundamental roles in maintaining immune homeostasis. SCFAs regulate the differentiation and function of regulatory T cells, enhance epithelial barrier integrity, and influence the activation of effector T cells involved in anti-tumor immunity (Zeng et al., 2025). Secondary bile acids, produced through microbial metabolism of primary bile acids, have also been recognized as important modulators of immune responses and cancer progression. These metabolites influence dendritic cell function, cytokine production, and immune cell trafficking within the tumor microenvironment. Furthermore, microbial metabolism of tryptophan generates a variety of bioactive compounds capable of activating aryl hydrocarbon receptor (AhR)-mediated signaling pathways, thereby regulating mucosal immunity and systemic immune responses (Luo et al., 2025).

Microfluidic Technologies for Gut Microbiome Research

The increasing recognition of the gut microbiome as a key determinant of cancer immunotherapy outcomes has created an urgent need for experimental platforms capable of accurately replicating the complex interactions among intestinal microorganisms, host tissues, immune cells, and therapeutic agents. Traditional in vitro culture systems and animal models have provided valuable insights into microbiome biology; however, they often fail to reproduce the dynamic physiological conditions present within the human gastrointestinal tract (Stancu, 2018). In this context, microfluidic technologies have emerged as powerful engineering tools that enable precise manipulation of fluids, cells, and microorganisms within microscale environments (Kanniyappan et al., 2026). By integrating biological and engineering principles, microfluidic platforms provide unprecedented opportunities to investigate microbiome-host interactions under highly controlled and physiologically relevant conditions (Mancera Azamar et al., 2025).

Microfluidics involves the manipulation of minute volumes of fluids through interconnected microchannels that typically range from a few micrometers to several hundred micrometers in diameter. The technology enables precise regulation of environmental parameters such as nutrient gradients, oxygen concentrations, pH, temperature, and fluid shear stress, all of which play crucial roles in shaping microbial behavior and host responses. Unlike conventional static culture systems, microfluidic devices allow continuous perfusion of media and real-time monitoring of biological processes, thereby more closely mimicking the dynamic environment of the human intestine (Mudugamuwa et al., 2024). Furthermore, the small volumes required for experimentation significantly reduce reagent consumption, lower operational costs, and facilitate high-throughput screening applications. These advantages have positioned microfluidics as a transformative platform for studying complex microbiome ecosystems and their influence on human health (Potenza et al., 2025).

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

One of the most significant contributions of microfluidic technology lies in its ability to model gut ecology with high precision. The gastrointestinal tract contains diverse microbial communities that exist within highly structured spatial and chemical gradients. Reproducing these conditions in traditional laboratory systems is challenging because microbial growth often becomes dominated by rapidly proliferating species, resulting in reduced ecological complexity (Teo et al., 2024). Microfluidic devices overcome these limitations by enabling controlled compartmentalization and spatial organization of microbial populations. Researchers can establish physiologically relevant oxygen gradients, nutrient distributions, and flow conditions that support the coexistence of aerobic, facultative anaerobic, and obligate anaerobic microorganisms within the same system (Kasahara et al., 2023).

Another major advantage of microfluidic systems is their ability to provide real-time monitoring of microbiological and immunological processes. Advanced imaging technologies, integrated biosensors, and fluorescence-based detection methods can be incorporated directly into microfluidic devices, allowing continuous observation of microbial growth, cellular responses, and molecular signaling events (Wang et al., 2025). This capability is particularly important for studying temporal changes in microbiome composition and immune activation during cancer immunotherapy. Real-time analysis enables researchers to capture transient biological phenomena that may be missed in endpoint assays and provides a more comprehensive understanding of microbiome-mediated therapeutic responses (Petrelli et al., 2025). Moreover, microfluidic systems facilitate parallel experimentation, enabling simultaneous testing of multiple microbial communities, drugs, or environmental conditions with minimal sample requirements (Oushyani Roudsari et al., 2024).

Microfluidic platforms have also become indispensable tools for investigating host–microbe interactions. By co-culturing intestinal epithelial cells with commensal or pathogenic microorganisms under physiologically relevant conditions, researchers can directly examine microbial colonization processes and their effects on host tissues (Kim et al., 2010). These studies have revealed critical insights into bacterial adhesion, epithelial barrier function, mucosal immune responses, and microbial metabolite production. The ability to recreate physical interfaces between microorganisms and host cells has significantly advanced our understanding of how the gut microbiome influences immune regulation and cancer development (Qiet al., 2023).

The study of microbial colonization and biofilm formation represents another important application of microfluidic technologies. Biofilms are highly organized microbial communities embedded within extracellular polymeric matrices that contribute to microbial persistence, resistance to antimicrobial agents, and chronic inflammation. Within the gastrointestinal tract, biofilm formation has been associated with dysbiosis, inflammatory bowel disease, and colorectal cancer (Sharma et al., 2023). Microfluidic devices enable controlled investigation of biofilm development under dynamic flow conditions that closely resemble physiological environments. Researchers can evaluate how microbial communities establish colonization niches, respond to environmental stresses, and interact with immune cells. Such studies provide valuable information regarding the role of biofilms in modulating cancer immunotherapy outcomes and influencing treatment resistance (Coppola et al., 2025).

In addition to microbial ecology studies, microfluidics has become an important platform for evaluating drug responses and therapeutic efficacy. The technology enables precise delivery of pharmaceuticals, microbial metabolites, and immunotherapeutic agents to cellular systems while allowing continuous monitoring of biological responses. This capability is particularly relevant in oncology, where treatment outcomes are increasingly recognized as being influenced by microbiome composition. Microfluidic platforms allow researchers to investigate how specific microbial species or metabolites alter responses to immune checkpoint inhibitors, chemotherapy, and combination therapies. Such information is

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

essential for developing microbiome-guided precision medicine strategies aimed at optimizing treatment efficacy and minimizing adverse effects (Al-wdan et al., 2023; Zhitlov et al., 2025).

Gut-on-a-Chip Systems

The evolution of organ-on-a-chip technology has further expanded the potential of engineering-based microbiome research. Organ-on-a-chip systems are microengineered devices designed to replicate the structural, mechanical, and functional characteristics of human organs. These platforms emerged as a response to the limitations of conventional cell culture models and animal experiments, offering more physiologically relevant alternatives for studying human diseases (Farhang Doost & Srivastava, 2024). By integrating living cells within microfluidic environments, organ-on-a-chip systems recreate tissue-specific architecture, biochemical signaling, and mechanical forces that are essential for normal organ function (Morais et al., 2024). The gut-on-a-chip represents one of the most successful examples of this technology and has become a valuable model for investigating microbiome-host interactions.

A defining feature of gut-on-a-chip systems is their ability to reproduce key physical and mechanical aspects of the intestinal environment. The gastrointestinal tract is continuously subjected to fluid flow generated by luminal contents and mechanical forces associated with peristaltic contractions. These mechanical stimuli influence epithelial differentiation, mucus production, microbial colonization, and immune responses (Morelli et al., 2023). Modern gut-on-a-chip devices incorporate controlled fluid flow and cyclic mechanical deformation to simulate these physiological conditions, thereby creating more realistic experimental models than static cultures (Valiei et al., 2023). Additionally, the establishment of oxygen gradients allows simultaneous cultivation of oxygen-dependent epithelial cells and anaerobic gut microorganisms, addressing one of the major challenges in microbiome research (Shang et al., 2025).

The incorporation of anaerobic compartments within gut-on-a-chip platforms has been particularly important for studying the human gut microbiota because many beneficial bacterial species cannot survive under atmospheric oxygen conditions. Advanced device designs maintain distinct oxygen environments while preserving communication between microbial and host compartments. These systems also support the formation of mucosal interfaces that closely resemble those found in vivo, enabling investigation of microbial adhesion, mucus interactions, and barrier function. Through these innovations, gut-on-a-chip technology provides a sophisticated platform for examining host–microbe communication and microbial regulation of immune responses (Trujillo-de Santiago et al., 2018; Comolli et al., 2023).

The application of gut-on-a-chip systems in cancer immunotherapy research is rapidly expanding. These platforms enable assessment of microbiome-derived metabolites, microbial communities, and host immune cells within integrated experimental systems. Researchers can evaluate how alterations in microbiome composition influence responses to immune checkpoint inhibitors, cytokine therapies, and emerging immunotherapeutic strategies (Donkers et al., 2023). Furthermore, gut-on-a-chip devices are increasingly being used for drug screening and prediction of patient-specific therapeutic responses. By incorporating patient-derived microbiota and immune cells, these systems offer opportunities for personalized microbiome testing and individualized treatment optimization (Li et al., 2024).

Tumor-on-a-Chip Technologies

The emergence of tumor-on-a-chip technology has significantly advanced the study of cancer biology by providing physiologically relevant platforms that accurately recapitulate the complexity of human tumors. Traditional two-dimensional cell cultures often fail to reproduce the architectural, biochemical, and mechanical characteristics of tumor tissues, while animal models may not fully reflect human-specific responses (Trujillo-de Santiago et al., 2019). Tumor-on-a-chip systems address these limitations by integrating microfluidic engineering with living cancer cells, stromal components, extracellular matrix

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

elements, and immune cells within controlled microenvironments. These platforms allow researchers to recreate key features of the tumor microenvironment, including nutrient gradients, oxygen distribution, vascular networks, and mechanical stresses that influence cancer progression and therapeutic responses (Xu et al., 2024).

A major advantage of tumor-on-a-chip systems is their ability to engineer realistic tumor microenvironments. Solid tumors exist within highly heterogeneous ecosystems characterized by abnormal vasculature, hypoxia, acidic pH, immune infiltration, and extracellular matrix remodeling. These factors collectively regulate tumor growth, metastasis, and therapeutic resistance. Microfluidic platforms enable precise control over these variables, allowing researchers to simulate physiological and pathological conditions observed in vivo. For example, gradients of oxygen and nutrients can be generated within microchannels to mimic hypoxic tumor regions, while engineered extracellular matrices provide structural support that resembles native tissues. Such biomimetic conditions facilitate more accurate investigation of cancer cell behavior and drug responses than conventional culture methods (Liu et al., 2022; Xia et al., 2026). Advanced tumor-on-a-chip systems provide physiologically relevant platforms for investigating immune infiltration, microbiome-mediated signaling, and therapeutic responses in cancer immunotherapy (Table 1).

The incorporation of immune cells into tumor-on-a-chip platforms has further expanded their utility for cancer immunotherapy research. Immune cell infiltration represents a critical determinant of immunotherapeutic success because the ability of cytotoxic T lymphocytes, natural killer cells, and antigen-presenting cells to penetrate tumor tissues directly influences anti-tumor activity (Kraja et al., 2025). Microfluidic systems allow real-time observation of immune cell migration, activation, and interactions with cancer cells under controlled conditions. These models have been used to investigate mechanisms governing T-cell trafficking, immune checkpoint regulation, and tumor immune evasion. By integrating patient-derived immune cells with tumor tissues, researchers can evaluate personalized immune responses and identify factors that contribute to resistance or sensitivity to immunotherapy (Chen et al., 2026).

The growing recognition of microbiome–tumor interactions has stimulated the development of tumor-on-a-chip systems capable of incorporating microbial signals into cancer models. Numerous studies have demonstrated that gut microorganisms influence tumor progression through immune modulation, metabolite production, and regulation of inflammatory pathways (Zhang et al., 2025). However, traditional experimental systems often fail to capture these complex interactions. Advanced tumor-on-a-chip platforms now enable the integration of microbial metabolites, bacterial components, and immune cells within tumor models, allowing researchers to examine how microbiome-derived factors affect cancer biology and treatment responses. For example, short-chain fatty acids produced by beneficial gut bacteria can be introduced into microfluidic tumor systems to evaluate their effects on immune activation and tumor suppression. Similarly, pathogenic bacterial metabolites may be studied for their role in promoting immune evasion and therapy resistance (Sousa et al., 2025).

One of the most promising applications of tumor-on-a-chip technology is drug resistance prediction. Resistance to chemotherapy, targeted therapies, and immune checkpoint inhibitors remains a major challenge in oncology. Conventional drug screening platforms frequently fail to predict clinical responses because they lack the biological complexity of human tumors. Tumor-on-a-chip systems overcome this limitation by reproducing patient-specific tumor characteristics, including stromal interactions, vascularization, and immune components. These platforms enable dynamic monitoring of cellular responses to therapeutic agents and facilitate identification of resistance mechanisms before clinical treatment. Integration of microbiome-derived metabolites into drug testing platforms may further improve predictive accuracy by accounting for the influence of gut microorganisms on drug metabolism and immune

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

responses (Hachey & Hughes, 2018; Motohashi et al., 2025).

Table 1. Tumor-on-a-Chip platforms for investigating gut microbiome–cancer interactions and immunotherapy responses.

Platform Type	Components	Biological Features	Applications	Major Advantages	References
Tumor-on-a-Chip	Cancer cells, extracellular matrix, microfluidic channels	Tumor architecture, hypoxia, nutrient gradients	Evaluation of checkpoint inhibitor efficacy	Physiologically relevant tumor modeling	Lin et al., 2025
Immune-Tumor-on-a-Chip	Tumor cells and immune cells	Immune infiltration and tumor killing	Assessment of T-cell-mediated responses	Real-time immune monitoring	Dabbagh Moghaddam et al., 2025
Microbiome-Tumor-on-a-Chip	Gut microbial metabolites and tumor tissues	Microbiome-mediated immune modulation	Investigation of microbiome influence on immunotherapy	Mimics host–microbe–tumor interactions	Luu et al., 2023
Vascularized Tumor-on-a-Chip	Endothelial cells and perfusion networks	Angiogenesis and drug transport	Drug delivery and resistance studies	Simulates in vivo vascular conditions	Poljak et al., 2026
Multi-Organ-on-a-Chip	Gut, liver, immune, and tumor compartments	Organ-organ communication	Personalized therapeutic evaluation	System-wide physiological modeling	Picollet-D'hahan et al., 2021

3D Bioprinting and Engineered Cancer Models

Complementing these advances, three-dimensional (3D) bioprinting has emerged as another transformative engineering approach for modeling cancer and microbiome interactions. Unlike conventional scaffold-based tissue engineering techniques, 3D bioprinting enables layer-by-layer fabrication of complex biological structures using bioinks containing living cells, biomaterials, and signaling molecules. This technology allows precise spatial organization of multiple cell types, resulting in tissue constructs that closely resemble native tumor architecture (Sánchez-Salazar et al,, 2021; Kazemi & Maralbashi, 2025).

The success of 3D bioprinting largely depends on the development of suitable bioinks capable of supporting both mammalian cells and microbial communities. Recent advances in microbiome-compatible bioinks have enabled the incorporation of beneficial and pathogenic microorganisms into engineered tissues without compromising cell viability. These bioinks often consist of hydrogels derived from alginate, gelatin methacrylate, collagen, or other biocompatible materials that mimic extracellular matrix properties while maintaining microbial growth conditions (Antony Jose et al., 2026).

A particularly exciting application of 3D bioprinting is the generation of patient-specific tumor models. Advances in tissue engineering and personalized medicine have enabled the use of patient-derived cancer cells, stromal cells, and immune cells to fabricate individualized tumor constructs. These models preserve the genetic and phenotypic characteristics of the original tumors, allowing researchers to investigate disease progression and therapeutic responses in a patient-specific manner. The incorporation of patient-derived microbiota into these constructs further

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

enhances their relevance by accounting for microbiome-associated variations in treatment outcomes. Such personalized models have the potential to revolutionize cancer research by enabling more accurate prediction of therapeutic efficacy and toxicity (Liu & Jin, 2025). Three-dimensional bioprinting enables the development of patient-specific tumor constructs that can be used for personalized drug screening and microbiome-based therapeutic evaluation (Table 2).

Table 2. Applications of 3D Bioprinting in cancer and microbiome research.

Application Area	Bioprinted Components	Purpose	Clinical Relevance	References
Tumor Modeling	Patient-derived cancer cells	Recreate tumor heterogeneity	Personalized cancer research	Wu et al., 2023
Microbiome-Compatible Models	Cancer cells and gut microorganisms	Study host–microbe interactions	Understanding microbiome-driven therapy responses	Contreras et al., 2016
Drug Screening Platforms	Tumor tissues and stromal cells	Evaluate treatment efficacy	Precision medicine	Motohashi et al., 2025
Immune-Oncology Models	Tumor and immune cells	Assess immunotherapeutic responses	Optimization of immunotherapy	Oli et al., 2024
Metastasis Models	Primary and secondary tissue constructs	Investigate cancer dissemination	Identification of metastatic mechanisms	Sparrer et al., 2025
Personalized Tumor Constructs	Patient-specific cells and microbiota	Predict individual treatment outcomes	Tailored therapeutic strategies	Krzyszczyk et al., 2018

Biosensors and Real-Time Monitoring

Alongside microfluidics and bioprinting, biosensor technologies are playing an increasingly important role in microbiome-guided cancer research. Biosensors are analytical devices that convert biological interactions into measurable signals, enabling rapid and sensitive detection of biomolecules, metabolites, and microorganisms. Their integration into cancer and microbiome research platforms allows continuous monitoring of biological processes and provides valuable information regarding disease progression and therapeutic responses (Kulkarni et al., 2022).

Electrochemical biosensors represent one of the most widely used biosensing technologies due to their high sensitivity, low cost, and rapid response times. These devices detect biochemical interactions through changes in electrical signals generated by redox reactions or molecular binding events. In microbiome research, electrochemical biosensors have been employed to detect microbial metabolites, inflammatory biomarkers, and immune mediators associated with cancer progression. Their compatibility with microfluidic systems makes them particularly useful for real-time monitoring of microbiome–immune–tumor interactions (Kim et al., 2024).

Volume 4, Issue 6, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

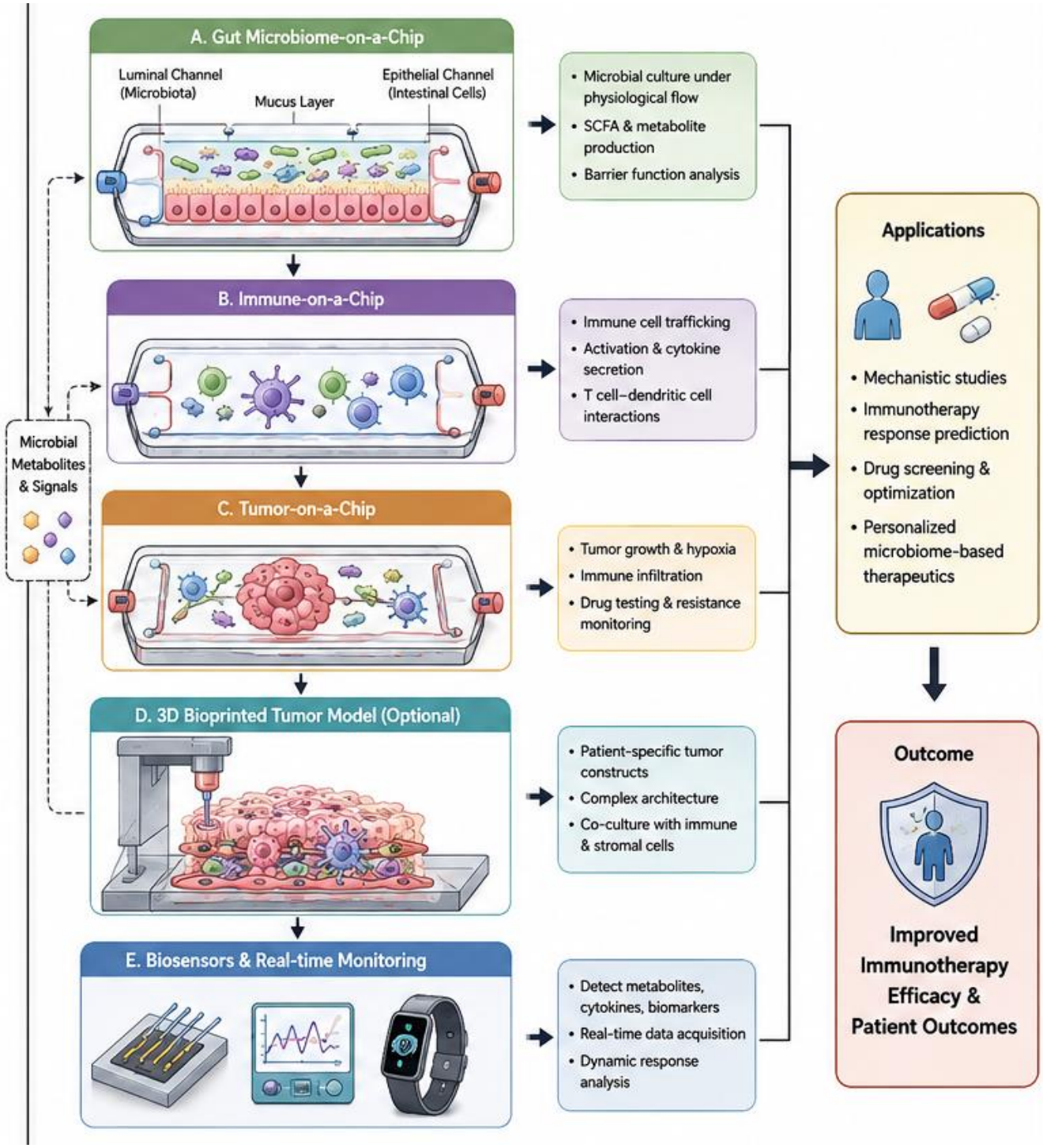


Fig. 2 Integrated engineering platforms for modeling microbiome–immune–tumor interactions and advancing precision immunotherapy.

Recent advances in wearable biosensor technology have expanded opportunities for real-time health monitoring beyond laboratory settings (Fig. 2). Wearable devices can continuously measure physiological parameters, inflammatory biomarkers, and metabolic indicators from sweat,

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

saliva, or interstitial fluids. Integration of microbiome-related biomarkers into wearable platforms may facilitate longitudinal monitoring of patient responses to immunotherapy and provide early indications of treatment efficacy or toxicity (Xian, 2026). The integration of electrochemical, optical, and wearable biosensors enables continuous monitoring of microbiome-derived biomarkers and immune responses during cancer treatment (Table 3).

Table 3. Biosensor technologies for monitoring microbiome-cancer-immunotherapy interactions.

Biosensor Type	Detection Principle	Target Analytes	Applications	References
Electrochemical Biosensors	Electrical signal generation	Cytokines, metabolites, microbial biomarkers	Real-time monitoring of immune responses	Mehrotra, 2016
Optical Biosensors	Fluorescence, absorbance, plasmon resonance	Microbial metabolites, proteins, DNA	Non-invasive biomarker detection	Blachowicz et al., 2026
Wearable Biosensors	Continuous physiological monitoring	Sweat biomarkers, inflammatory markers	Longitudinal patient monitoring	Ma et al., 2026
Microbiome Monitoring Devices	Integrated molecular detection systems	Gut microbial composition	Personalized microbiome profiling	Damhorst et al., 2021
Lab-on-a-Chip Biosensors	Microfluidic-based detection	Drug metabolites and microbial products	High-throughput therapeutic screening	Chi et al., 2016
Multiplex Biosensors	Simultaneous biomarker detection	Multiple immune and microbial markers	Precision oncology applications	Li et al., 2025

Translational Challenges

Despite remarkable advances in microfluidics, organ-on-a-chip technologies, biosensors, and three-dimensional bioprinting, several translational challenges continue to hinder their widespread adoption in microbiome-guided cancer immunotherapy research and clinical practice. One of the most significant limitations is the lack of standardization across experimental platforms. Different laboratories frequently employ distinct device architectures, fabrication materials, cell sources, culture conditions, and analytical protocols, resulting in substantial variability in experimental outcomes. Such inconsistencies complicate data comparison and reduce reproducibility, which remains a fundamental requirement for scientific validation and regulatory approval. Furthermore, variations in microbiome composition among individuals introduce additional complexity, making it difficult to establish universally applicable experimental models and biomarkers.

Manufacturing challenges also represent a major obstacle to large-scale implementation of engineering-based biomedical platforms. Many organ-on-a-chip and tumor-on-a-chip devices require sophisticated fabrication techniques, specialized materials, and highly controlled production environments. Although academic laboratories have demonstrated impressive proof-of-concept models, scaling these technologies for commercial production remains technically demanding and economically costly. Device-to-device variability, limited durability, and difficulties in maintaining long-term microbial cultures further restrict their practical application. Similarly, three-dimensional bioprinting technologies often face challenges related to bioink optimization, printing resolution,

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

structural stability, and preservation of cell viability, all of which influence model reliability and translational potential.

Regulatory barriers constitute another critical challenge. Existing regulatory frameworks were primarily developed for conventional pharmaceuticals and medical devices and are not fully equipped to evaluate complex bioengineered systems that integrate living cells, microorganisms, and artificial intelligence-based analytical tools. The absence of standardized validation criteria creates uncertainty regarding safety assessment, quality control, and clinical implementation. Additionally, the use of patient-derived tissues and microbiota raises ethical and regulatory concerns related to informed consent, data privacy, and biological sample management. Establishing clear regulatory guidelines will be essential for facilitating clinical translation and commercialization of these emerging technologies.

Clinical validation remains one of the most important yet underdeveloped aspects of microbiome-engineering research. Although numerous studies have demonstrated promising results in laboratory settings, relatively few technologies have undergone rigorous clinical testing. Large-scale, multicenter validation studies are required to confirm the predictive accuracy, reliability, and clinical utility of microbiome-based engineering platforms. Furthermore, patient heterogeneity, differences in microbiome composition, lifestyle factors, dietary habits, and genetic backgrounds can significantly influence therapeutic responses, necessitating extensive validation across diverse populations. Without robust clinical evidence, the transition from experimental models to routine clinical applications will remain limited.

Future Perspectives

The future of microbiome-guided cancer immunotherapy will likely be shaped by the convergence of microbiology, biomedical engineering, nanotechnology, artificial intelligence, and precision medicine. Emerging microbiome-on-a-chip platforms are expected to represent the next generation of experimental systems by integrating host tissues, immune cells, microbial communities, and tumor microenvironments within a single dynamic device. These advanced platforms will provide unprecedented opportunities to investigate complex host–microbe interactions and predict patient-specific responses to immunotherapeutic interventions.

Recent advances in microbial engineering and beneficial microorganism-based technologies have demonstrated the potential of manipulating microbial communities to improve biological outcomes in diverse systems (Maqbool et al., 2025; Khan et al., 2026; Ullah et al., 2026). Similar approaches could be adapted to human microbiome research through the development of engineered probiotics, synthetic microbial consortia, and microbiome-editing strategies aimed at enhancing anti-tumor immunity. The concept of beneficial microorganisms as biological engineers, widely explored in agricultural systems, may provide a useful framework for designing next-generation therapeutic microbiota capable of improving immunotherapy responsiveness (Iqbal et al., 2026).

Nanotechnology is also expected to play an increasingly important role in microbiome-based precision oncology. Green-synthesized nanoparticles, nanocomposites, and graphene-based biomaterials have demonstrated remarkable potential for targeted delivery, biosensing, antimicrobial activity, and biomedical applications (Khan et al., 2025; Khan et al., 2026; Ullah et al., 2026). Future integration of nanotechnology with organ-on-a-chip systems may enable real-time monitoring of microbial metabolites, immune biomarkers, and tumor-derived signals at unprecedented sensitivity. Such nano-enabled platforms could facilitate early prediction of treatment response, identification of resistance mechanisms, and optimization of therapeutic interventions.

Furthermore, increasing understanding of microbial interactions and community dynamics may facilitate the rational design of synthetic microbiomes optimized for therapeutic applications. Lessons learned from studies investigating microbial cooperation, biodegradation pathways, and microbial

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

ecosystem engineering may provide valuable insights for manipulating human-associated microbial communities in cancer patients (Khan et al., 2026; Khan et al., 2025).

Ultimately, the integration of microbiome science, advanced engineering technologies, nanotechnology, synthetic biology, and artificial intelligence is expected to transform cancer immunotherapy from a population-based approach into a truly personalized therapeutic paradigm. Achieving this vision will require interdisciplinary collaboration among microbiologists, oncologists, engineers, computational scientists, and nanotechnologists to develop clinically validated platforms capable of improving treatment efficacy and patient outcomes.

Conclusions

The gut microbiome plays a fundamental role in shaping cancer immunotherapy outcomes by regulating immune activation, microbial metabolite production, and tumor microenvironment dynamics. This review highlights that beneficial microbial taxa and their metabolites can enhance therapeutic efficacy, whereas dysbiosis may contribute to treatment resistance. Advanced engineering technologies, including microfluidics, gut-on-a-chip, tumor-on-a-chip, 3D bioprinting, and biosensors, have significantly improved our ability to model and analyze microbiome–immune–tumor interactions under physiologically relevant conditions. These platforms provide valuable opportunities for mechanistic studies, drug screening, response prediction, and personalized treatment development. Despite promising advances, challenges related to standardization, scalability, regulatory approval, and clinical validation must be addressed before widespread clinical adoption. Future integration of microbiome-on-a-chip systems, artificial intelligence, smart biosensors, and microbiome engineering strategies is expected to accelerate the development of precision immunotherapy. Collectively, the convergence of microbiology and mechanical engineering offers a transformative framework for translating microbiome discoveries into personalized cancer treatment and improving patient outcomes.

REFERENCES

Al-wdan, O. A., Sharallah, O. A., Abdelwahab, N. A., Mohammed, A. O., Elmowafy, E., & Soliman, M. E. (2023). Insights into microfabrication and implementation of microfluidics in pharmaceutical drug delivery and analysis. *OpenNano*, *12*, 100156.

An, L., Liu, Y., & Liu, Y. (2025). Organ-on-a-Chip Applications in Microfluidic Platforms. *Micromachines*, *16*(2), 201. https://doi.org/10.3390/mi16020201

Antony Jose, S., Evtimow, A., & Menezes, P. L. (2026). Advances in 3D Bioprinting: Materials, Processes, and Emerging Applications. *Micromachines*, *17*(3), 282. https://doi.org/10.3390/mi17030282

Araji, G., Maamari, J., Ahmad, F. A., Zareef, R., Chaftari, P., & Yeung, S. J. (2021). The Emerging Role of the Gut Microbiome in the Cancer Response to Immune Checkpoint Inhibitors: A Narrative Review. *Journal of immunotherapy and precision oncology*, *5*(1), 13–25. https://doi.org/10.36401/JIPO-21-10

Bein, A., Shin, W., Jalili-Firoozinezhad, S., Park, M. H., Sontheimer-Phelps, A., Tovaglieri, A., Chalkiadaki, A., Kim, H. J., & Ingber, D. E. (2018). Microfluidic Organ-on-a-Chip Models of Human Intestine. *Cellular and molecular gastroenterology and hepatology*, *5*(4), 659–668. https://doi.org/10.1016/j.jcmgh.2017.12.010

Bertorello, S., Cei, F., Fink, D., Niccolai, E., & Amedei, A. (2024). The Future Exploring of Gut Microbiome-Immunity Interactions: From In Vivo/Vitro Models to In Silico Innovations. *Microorganisms*, *12*(9), 1828. https://doi.org/10.3390/microorganisms12091828

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Blachowicz, T., Ehrmann, G., Stepula, E., & Ehrmann, A. (2026). Optical Biosensors—Principles of Operation and Applications. *Micromachines*, *17*(5), 579. https://doi.org/10.3390/mi17050579

Chen, X., Tan, D., Liu, S., Luo, R., Liu, Y., Zhang, M., Li, S., & Xu, J. (2026). Applying microfluidic technology to interpret the tumor immune microenvironment and cancer immunotherapy. *Cancer biology & medicine*, *23*(2), 169–185. https://doi.org/10.20892/j.issn.2095-3941.2025.0541

Chi, C. W., Ahmed, A. R., Dereli-Korkut, Z., & Wang, S. (2016). Microfluidic cell chips for high-throughput drug screening. *Bioanalysis*, *8*(9), 921–937. https://doi.org/10.4155/bio-2016-0028

Comolli, J., Walsh, D. I., 3rd, Bobrow, J., Lennartz, C. L., Guido, N. J., & Thorsen, T. (2023). An in vitro platform for study of the human gut microbiome under an oxygen gradient. *Biomedical microdevices*, *25*(2), 14. https://doi.org/10.1007/s10544-023-00653-3

Contreras, A. V., Cocom-Chan, B., Hernandez-Montes, G., Portillo-Bobadilla, T., & Resendis-Antonio, O. (2016). Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine. *Frontiers in physiology*, *7*, 606. https://doi.org/10.3389/fphys.2016.00606

Coppola, F., Fratianni, F., Bianco, V., Wang, Z., Pellegrini, M., Coppola, R., & Nazzaro, F. (2025). New Methodologies as Opportunities in the Study of Bacterial Biofilms, Including Food-Related Applications. *Microorganisms*, *13*(5), 1062. https://doi.org/10.3390/microorganisms13051062

Dabbagh Moghaddam, F., Anvar, A., Ilkhani, E., Dadgar, D., Rafiee, M., Ranjbaran, N., Mortazavi, P., Ghoreishian, S. M., Huh, Y. S., & Makvandi, P. (2025). Advances in engineering immune-tumor microenvironments on-a-chip: integrative microfluidic platforms for immunotherapy and drug discovery. *Molecular cancer*, *24*(1), 271. https://doi.org/10.1186/s12943-025-02479-4

Damhorst, G. L., Adelman, M. W., Woodworth, M. H., & Kraft, C. S. (2021). Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application. *The Journal of infectious diseases*, *223*(12 Suppl 2), S270–S275. https://doi.org/10.1093/infdis/jiaa689

Donkers, J. M., van der Vaart, J. I., & van de Steeg, E. (2023). Gut-on-a-Chip Research for Drug Development: Implications of Chip Design on Preclinical Oral Bioavailability or Intestinal Disease Studies. *Biomimetics (Basel, Switzerland)*, *8*(2), 226. https://doi.org/10.3390/biomimetics8020226

Duan, H., Xu, B., Luo, P., Chen, T., & Zou, J. (2025). Microbial metabolites and their influence on the tumor microenvironment. *Frontiers in immunology*, *16*, 1675677. https://doi.org/10.3389/fimmu.2025.1675677

Fan, S., Jiang, Z., Zhang, Z., Xing, J., Wang, D., & Tang, D. (2023). Akkermansia muciniphila: a potential booster to improve the effectiveness of cancer immunotherapy. *Journal of cancer research and clinical oncology*, *149*(14), 13477–13494. https://doi.org/10.1007/s00432-023-05199-8

Farhang Doost, N., & Srivastava, S. K. (2024). A Comprehensive Review of Organ-on-a-Chip Technology and Its Applications. *Biosensors*, *14*(5), 225. https://doi.org/10.3390/bios14050225

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Ghemrawi, R., Abuamer, L., Kremesh, S., Hussien, G., Ahmed, R., Mousa, W., Khoder, G., & Khair, M. (2024). Revolutionizing Cancer Treatment: Recent Advances in Immunotherapy. *Biomedicines*, *12*(9), 2158. https://doi.org/10.3390/biomedicines12092158

Guo, X., Chen, W., Zhang, Y., Xu, J., Li, J., Xu, H., ... & Zhou, Y. (2025). Microbial Anti-Inflammatory Molecule (MAM) secreted by Faecalibacterium prausnitzii ameliorates colitis through autophagy and gut microbiota modulation. *Journal of Translational Medicine*.

Hachey, S. J., & Hughes, C. C. W. (2018). Applications of tumor chip technology. *Lab on a chip*, *18*(19), 2893–2912. https://doi.org/10.1039/c8lc00330k

Incognito, D., Ciappina, G., Gelsomino, C., Picone, A., Consolo, P., Scano, A., Franchina, T., Maurea, N., Quagliariello, V., Berretta, S., Ottaiano, A., & Berretta, M. (2025). Fusobacterium Nucleatum in Colorectal Cancer: Relationship Among Immune Modulation, Potential Biomarkers and Therapeutic Implications. *International journal of molecular sciences*, *26*(19), 9710. https://doi.org/10.3390/ijms26199710

Iqbal M, Ullah N, Younis T, Rahman L, Khan Z (2026) Investigating the efficiency of endophytic bacteria from *Fagonia indica* in plant growth promotion. Pak J Bot 58(6). http://dx.doi.org/10.30848/PJB2026-6(9)

Jasemi, S., Molicotti, P., Fais, M., Cossu, I., Simula, E. R., & Sechi, L. A. (2025). Biological Mechanisms of Enterotoxigenic *Bacteroides fragilis* Toxin: Linking Inflammation, Colorectal Cancer, and Clinical Implications. *Toxins*, *17*(6), 305. https://doi.org/10.3390/toxins17060305

Kanniyappan, H., Paramasivan, M., Narayanaswamy, V., Konety, R., Perumal, G., Lin, Y., ... & Mathew, M. T. (2026). Microfluidics in biomedical research and its application in orthopedics: a perspective review. *Microfluidics and Nanofluidics*, *30*(1), 2.

Kasahara, K., Leygeber, M., Seiffarth, J., Ruzaeva, K., Drepper, T., Nöh, K., & Kohlheyer, D. (2023). Enabling oxygen-controlled microfluidic cultures for spatiotemporal microbial single-cell analysis. *Frontiers in microbiology*, *14*, 1198170. https://doi.org/10.3389/fmicb.2023.1198170

Kazemi, M., & Maralbashi, S. (2025). Advances in 3D bioprinting for medical application: opportunities and challenges. *Biomedical engineering online*, *25*(1), 11. https://doi.org/10.1186/s12938-025-01498-y

Khan A, Anas M, Ullah N, Khattak WA, Ali M, Maaza M, Shinwari ZK (2025) Harnessing green nanotechnology: exploring the potential of silver, copper, and their nanocomposites for biomedical and agricultural applications. Pak J Bot 57(6). https://doi.org/10.30848/PJB2025-6(5)

Khan A, Khan RA, Anas M, Qadri TA, Ashiq B, Younis T, Ullah N, Shinwari ZK (2026) Biogenic nanoparticles and green nanocomposites as sustainable antimicrobial strategies against bacteria, fungi and viruses. Nano-Horizons: Journal of Nanosciences and Nanotechnologies 5: 31. https://doi.org/10.25159/3005-2602/20247

Khan B, Ullah N, Maqbool H, Khan F, Khan I, Khalid A, Chaudhary HJ (2026) Unravelling the mechanistic role of soil microbial interactions in the suppression of phytopathogens in vegetable agroecosystems of Pakistan. Curr Microbiol 83(1):70. https://doi.org/10.1007/s00284-025-04651-x

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Khan I, Ullah N, Maqbool H, Hashmi A, Khan B, Khalid A, Chaudhary HJ (2025) Holistic review on *Paenibacillus*: The multifunctional genus in heavy metal detoxification, pesticide degradation, and abiotic stress mitigation for sustainable agriculture. Plant Soil 1–36. https://doi.org/10.1007/s11104-025-08064-4

Kim, J., Hegde, M., & Jayaraman, A. (2010). Microfluidic co-culture of epithelial cells and bacteria for investigating soluble signal-mediated interactions. *Journal of visualized experiments : JoVE*, (38), 1749. https://doi.org/10.3791/1749

Kim, J., Jeong, J., & Ko, S. H. (2024). Electrochemical biosensors for point-of-care testing. *Bio-Design and Manufacturing*, 7(4), 548-565.

Kraja, F. P., Jurisic, V. B., Hromić-Jahjefendić, A., Rossopoulou, N., Katsila, T., Mirjacic Martinovic, K., De Las Rivas, J., Diaconu, C. C., & Szöőr, Á. (2025). Tumor-infiltrating lymphocytes in cancer immunotherapy: from chemotactic recruitment to translational modeling. *Frontiers in immunology*, *16*, 1601773. https://doi.org/10.3389/fimmu.2025.1601773

Krzyszczyk, P., Acevedo, A., Davidoff, E. J., Timmins, L. M., Marrero-Berrios, I., Patel, M., White, C., Lowe, C., Sherba, J. J., Hartmanshenn, C., O'Neill, K. M., Balter, M. L., Fritz, Z. R., Androulakis, I. P., Schloss, R. S., & Yarmush, M. L. (2018). The growing role of precision and personalized medicine for cancer treatment. *Technology*, 6(3-4), 79–100. https://doi.org/10.1142/S2339547818300020

Kulkarni, M. B., Ayachit, N. H., & Aminabhavi, T. M. (2022). Biosensors and Microfluidic Biosensors: From Fabrication to Application. *Biosensors*, *12*(7), 543. https://doi.org/10.3390/bios12070543

Lei, W., Zhou, K., Lei, Y., Li, Q., & Zhu, H. (2025). Gut microbiota shapes cancer immunotherapy responses. *NPJ biofilms and microbiomes*, *11*(1), 143. https://doi.org/10.1038/s41522-025-00786-8

Li, J., Hu, J., Yang, Y., Zhang, H., Liu, Y., Fang, Y., Qu, L., Lin, A., Luo, P., Jiang, A., & Wang, L. (2025). Drug resistance in cancer: molecular mechanisms and emerging treatment strategies. *Molecular biomedicine*, *6*(1), 111. https://doi.org/10.1186/s43556-025-00352-w

Li, Z., Guo, M., & Zhong, W. (2025). Multiplex Detection of Biomarkers Empowered by Nanomaterials. *Precision chemistry*, *3*(6), 297–318. https://doi.org/10.1021/prechem.4c00096

Li, Z., Xiong, W., Liang, Z., Wang, J., Zeng, Z., Kołat, D., Li, X., Zhou, D., Xu, X., & Zhao, L. (2024). Critical role of the gut microbiota in immune responses and cancer immunotherapy. *Journal of hematology & oncology*, *17*(1), 33. https://doi.org/10.1186/s13045-024-01541-w

Lin, C., Zhang, Z., Yang, F., Gu, S., Zuo, J., Wu, Y., Zhang, J., Zhou, T., Zhang, Y., Chen, Z., Gu, Z., & Shen, Z. (2025). Innovative organ-on-a-chip platforms for exploring tumorigenesis and therapy in head and neck cancer. *Journal of translational medicine*, *23*(1), 798. https://doi.org/10.1186/s12967-025-06824-5

Liu, S., & Jin, P. (2025). Advances and Challenges in 3D Bioprinted Cancer Models: Opportunities for Personalized Medicine and Tissue Engineering. *Polymers*, *17*(7), 948. https://doi.org/10.3390/polym17070948

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Liu, X., Su, Q., Zhang, X., Yang, W., Ning, J., Jia, K., Xin, J., Li, H., Yu, L., Liao, Y., & Zhang, D. (2022). Recent Advances of Organ-on-a-Chip in Cancer Modeling Research. *Biosensors*, *12*(11), 1045. https://doi.org/10.3390/bios12111045

Luo, W., Li, R., Pan, C., & Luo, C. (2025). Gut microbiota-derived metabolites in immunomodulation and gastrointestinal cancer immunotherapy. *Frontiers in immunology*, *16*, 1710880. https://doi.org/10.3389/fimmu.2025.1710880

Luu, M., Schütz, B., Lauth, M., & Visekruna, A. (2023). The Impact of Gut Microbiota-Derived Metabolites on the Tumor Immune Microenvironment. *Cancers*, *15*(5), 1588. https://doi.org/10.3390/cancers15051588

Ma, X., Wang, J., Gao, X., Zhang, Y., & Wen, D. (2026). Recent Advances in Wearable Biosensors for Stress and Emotion Monitoring. *Advanced Sustainable Systems*, *10*(5), e70509.

Mancera Azamar, K. M., Sudi, S. D., Mohammadalizadeh, Z., Coffin, C., Parker, I. K., & Porras, A. M. (2025). Innovative engineering approaches to model host-microbiome interactions in vitro. *Advanced drug delivery reviews*, *226*, 115677. https://doi.org/10.1016/j.addr.2025.115677

Maqbool H, Rehman FU, Khan I, Ullah N, Sajad MA, Mohammad N, Chaudhary HJ (2025) Exploring the role of plant growth-promoting bacteria in biodegradation of plastic: a review. Water Air Soil Pollut 236(6): 335. http://dx.doi.org/10.1007/s11270-025-07972-6

Mehrotra P. (2016). Biosensors and their applications - A review. *Journal of oral biology and craniofacial research*, *6*(2), 153–159. https://doi.org/10.1016/j.jobcr.2015.12.002

Morais, A. S., Mendes, M., Cordeiro, M. A., Sousa, J. J., Pais, A. C., Mihăilă, S. M., & Vitorino, C. (2024). Organ-on-a-Chip: *Ubi sumus?* Fundamentals and Design Aspects. *Pharmaceutics*, *16*(5), 615. https://doi.org/10.3390/pharmaceutics16050615

Morelli, M., Kurek, D., Ng, C. P., & Queiroz, K. (2023). Gut-on-a-Chip Models: Current and Future Perspectives for Host-Microbial Interactions Research. *Biomedicines*, *11*(2), 619. https://doi.org/10.3390/biomedicines11020619

Motohashi, S., Katsuta, E., & Ban, D. (2025). Advances and Challenges in Drug Screening for Cancer Therapy: A Comprehensive Review. *Bioengineering*, *12*(12), 1315. https://doi.org/10.3390/bioengineering12121315

Motohashi, S., Katsuta, E., & Ban, D. (2025). Advances and Challenges in Drug Screening for Cancer Therapy: A Comprehensive Review. *Bioengineering (Basel, Switzerland)*, *12*(12), 1315. https://doi.org/10.3390/bioengineering12121315

Mudugamuwa, A., Roshan, U., Hettiarachchi, S., Cha, H., Musharaf, H., Kang, X., Trinh, Q. T., Xia, H. M., Nguyen, N. T., & Zhang, J. (2024). Periodic Flows in Microfluidics. *Small (Weinheim an der Bergstrasse, Germany)*, *20*(50), e2404685. https://doi.org/10.1002/smll.202404685

Oli, A. N., Adejumo, S. A., Rowaiye, A. B., Ogidigo, J. O., Hampton-Marcell, J., & Ibeanu, G. C. (2024). Tumour Immunotherapy and Applications of Immunological Products: A Review of Literature. *Journal of immunology research*, *2024*, 8481761. https://doi.org/10.1155/2024/8481761

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Oushyani Roudsari, Z., Esmaeili, Z., Nasirzadeh, N., Heidari Keshel, S., Sefat, F., Bakhtyari, H., & Nadri, S. (2024). Microfluidics as a promising technology for personalized medicine. *BioImpacts : BI*, *15*, 29944. https://doi.org/10.34172/bi.29944

Park, U., Heo, J. Y., Chun, S. M., Lee, J. C., Lee, S. H., & Lee, S. W. (2026). Harnessing the Gut Microbiota to Improve Cancer Immunotherapy: Focus on Lung Cancer. *Immune network*, *26*(1), e7. https://doi.org/10.4110/in.2026.26.e7

Pei, B., Peng, S., Huang, C., & Zhou, F. (2024). Bifidobacterium modulation of tumor immunotherapy and its mechanism. *Cancer immunology, immunotherapy : CII*, *73*(5), 94. https://doi.org/10.1007/s00262-024-03665-x

Petrelli, F., Ghidini, A., Dottorini, L., Ghidini, M., Zaniboni, A., & Tomasello, G. (2025). Clinical Evidence for Microbiome-Based Strategies in Cancer Immunotherapy: A State-of-the-Art Review. *Medicina (Kaunas, Lithuania)*, *61*(9), 1595. https://doi.org/10.3390/medicina61091595

Picollet-D'hahan, N., Zuchowska, A., Lemeunier, I., & Le Gac, S. (2021). Multiorgan-on-a-chip: a systemic approach to model and decipher inter-organ communication. *Trends in Biotechnology*, *39*(8), 788-810.

Poljak, I., Chiappini, C., & Adriani, G. (2026). Engineering perfusion to meet tumor biology: are vascularized tumor-on-a-chip models ready to drive therapy innovation?. *Lab on a Chip*.

Potenza, L., Krzak, J., Andrzejewski, M., Pyzik, A., & Kaminski, T. S. (2025). Ultra-high throughput droplet microfluidics for cultivation and functional screening of environmental microbial strains and consortia.

Qi, P., Lv, J., Yan, X., Bai, L., & Zhang, L. (2023). Microfluidics: Insights into Intestinal Microorganisms. *Microorganisms*, *11*(5), 1134. https://doi.org/10.3390/microorganisms11051134

Sánchez-Salazar, M. G., Álvarez, M. M., & Trujillo-de Santiago, G. (2021). Advances in 3D bioprinting for the biofabrication of tumor models. *Bioprinting*, *21*, e00120.

Shang, T., Zhang, R., Liu, Y., & Shi, S. (2025). Intestinal oxygen and microbiota crosstalk: implications for pathogenesis of gastrointestinal diseases and emerging therapeutic strategies. *Gut pathogens*, *17*(1), 100. https://doi.org/10.1186/s13099-025-00783-4

Sharma, S., Mohler, J., Mahajan, S. D., Schwartz, S. A., Bruggemann, L., & Aalinkeel, R. (2023). Microbial Biofilm: A Review on Formation, Infection, Antibiotic Resistance, Control Measures, and Innovative Treatment. *Microorganisms*, *11*(6), 1614. https://doi.org/10.3390/microorganisms11061614

Signore, M. A., De Pascali, C., Giampetruzzi, L., Siciliano, P. A., & Francioso, L. (2021). Gut-on-Chip microphysiological systems: Latest advances in the integration of sensing strategies and adoption of mature detection mechanisms. *Sensing and Bio-Sensing Research*, *33*, 100443.

Sousa, M. G. C., Brasino, D. S. K., Krieger, M., Dindar, D. A., Duhen, R., Zhang, Z., Franca, C. M., & Bertassoni, L. E. (2025). Host-microbe-cancer interactions on-a-chip. *Frontiers in bioengineering and biotechnology*, *13*, 1505963. https://doi.org/10.3389/fbioe.2025.1505963

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Sparrer, D., Blazquez, R., Keil, F., Einhell, S., Lüke, F., Uderhardt, S., Gerner, C., Wendl, C. H. R., Proescholdt, M., Schulz, C., Kandulski, A., Haferkamp, S., Schlitt, H. J., Bäuerle, T., Franze, K., Mayr, R., Rechenmacher, M., Hau, P., Hirsch, D., Heudobler, D., ... Pukrop, T. (2025). Primary and secondary metastatic dissemination: multiple routes to cancer-related death. *Molecular cancer*, *24*(1), 203. https://doi.org/10.1186/s12943-025-02389-5

Stancu A. L. (2018). Gut Microbiome and the Response to Immunotherapy in Cancer. *Discoveries (Craiova, Romania)*, *6*(3), e84. https://doi.org/10.15190/d.2018.4

Teo, A. J. T., Ng, S. K., Khoo, K., Wong, S. H., & Li, K. H. H. (2024). Microfluidic Gastrointestinal Cell Culture Technologies-Improvements in the Past Decade. *Biosensors*, *14*(9), 449. https://doi.org/10.3390/bios14090449

Trujillo-de Santiago, G., Flores-Garza, B. G., Tavares-Negrete, J. A., Lara-Mayorga, I. M., González-Gamboa, I., Zhang, Y. S., Rojas-Martínez, A., Ortiz-López, R., & Álvarez, M. M. (2019). The Tumor-on-Chip: Recent Advances in the Development of Microfluidic Systems to Recapitulate the Physiology of Solid Tumors. *Materials (Basel, Switzerland)*, *12*(18), 2945. https://doi.org/10.3390/ma12182945

Trujillo-de Santiago, G., Lobo-Zegers, M. J., Montes-Fonseca, S. L., Zhang, Y. S., & Alvarez, M. M. (2018). Gut-microbiota-on-a-chip: an enabling field for physiological research. *Microphysiological systems*, *2*, 7.

Ullah N, Khan A, Younis T, Maqbool H, Iqbal M, Ali M, Shinwari ZK (2025) Advances in nanocomposite-based fertilizers for sustainable agricultural practices. Proc Pak Acad Sci 62(1). http://dx.doi.org/10.53560/PPASB(62-1)1071

Ullah, N., Khan, A., Maqbool, H., Ali, M., Munawar, K. S., Fallatah, A. M., & Shinwari, Z. K. (2026). Green synthesis and biomedical evaluation of graphene oxide nanoparticles using *Monotheca buxifolia* extract. 3 Biotech, 16(4), 144. https://doi.org/10.1007/s13205-026-04758-3

Ullah, N., Khan, A., Maqbool, H., Bib, F., 2026. Plant Growth-Promoting Bacteria as Natural Engineers for Organophosphate Degradation and Crop Productivity. *Journal of Soil Science and Plant Nutrition*. https://doi.org/10.1007/s42729-026-03249-x

Valiei, A., Aminian-Dehkordi, J., & Mofrad, M. R. K. (2023). Gut-on-a-chip models for dissecting the gut microbiology and physiology. *APL bioengineering*, *7*(1), 011502. https://doi.org/10.1063/5.0126541

Wang, S., Guan, X., & Sun, S. (2025). Microfluidic Biosensors: Enabling Advanced Disease Detection. *Sensors (Basel, Switzerland)*, *25*(6), 1936. https://doi.org/10.3390/s25061936

Wu, B. X., Wu, Z., Hou, Y. Y., Fang, Z. X., Deng, Y., Wu, H. T., & Liu, J. (2023). Application of three-dimensional (3D) bioprinting in anti-cancer therapy. *Heliyon*, *9*(10), e20475. https://doi.org/10.1016/j.heliyon.2023.e20475

Xia, M., Wu, G., Wu, D., Hu, W., Deng, H., & Wang, S. (2026). Organoids, organ-on-a-chip, and microtumors: Biomimetic 3D tumor models advancing drug development and precision medicine. *Acta Pharmaceutica Sinica B*.

Xian X. (2026). Recent Advances in Wearable Biosensors for Human Health Monitoring. *Biosensors*, *16*(1), 27. https://doi.org/10.3390/bios16010027

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Xu, H., Wen, J., Yang, J., Zhou, S., Li, Y., Xu, K., Li, W., & Li, S. (2024). Tumor-microenvironment-on-a-chip: the construction and application. *Cell communication and signaling : CCS*, *22*(1), 515. https://doi.org/10.1186/s12964-024-01884-4

Zeng, L., Qian, Y., Cui, X., Zhao, J., Ning, Z., Cha, J., Wang, K., Ge, C., Jia, J., Dou, T., Chen, H., Liu, L., Bao, Z., & Jian, Z. (2025). Immunomodulatory role of gut microbial metabolites: mechanistic insights and therapeutic frontiers. *Frontiers in microbiology*, *16*, 1675065. https://doi.org/10.3389/fmicb.2025.1675065

Zhang, W., Xiang, Y., Ren, H., Liu, Y., Wang, Q., Ran, M., Zhou, W., Tian, L., Zheng, X., Qiao, C., Liu, Y., & Yan, M. (2025). The tumor microbiome in cancer progression: mechanisms and therapeutic potential. *Molecular cancer*, *24*(1), 195. https://doi.org/10.1186/s12943-025-02403-w

Zhitlov, M. Y., Korshun, V. A., & Alferova, V. A. (2025). Microfluidics to Meet Antibiotic Resistance: A Growing Research Frontier. *Antibiotics (Basel, Switzerland)*, *14*(12), 1232. https://doi.org/10.3390/antibiotics14121232