The Role of the Gut Microbiome in Modulating Anti-Cancer Drug Response: Mechanisms, Clinical Evidence, and Therapeutic Strategies

By

Md. Minhajul Kabir Shakib

22346053

Md. Abu Sufian Zayed

22346010

Md. Mahmudur Rahman

22346016

A thesis submitted in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.) to the School of Pharmacy

School of Pharmacy

BRAC University

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Declaration

It is hereby declared that

1. The thesis submitted is our own original work while completing a degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

Signatures of the Students

_____

Md. Minhajul Kabir Shakib

22346053

_____

Md. Abu Sufian Zayed

22346010

_____

Md. Mahmudur Rahman

22346016

Approval

The thesis titled “The Role of the Gut Microbiome in Modulating Anti-Cancer Drug Response: Mechanisms, Clinical Evidence, and Therapeutic Strategies” submitted by Md. Minhajul Kabir Shakib (22346053), Md. Abu Sufian Zayed (22346010) and Md. Mahmudur Rahman (22346016) has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

_____

Dr. Sabrina Sharmin
Associate Professor
School of Pharmacy, BRAC University

Approved By:

_____

Dr. Sharmind Neelotpol
Professor and Chairperson
School of Pharmacy, BRAC university

Ethics Statement

There is no involvement of animal or human trials in this project.

Abstract

This thesis shows and gives us an idea about how the gut microbiome influences the efficacy, effectiveness, and safety of anti-cancer treatments. Our intestine holds a large community of bacteria, fungi, viruses that modulate breakdown, metabolism, immunity, and our health. Modern research shows that these microorganisms can directly influence how carcinogenic drugs act in the body with both of their advantages and their side effects, toxic effects and adverse effects. Microbial enzymes can activate or metabolize anti-cancer drugs. Thus, providing stronger treatment, weaker, or more harmful one. Any hindrance in the gut microbiome (dysbiosis) can induce inflammation, weaken the gut wall, and decrease treatment response. This study has talked about some microbial metabolites, like short-chain fatty acids. This one can either support anti-cancer immunity or, in other cases, induce tumor growth that depends on context. Evidence from clinical trials shows that patients with more microbial ecosystems and specific good species led to responses better in both immunotherapy and chemotherapy. But some other patients suffer increased drug toxicity when their gut microbiome is hampered. Finally, the thesis talks about the major challenges in this area. It also drafts future paths. To conclude, the gut microbiome is an important but underused weapon in carcinogenic medicines. It has a strong potential to improve treatment strategies and outcomes.

Keywords: Gut microbiome, cancer therapy, prebiotics, probiotics, dysbiosis, chemotherapy response, immunotherapy response, drug metabolism, oncology, precision oncology.

Dedication

“Dedicated to our parents”

Acknowledgment

First and foremost, we would like to express our gratitude to the Almighty for his endless gifts, which have been given to us in an effort to provide us with the strength and determination to complete this project.

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Table of contents

Declaration ..... **ii**

Approval ..... **iii**

Ethics Statement ..... **iv**

Abstract/ Executive Summary ..... **v**

Dedication ..... **vi**

Acknowledgement ..... **vii**

List of Tables ..... **viii**

List of Figures ..... **ix**

List of Acronyms ..... **x**

Chapter 01: Introduction **1**

1.1 Gut microbial and cancer **1**

1.2 Aim of the project **3**

1.3 Objective of the review **3**

Chapter 2: Methodology **4**

Chapter 3: The biological system of the gut microbiome **5**

3.1 Types of Gut microbiome and function **5**

3.2 Microbial diversity, homeostasis and dysbiosis **6**

3.3 Microbial metabolites: Short chain fatty acids and their function **7**

Chapter 4: Mechanisms of microbiome modulation of anti-cancer drug response **9**

4.1 Micriobial drug metabolism **9**

4.2 Immune system modulation **11**

4.3 Microbial metabolite mediated regulation **11**

4.4 Pharmacokinetics/pharmacodynamics of tumor microenvironment (TME) **12**

Chapter 5: Clinical evidence of gut microbiome in cancer therapy **14**

5.1 Evidence in immunotherapy **14**

5.2 Microbiome and immunotherapy toxicity **15**

5.3 Evidence in chemotherapy **15**

Chapter 6: Therapeutic modulation strategies **16**

6.1 Fecal microbiota transplantation (FMT) **16**

6.2 Probiotics, Prebiotics and Synbiotics **17**

6.3 Dietary and Nutritional intervention **18**

6.4 Microbiome targeted pharmacological agent **19**

6.5 Engineered Microbes and synthetic biology **19**

Chapter 7: Challenges and Limitation **21**

7.1 Technical limitation **21**

7.2 Biological complexity **22**

7.3 Ethical and Safety concern **23**

7.4 Data gaps and Future Direction **24**

Chapter 8: Future Perspective and Precision oncology **25**

8.1 The microbiome as a predictive biomarker **25**

8.2 Multi omics integration in microbiome guided oncology **26**

8.3 Personalized microbiome Therapeutics **27**

8.4 Translational Roadmap for clinical implementation **27**

Chapter 9: Conclusion **29**

Bibliography **30**

List of figures

Fig 1- Metabolic Activation of Irinotecan by the Gut Microbiome in Modulating SN-38 Toxicity.

List of Acronyms

FMT- Fecal Microbiota Transplantation

PD-1- Programmed Cell Death Protein-1

PD-L1- Programmed Death-Ligand 1

PK/PD- Pharmacokinetics/Pharmacodynamics

SCFA- Short-Chain Fatty Acid

5-FU- 5-Fluorouracil

GUS- β-Glucuronidase

NSCLC- Non-Small Cell Lung Cancer

ICI- Immune Checkpoint Inhibitor

UGT- UDP-Glucuronosyltransferase

TME- Tumor Microenvironment

CRC- Colorectal Cancer

ER+- Estrogen Receptor-Positive

CTL- Cytotoxic T-Lymphocyte

DNA- Deoxyribonucleic Acid

RNA- Ribonucleic Acid

Chapter 01

Introduction

1.1 Gut microbiome and cancer

One pillar of human physiology is the gut microbiome that we now appreciate. It compromises billions of microorganisms that influence metabolism, digestion, immunity, and host signaling. The community of microbe systems has dynamic performances and high diversity among individuals but forms a stable functional relation with the host in health. The classification and characterization of microbiomes have been growing past the previous decade's results to formulate a link between these organisms with mechanisms and treatment responses of disease.

The human gut microbiome is a complex and dynamic ecosystem hosting countless numbers of microorganisms. Host gut microbiomes have an influence on cancer development, progression, and therapeutic response. But the most notable one is the ability of the microbiome to shape response and toxicity of different anti-carcinogenic agents (chemotherapy, immunotherapy, targeted therapies) has transformed individualized care in cancer (Böhm et al., 2025).

Other than drug metabolism, the microbiome in the gut has an important impact on modulating immune response that is required for immunotherapy successfully. In this case, several articles and journals from recently published studies suggest that the microbiome may alter TME and immune surveillance by creating an influence on the composition and function of immune cells. Some bacterial species, such as *Bacteroides fragilis* and *Akkermansia muciniphila* are revealed to increase anti-tumor immunity by activating different types of immune cells including dendritic cells and T lymphocytes (Zhao et al., 2023; Sun et al., 2023).

The microbiome plays a desired role in immunotherapy. It also plays an important role in tumor immune therapy. It has been proved that dysbiosis can create immune tolerance in the TME. As a result, limiting therapies are working to stimulate the immune response. For example, bacteria of the gut imbalance can cause the increased level of immunity-suppressive metabolites like short-chain fatty acids (SCFAs) that have been seen to modulate immune cells and induce tumor growth (Sun et al., 2023). This shows the significance of a proper gut microbiome for keeping the efficacy of cancer immunotherapy.

Moreover, drug metabolic rates and immune responses affect the toxicity of cancer therapy. One of the most common and toxic side effects of chemotherapy is gastrointestinal toxicity that results in diarrhea, nausea, and mucositis. The gut microbiome plays an important role in microbe-mediated toxic effects or side effects. Plus, antibiotics also modify the gut microbiome that have been also reported to mediate toxicity of chemotherapeutic drugs like 5-FU and cisplatin (Gori et al., 2019). In addition, discoveries that either restart or support the maintenance of this microbial family profile have seen a potential to induce toxicity associated with treatment and therapy and to induce QoL of patients (Cullin et al., 2021). To conclude, these results show the potential of microbiome-directed interventions as adjuncts to modern cancer therapies and treatment.

In addition to its impact on treatment response and toxicity, the gut microbiota is now being evaluated as a candidate for diagnostic and prognostic tool for cancer. Bacteria such as Bacteroides and Prevotella have been linked to better responses to immunotherapies and open the door for use of microbiome profiling as a personalized therapy (Sun et al., 2023). These microbiome communities have already predicted that biomarkers might help in diseased patients with therapeutic strategies, reducing unwanted side effects and toxic effects and increasing response rates.

The gut microbes are important in modulating the response to cancer treatments and therapies even through immune function, drug metabolism, and treatment toxicities. As now in modern day research that the complex relationship between the microbiome and cancer treatment continues to discover, it becomes more understanding that hampering the gut microbiome may give new ways to therapeutic results that can be improved and side effects decreased. This can be a possible game changer in cancer treatment medicine, thereby allowing more efficient and less toxic treatment options for cancer suffering patients. Understanding gut microbiome and drug interactions is important for advancing cancer medicine. The gut microbiome not only interacts with our immune functions but also modulates our systemic metabolism and drug pharmacokinetics, pharmacodynamics, and immune function. Manipulating microbial profiling with modern oncology practice can help identify responders and non-responders before treatment starts. This could decrease unnecessary toxicity, increase survival results, and allow targeted modulation of the gut microbiome to improve treatment success rates.

1.2 Aim of this project

The study aims to clearly explain the process of how the gut microbiome really modulates anti-cancer drug responses. It also focuses on the biological mechanisms, clinical evidence and the therapeutic strategies which show genuine potential not theoretical concepts with no practical value. The goal is to provide an evidence-based understanding and knowledge of how gut microorganisms have an effect on drug metabolism, immune response, treatment results, side effects and toxicity and to explain where the science is strong, where it is weak and where this area needs to stop just thinking and start creating stronger information.

1.3 Objectives of this review

The objectives of this review are to-

- Explain how the gut microbiome manipulates the mechanism and activity of many cancer drugs.
- Provide a summary of clinical evidence connecting microbiome patterns to treatment outcomes.
- Determine the usefulness of various interventions such as FMT, prebiotics, probiotics, diet.
- Understand the major scientific and practical barriers that are limiting microbiome guided cancer therapy and immunotherapy.

Chapter 02

Methodology

A planned way was used to introduce the role of the gut microbiome that modulates cancer treatment responses. Initially, an overall search was included in multiple trusted, well-reviewed, and well-known scientific sources like PubMed, Google scholars, and Scopus etc. The focus was on research that was published between 2015 and 2025. The objective of this search was to find studies on techniques of the gut microbiome that have an influence on efficacy, effectiveness, breakdown, metabolism, toxicity, and side effects of cancer therapies and treatments. This search was also done with understanding immunotherapies, chemotherapy, and targeted therapies. When all the studies were gathered, their headlines and abstract were checked thoroughly. This was done to ensure they were like the study's aim. Full-text articles were then properly read to gather all the important information and processes such as study focus, aim, objective, cancer types and responses, mechanisms, treatments, therapies, and how all of this was related and interacted with those sectors. Studies that tested therapies like probiotics, prebiotics, or Fecal Microbiota Transplants (FMT) that enhance treatment were also included because they might offer potential ways to ensure carcinogenic treatments and therapies were proper and reduce potential toxic, adverse and side effects. The quality of the research was assayed based on their structure, design, sample sizes, and the techniques used to gather, collect and analyze information, After searching , collecting and reviewing all the researches, the results were combined to ensure a clear and proper knowledge and understanding of how the gut microbiome has an effect on carcinogenic treatments and therapies and how this knowledge and understanding could lead to ensure better patient care. At the end, the study said that while more research and discoveries were needed, there was a potential to manipulate the gut microbiome to create more personalized and individualized effective cancer treatment and therapies.

Chapter 3

The Biological System of the Gut Microbiome

The biological system of the Gut microbiome is highly complex and dynamic, and has a wide range of microorganisms, including bacteria, viruses, fungi and archaea. It also has the highest levels of bacteria and the most diverse microbiome in humans. This microbial population is essential for the hosts overall health and disease status because it affects many important physiological processes, including digestion, immunological regulation, metabolism and disease development. The microbiome is gradually recognized as an essential factor in tumor growth, spread and response to treatment.

3.1 Types of gut microbiota and function

There are many different types of bacteria in the gut microbiome but four main types are Firmiculates, Bacteroidetes, Proteobacteria and actinobacteria are the most common and most necessary for their roles (Li et al., 2023).

3.1.1 Firmiculates

In the human gut Firmiculates are the most important group of bacteria in the human gut. They produce short chain fatty chain fatty acids by fermentation of dietary. fiber like butyrate, acetate, propionate (Xie et al., 2025).They helps to reduce inflammation, support immune function and maintain intestinal health. Butyrate is very important for the gut because it fights against inflammation and maintains a strong epithelial barrier (Cheng et al., 2020).

3.1.2 Bacteroidetes

It is another important bacteria in the human gut. They can also produce short chain fatty acid like Acetate and Propionate and they help regulate metabolism, alter immune function and support gut health.They also regulate the gut barrier function , inflammation control and immunological modulation which prevent the chronic disease such as cancer (Li et al., 2023).

3.1.3 Actinobacteria and Proteobacteria

Actinobacteria and Proteobacteria are also important for gut health but they are less common in healthy people. Proteobacteria are often associated with inflammation and connected to disorders such as Colorectal cancer. (Cheng et al., 2020).

Actinobacteria also play an important role in the synthesis of essential compounds and control immunological function . (Cheng et al., 2020).

3.2 Microbial diversity, homeostasis and dysbiosis.

Gut microbiome plays an important role maintaining a healthy gut through the diversity and balance of the gut microbiome. Which is essential for digestion, disease resistance and immune regulation.

3.2.1 The variety of microbes and homeostasis

Diverse microbiomes ensure the successful execution of essential processes including digestion, immune control and barrier maintenance despite the loss or reduction of come bacterial species (Dumitru et al., 2025). High microbial diversity helps the gut adapt to dietary changes and resist infection which is related to good health and resilience against disease (Böhm et al., 2025).

Homeostasis refers to the balance between the microbiome and the host. Beneficial microorganisms and their metabolites help the host stay healthy and the immune system accepts these microbes. Dysbiosis or disruption of this balance is related to increased risk of disorders including cancer (Xie et al., 2025). By reduction of microbial diversity and over growth of harmful bacteria can lead to inflammation, immune dysfunction, and higher cancer risk (Xie et al., 2025).

3.2.2 Dysbiosis and cancer risk

Dysbiosis has been shown to facilitate cancer development and progression. Changes in gut bacteria can make the gut more permeable which allows hazardous bacteria and their toxins to enter the bloodstream. Which includes systemic inflammation which may facilitate carcinogenesis by modifying immune response and establishing a pro- inflammatory environment favorable to cancer progression (Böhm et al., 2025. Dysbiosis has also been related to worse responses to cancer treatments like chemotherapy and immunotherapy (Liu et al., 2023).

3.3 Microbial metabolites: Short chain fatty acid and their functions

During the fermentation of dietary fibers gut microbiota produce short chain fatty acids (SCFAs), which are the most important metabolites. Butyrate, acetate and propionate are the most common SCFAs. The bacterial phyla Firmiculates and Bacteroidetes produce most of the short chain fatty acids which are essential for maintaining gut health and preventing disease (Li et al., 2023).

3.3.1 SCFAs and the physiology of the host

Short chain fatty acids are very important for maintaining gut health. Butyrate helps regulate the gut barrier by facilitating tight junction formation, boosting mucus production and improving fluid and electrolyte flow (Dumitru et al., 2025).

SCFAs modulate the immune function by stimulating immune cells, macrophages, T cells and regulatory T cells (Xie et al., 2025). That can lead to preserving immunological homeostasis and inhibit chronic inflammation and is involved in metabolic and immunological response (Böhm et al., 2025). They also express that this kind of modulation influences immunological responses, cell differentiation and proliferation that are important for the safeguarding of host against cancer and other disease

3.3.2 SCFAs in cancer: prevention and treatment

SCFAs lower inflammation which is one of the leading causes of cancer growth in the gut (Li et al., 2023). SCFAs also regulate the tumor microenvironment which is essential for maintaining immune function and improving the efficacy of cancer treatment (Dumitru et al., 2025). SCFAs also play a role in the body to chemotherapy and immunotherapy. SCFAs produced by microbiota enhance the efficacy of immune checkpoint inhibitors (ICIs) by altering the tumor microenvironment and promoting the activation of cytotoxic T lymphocytes (CTLs). Which improves the immune system ability to find and kill cancer cells (Xie et al., 2025). In prostate cancer short chain fatty acid (SCFAs) such as butyrate has been shown to increase tumor invasiveness and foster a pro- tumor immunological environment (Liu et al., 2023).

Chapter 4

Mechanisms of microbiome modulation of anti- cancer drug response.

The human gut microbiome constitutes a diverse and dynamic ecosystem which plays a vital role in host physiology influencing the metabolism, immune system modulation, epithelial barrier maintenance and intercellular signaling (Hillege et al., 2024). The gut microbiome significantly influences the efficacy, toxicity and resistance of anti-cancer drugs including chemotherapy, immunotherapy and targeted therapies (Tang et al., 2023).

We examine four principal mechanistic domains through which the gut microbiome modulates anti-cancer drug response: (1) microbial drug metabolism, (2) immune system modulation, (3) microbial metabolite-mediated regulation, and (4) pharmacokinetic/pharmacodynamics (PK/PD) and tumor microenvironment (TME) interactions.

4.1 Microbial drug metabolism

Microbial drug metabolism refers to the capacity of gut microorganisms to activate, inactivate or degrade anti-cancer agents or their metabolites thereby altering the therapeutic response and toxicity of drugs. The gut microbiome can either enhance or reduce the efficacy of cancer therapies.

4.1.1 Irinotecan Chemotherapy for Colorectal Cancer

Irinotecan is a chemotherapy drug widely used to treat colorectal cancer. After administration Irinotecan is metabolized in the liver into its active metabolites, SN- 38 (7-ethyl-10-hydroxycamptothecin), by UDP-glucuronosyltransferases (UGT) which works by damaging the DNA of the cancer cells and leading to their death. In the gut certain bacteria, particularly Clostridium and Bacteroidetes species produce an enzyme called β-glucuronidase (GUS). This enzyme acts on the inactive form of SN-38 (SN-38 glucuronide) which is a conjugated form that circulates in the body after liver metabolism.

The GUS enzyme cleaves the glucuronide group from SN-38 glucuronide effectively reactivating SN-38 in the gut lumen. As a result, active SN-38 is released in the intestine and

where it can lead to increased exposure of the gut lining to the drug (Hillege et al., 2024). As a result, active SN-38 is released locally in the intestines, where it can lead to increased exposure of the gut lining to the drug. The higher concentration of SN-38 in the gut leads to more severe gastrointestinal side effects including diarrhea, including the uterus and estrogen receptor-positive (ER+) cancer cells, which are the most common toxicities associated with Irinotecan therapy. This underscores the importance of the gut microbiome in modulating the toxicity of chemotherapy drugs like Irinotecan (Hillege et al., 2024).

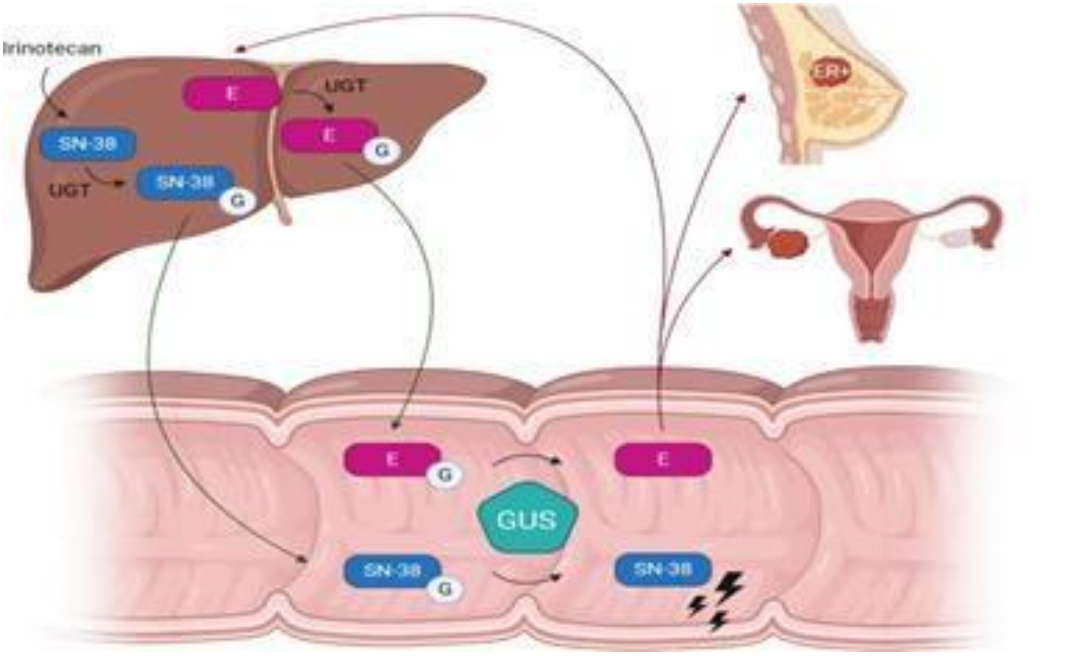

Fig 1- Metabolic Activation of Irinotecan by the Gut Microbiome in Modulating SN-38 Toxicity (Hillege et al., 2024).

4.2 Immune system modulation

The gut microbiome significantly influences both innate and adaptive immune responses, which are crucial for the success of immunotherapies and chemotherapy. The modulation of immune responses by gut microbiome plays a key role in shaping therapeutic outcomes.

4.2.1 Pembrolizumab – Immune checkpoint inhibitor for Non-small cell lung cancer.

The abundance of *Akkkermansia muciniphila* in the gut microbiome has been associated with improved response to PD-1/ PD-L1 inhibitors such as Pembrolizumab in NSCLC patients. *Akkermansia muciniphila* increases mucosal barrier integrity, promotes dendritic cell mutation and enhances T cell priming (Grenda et al., 2022).

4.2.2 Immune response to chemotherpy

Immune response influenced by *Bacteroides fragilis* in patients undergoing Cyclophosphamide treatment (Kang et al., 2024).Also shown that Bacteria increase T cell activation, improving immune response to chemotherapy.

Akkermansia muciniphila and Faecalibacterium prausnitzii as a predictive biomarker for immunotherapy responses which is assessed by microbiome profiling (Grenda et al., 2022).

By changing the dietary, probiotics or fecal microbiota transplantation can help increase or optimize the immunotherapy outcomes (Grenda et al., 2022).

4.3 Microbial metabolite mediated regulation

Gut microbial metabolites such as short chain fatty acids, bile acid and tryptophan catabolites play an important role in immune response, regulating tumor behavior and sensitivity of drugs(Zhou et al., 2025). These metabolites also influence cancer treatment by modulation of immune tolerance and altering the gene expression.

4.3.1 5-Fluorouracil (5-FU) : Chemotherapy for Colorectal Cancer

Micriota metabolites such as Butyrate and propionate act as a histone deacetylase inhibitors which can modify gene expression in tumor, immune cells and influencing the response **5-Fluorouracil** (Zhou et al., 2025).

Metabolites like Butyrate and Propionate are also shown to alter DNA repair pathways and improve the chemotherapy efficacy(Zhou et al., 2025).

4.3.2. Cyclophosphamide chemotherapy

Butyrate produced by bacteria such as *Clostridium* have been shown to promote the immune response and reduce chemotherapy induced inflammation which can enhance the effectiveness of cyclophosphamide(Fan et al., 2023).

4 .4 Pharmacokinetics/Pharmacodynamics and tumor Microenvironment (TME)

The gut microbiome influences the pharmacokinetics and pharmacodynamics of anti-cancer agents which can influence the drug absorption, distribution, metabolism and excretion. The microbiota influences the tumor microenvironment which plays an important role in how the drugs are delivered to tumors and how they can effectively penetrate the tumor tissues.

4.4.1 Anlotinib : Multi targeted tyrosine kinase inhibitors for Non small cell lung cancer

Microbial dysbiosis can elevate the level of endotoxin which can disrupt the vascular integrity and reduce the effectiveness of targeted therapies such as **Anlotinib** (Tang et al., 2023). Microbiome also influence on the vascular endothelial growth factor

The microbiome's influence on the vascular endothelial growth factor (VEGF) pathway is an example of how the microbiota can modulate the TME factors

Akkermansia and Ruminococcus are beneficial microbes which are associated with and reduce the activation of pro angiogenic pathways in the tumor microenvironment (Zhou et al. (2025) Which also includes the VEGF pathway and promotes the tumor blood vessel formation . Patients with these microbiota profiles showed lower VEGF related activity and this is contributing to better treatment responses.

4.4.2 Tamoxidel : targeted therapy for Breast cancer

Microbiota affect the pharmacokinetics of Tamoxifen . Gut microbiomes such as *Lactobacillus spp. and Bifidobacterium spp.* can enhance the conversion of Tamoxifen to its active metabolite endoxifen which improves the drug efficacy and reduces the toxicity (Sadeghloo & Sadeghi, 2025).

Chapter 5

Clinical evidence of gut microbiome in cancer therapy

5.1 Evidence in immunotherapy

Gut microbiome is a key determinant of cancer immunotherapy outcomes. Immune check point inhibitor response influenced by the composition, diversity and functional activity of gut microbiome. Patients with higher microbial diversity and enrichment of specific taxa like Akkermansia and Ruminococcus exhibited significantly improved progression free and overall survival ,especially in melanoma and NSCLC patients (Xie et al., 2025).

Clinical evidence have gut microbiome enhance antitumor immunity by promoting dendritic cell maturation and modulating immunoregulatory pathways such as regulatory T cells and myeloid derived suppressors cells (Gopalakrishnan et al)

Longitudinal patient monitoring further tells that both baseline microbiome composition and dynamic microbial shifts during anti -PD-1 therapy correlate with treatment response in unresectable melanoma (Xie et al., 2025).

In a recent metagenomic and clinical study identified microbial biomarkers strongly associated with melanoma immunotherapy response. The interactions between key bacteria and fungi were also linked to clinical outcomes, focusing on the broader role of the microbiome ecosystem in shaping immune drug efficacy(Zhou et al. 2025).

Clinical review by Najmi et al., (2022) highlights that microbiome modulation strategies such as dietary intervention, probiotics or fecal microbiota transplantation(FMT) can enhance immunotherapy response in metastatic melanoma patients.

5.2 Microbiome and Immunotherapy toxicity

Diverse and balanced gut microbiomes enhance immunotherapy effectiveness,it also influences the development of immune related adverse events like hepatitis, dermatitis, hepatitis and colitis. Dysbiosis, characterized by reduced beneficial species and increased pathogenic species, has been consistently related to irAEs and decreases the therapeutic response (Xie et al., 2025). Clinical investigation has been shown that alteration in Firmiculates and Bacteroidetes correlate with incidence of irEAs during ICI therapy (Gopalakrishnan et al., 2018).

Strategies such as probiotics, prebiotics and FMT are being investigated to restore microbial homeostasis and reduce toxicity burden (Najmi et al., 2022).

5.3 Evidence of Chemotherapy

Gut microbiome plays a significant role in chemotherapy response, efficacy and toxicity. Böhm et al. (2025) demonstrated that specific microbial species including *Streptococcus mutans, Enterococcus casseliflavus and Bacteroides fragilis* were associated with chemotherapy response in patients with gastrointestinal, lung and esophageal cancers.

Gut microbiota can activate or inactive chemotherapy agents, engage the immune system , influence bioavailability of the agent and enhance tumor cell killing (Li et al., 2024).

Advanced esophageal squamous cell carcinoma (ESCC) and patients with a higher *Bactroides plebeius* showed increased outcomes under paclitaxel cisplatin chemotherapy (Li et al., 2024).

5.3.1 Microbiome related toxicity in chemotherapy

Dysbiosis damages the intestinal barrier, increases systemic inflammation and also increases the susceptibility of infection (Li et al., 2024). They highlight that decline of SCFAs producing bacteria worsen gastrointestinal toxicity.

Bacteroides plebeius abundance predicted better chemotherapy response and increased levels of *Bacteroides uniformis* and *Bacteroides plebeius* were also associated with high toxicities (Li et al., 2024).

Chapter 6

Therapeutic Modulation Strategies

In the current practice of anticancer therapy gut-microbiota modulation is very crucial and significant. That's why the strategies including (FMT) and probiotics of microbiome modulating drugs have a great potential in altering the therapeutic response of the patients and minimizing their side effect.

6.1 Fecal Microbiota Transplantation (FMT)

6.1.1 Routes of Administration and Clinical Use

Fecal microbiota transplantation may be administered through colonoscopy, oral capsules and enema or a nasoduodenal tubes. FMT can be delivered in several ways, including colonoscopy, oral capsules, enemas, and nasoduodenal or nasojejunal tubes. Colonoscopic administration allows the material to be placed directly into the lower gut, while capsule-based FMT has become increasingly popular because it is non-invasive and generally more acceptable to patients. In practice, the route of administration is usually selected based on the patient's overall condition, the site and extent of disease, and the specific therapeutic objectives. Within oncology, FMT is being used more frequently to correct treatment-induced dysbiosis arising from chemotherapy, radiotherapy, and broad-spectrum antibiotic use, with the aim of maintaining gut barrier integrity and supporting an effective immune response.

6.1.2 Engraftment, Immunomodulation, and Immunotherapy Response

Recent work has made it clear that FMT can do more than just fix dysbiosis it can also reshape host immunity and make tumours more responsive to immune checkpoint inhibitors. When donor microbes successfully engraft, they help to restore microbial diversity over the long term, support epithelial healing, and activate key immune pathways that underpin effective anti-tumour responses. In fact, several studies report that transferring stool from patients who respond to checkpoint inhibitors to those who do not can partially "re-sensitise" non-responders to PD-1/PD-L1 therapy, largely by enriching bacterial groups linked to T-cell activation and anti-cancer immunity (Ren et al., 2025; Wang et al., 2025). Taken together, these observations position FMT

as a promising supportive, or adjunctive, strategy alongside immunotherapy rather than a stand-alone alternative.

6.2 Probiotics, Prebiotics, and Synbiotics

6.2.1 Beneficial and Next-Generation Probiotic Strains

Probiotics have been investigated in considerable detail because of their capacity to stabilise the gut microbiota and lessen treatment-related side effects. In routine practice, strains belonging to *Lactobacillus* and *Bifidobacterium* are most often used, as they are linked with tighter epithelial barrier function, lower levels of gut inflammation, and a reduced risk of chemotherapy-associated mucositis. More recently, so-called "next-generation" probiotics, particularly *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, have attracted attention because they can shape immune signalling in ways that feedback on treatment response, especially in the context of immunotherapy (Fratila et al., 2023; Cho et al., 2024).

6.2.2 Prebiotics, SCFA Pathways, and Synbiotic Synergy

Prebiotics, typically fermentable fibres such as inulin, fructooligosaccharides and various forms of resistant starch, selectively nourish bacteria that produce short-chain fatty acids (SCFAs). These SCFAs – with butyrate being especially important help to maintain epithelial integrity, support the function of regulatory T cells and dampen pro-inflammatory cytokine signalling, which together can make cancer treatment more tolerable for patients (Christina et al., 2025). When prebiotics are paired with specific probiotic strains in so called synbiotic formulations, they can further promote bacterial colonisation and enhance beneficial metabolic interactions in the gut. Even so, in individuals who are immunocompromised or neutropenic, these interventions need to be used cautiously because, although uncommon, probiotic-associated infections have been reported{Citation} (Shi et al., 2024).

6.3 Dietary and Nutritional Interventions

6.3.1 Dietary Patterns and Microbiome Modulation

Diet probably has more influence on the gut microbiome than almost any other day-to-day factor. When someone regularly eats a typical Western-style diet heavy in saturated fat, added sugar and highly processed foods – the gut community tends to shift towards dysbiosis, with more chronic low-grade inflammation and a clear loss of microbial diversity. By contrast, a Mediterranean-type pattern, with plenty of fibre, fruits, vegetables, polyphenol-rich foods and unsaturated fats, tends to favour beneficial taxa, increase SCFA generation and support healthier metabolic and immune regulation (Knisely et al., 2023)

6.3.2 Nutrient–Immune Interactions and Treatment Response

Certain nutrients seem to do much more than simply provide energy or basic building blocks; they actively tune immune pathways. Polyphenols, omega-3 fatty acids, key vitamins and even fermented foods can alter dendritic cell behaviour, support epithelial repair and shape how naïve T cells differentiate into different functional subsets. Diet also talks to cancer treatment in a very practical way: patterns that are high in fibre and that favour SCFA production are generally linked with better tolerance of chemotherapy and, in many cases, stronger responses to immunotherapy, whereas diets dominated by saturated and total fat may interfere with drug absorption and blunt therapeutic efficacy (Shi et al., 2024; Christina et al., 2025). Altogether, these observations strongly argue for personalised nutritional planning as an integral part of modern, integrative cancer care rather than an optional add-on.

6.4 Microbiome-Targeted pharmacological agents

6.4.1 Postbiotics and Microbial Metabolite Modulation

Postbiotics meaning the bioactive substances produced by microbes, including SCFAs, small peptides and structural cell-wall fragments are attractive because they can deliver many of the benefits of microbiome modulation without the safety concerns that come with giving live organisms. Among these, metabolites such as butyrate and inosine stand out, as they have been shown to strongly influence immune function, for example by boosting $CD8^+$ T-cell activity and making immune checkpoint inhibitors work more effectively through stimulation of Th1-type immune pathways (Lu & Tong, 2024). Taken together, these data point towards metabolite-focused, or postbiotic-based, strategies as a promising direction for future cancer therapies.

6.4.2 Antibiotic Effects and Precision Microbiome Interventions

Broad-spectrum antibiotics can profoundly disturb gut microbial communities, and this disruption has repeatedly been linked with worse outcomes in patients treated with immunotherapy. When these agents are used liberally during cancer care, they often wipe out many of the beneficial taxa that support immune tone, which in turn can blunt anti-tumour immune responses (Ren et al., 2025). Moving forward, more precise, microbiome-aware antibiotic prescribing will likely need to be built into standard cancer treatment protocols.

6.5 Engineered Microbes and Synthetic Biology

6.5.1 Living Therapeutics and Gene Circuit Engineering

Recent advances in synthetic biology have made it possible to build engineered microbial strains that can carry out very specific therapeutic tasks. These so-called “living therapeutics” are designed to sense cues associated with the tumour microenvironment and, in response, to release anti-cancer agents such as cytokines, molecules that mimic checkpoint inhibitors, or even locally acting cytotoxic factors right at the tumour site. In principle, this strategy offers a way to concentrate treatment where it is needed most, while keeping systemic exposure, and therefore off-target toxicity, to a minimum(Cho et al., 2024).

6.5.2 CRISPR Editing, Kill-Switch Systems, and Clinical Advancement

CRISPR-based tools now make it possible to edit bacterial genomes with a high degree of precision, so specific changes can be introduced to improve safety, fine-tune metabolic activity or add therapeutic gene cassettes tailored to cancer treatment. In parallel, many of these engineered strains are built with built-in safety valves, such as genetic “kill switches” that trigger programmed self-destruction if the organism escapes its intended niche, thereby limiting unwanted colonisation or environmental spread (Mousavinasab et al., 2023). Early-phase clinical studies using modified *E. coli* Nissle have reported encouraging signals, both in terms of feasibility and biological activity, suggesting that synthetic biology is likely to develop into a genuinely transformative platform for microbiome-based cancer therapy.

Chapter 7

Challenges, Controversies and Knowledge Gaps

Our understanding of cancer biology and how we respond to treatment has profoundly changed since this game-changing gut microbiome research. But integrating such microbiome discoveries into standard cancer treatments will be a grueling slog, host-bacteria relationships and different gut profiling approaches and ethical-safety worries about manipulating microbial communities. There are several pressing questions that remain open, which would be require sophisticated computational methods and multilayered systems genomics strategies to deconvolute. This article provides a deep dive into the scientific, ethical and practical challenges (coretar) of studying the micro-cancerome to date; remaining questions (unmentionables); and what's in store next including evidence-driven personalized microbiome-based therapies to tighten the screws "by driving forward preclinical research platforms."

7.1 Technical Limitations

7.1.1 Sequencing and Bioinformatics Inconsistencies

Variability of different sequencing techniques is a significant driver of variability in microbiome research. Although the 16S rRNA technique is commonly used and economical, it can only produce results at the genus level and cannot achieve functional hydration resolution. In contrast, whole metagenome sequencing gives a broader-scaled view but with the disadvantage that it is expensive and computationally intensive (Shi et al., 2024). In addition, there is no standard agreed upon bioinformatics pipeline and this can also create difficulties for interpreting the data. Because of various criteria for filtering, clustering algorithms, and databases to be used as a reference database (which every small RNA sequencing analysis need) for specific research group may obtain different results even from the same data set (Cho et al., 2024). Furthermore, batch effects including the differences in sequencing platforms, reagent batches or technical personnel become another layer of noise and jeopardize the reliability and reproducibility of the observed results (Fratila et al., 2023).

7.1.2 Rare Taxa and Database Limitations

The detection of microbial taxa with low abundance is a challenging task even if those have possible functions, such as immune modulation and metabolic signaling (Christina et al., 2025). Compounding this problem, a large number of microbial sequences are still unidentified owing to deficits in the coverage and outdatedness of reference databases, particularly anaerobic bacteria and tumor-inhabiting microbes (Mousavinasab et al., 2023). These shortcomings have made it difficult for us to know the exact profile of microbial communities in and around tumors, as well as their functional relevance in the context of cancer treatments and therapeutic responses.

7.2 Biological Complexity

7.2.1 Microbiome Dynamics and Host Variability

Gut microbiome is a changing ecosystem, and so one that will be in constant flux which dependant on variables like exposure to our environment, sleep and stress schedules, medications and diet. This inherent variability hampers the pursuit of stable microbial biomarkers of cancer progression or treatment response.

In the communities of microbes also thrive in complex environments through cooperation, competition and metabolic trade-offs among species. So these associations and non-linear microbiome responses to interventions add yet another layer of complexity to our understanding of how the microbiome influences cancer therapy (Wang et al., 2025).

7.2.2 Host–Microbiome–Tumor Interactions

Microbial metabolites such as short-chain fatty acids and inosine are also known to modulate immune response, epithelial function, and cytokine signaling further... making it difficult to identify direct cause-and-effect relationships (Lu & Tong, 2024). Moreover, recent research has suggested that cancers have their own distinct microbiome-associated to them and could modulate the tumor microenvironment, immune cell infiltration or even response towards

therapy. However, these tumor microbiota remain incompletely described, with large gaps in our understanding (Ren et al., 2025).

7.2.3 Confounders and Causality Gaps

Clinical investigations into the relationship between microbiome and cancer therapy are plagued with confounders such as antibiotics, proton pump inhibitors, steroids and chemotherapy themselves all acting to substantially modulate microbial composition independent of cancer biology (Christina et al., 2025). In addition, differences between individuals, including age, sex, genetic background, diet and lifestyle make it very challenging to identify generalizable microbial indicators (Shi et al., 2024).

7.3 Ethical and Safety Concerns

7.3.1 Long-Term Safety, Equity, and Regulatory Issues

The effects of manipulation of the microbiome on the long-term health outcomes are not well described and may have involved metabolism, immune status in what was previously in a stable ecological balance within the gut ecosystem (Christina et al., 2025). The prohibitive cost of sequencing technologies, a multi-omics analyses and FMT are also posing grave concerns about equity and global access (Cho et al., 2024). There are also ethical considerations in microbiome biobanking, like privacy and consent (ownership) of the genetic data of microflora which is not yet resolved from a regulatory standpoint (Fratila et al., 2023). The rise of unregulated "DIY FMT" communities, demonstrates the need for coherent policy regulations (Cammarota et al., 2017). Furthermore, synthetic biology raises new ethical issues especially with engineered microbes and viruses, having strict biosafety considerations to prevent accidental release in the environment or its misuse (Mousavinasab et al., 2023).

7.4 Data Gaps and Future Directions

7.4.1 Limited Longitudinal Studies and Mechanistic Insights

The majority of human microbiome studies conducted to date are cross-sectional or brief in duration and therefore do not provide insight into the preservation of long-term microbial evolutionary dynamics during progression of cancer, or across prolonged therapeutic interventions (Knisely et al., 2023). The mechanistic underpinnings of these interactions, which include the microbial metabolism of chemotherapeutic agents and immune checkpoint inhibitor effectiveness remain incompletely characterized (Wang et al., 2025). Moreover, tumor microbiomes in situ are relatively unexplored because of constraints with sampling as well as concerns about contamination (Ren et al., 2025).

Chapter 8

Future Perspectives in Precision Oncology

The science of microbiome transforming precision is a part of an oncology department. Gut microbiome which also plays a critical role in immune regulation therapy, tumor signaling method and drug metabolism. There is the potential for a new model of predicting how patients will respond to the treatments and how it works for enhancing therapies. In the first development of research the microbial biomarkers personalized microbiome therapies and their successful translational workflows should have been considered as general practice in treatment which is also important in cancer therapy. So the perspective should have helped to realize the full potential for microbiome based on their precision medication. Here this chapter will review all information about gut microbiome in which the progress can be made in the exciting field with promising work and more individualized with sufficient cancer treatment in their work place.

8.1 The Microbiome as a predictive Biomarker

8.1.1 Microbiome-Based Prediction of Therapeutic Response and Toxicity

The discovery of microbiome-derived biomarkers is an important frontier in precision oncology which can predict responses to immunotherapy. There are some microbiomes, for example- *Akkermansia muciniphila* & *Faecalibacterium prausnitzii* which have been linked their favorable responses for the patients who are treated with PD-1/PD-L1 checkpoint inhibitors. The activation of T cells and the presentation of antigens is the strengthening of these microbes and also a tumor microenvironment generating is more treatable. Treatment-related toxicities, for example- immunotherapy induced colitis that improves risk evaluation and preventive interventions in microbiota profiles which represent early biomarkers for prediction.

8.1.2 Artificial Intelligence, Standardization, and Regulatory Challenges

For finding complicated and important microbial signatures machine learning AI models are becoming very needed which are linked to their treatment response, replace and the resistance methods (Cho et al., 2024). The dynamic interactions in both microbes, immune cells, and tumor pathways are advanced models which depend on multi-omics datasets to impress. By the absence of specialised sequencing protocols methods, the clinical applicability of these models is constrained which is understanding their importance. So the variability in data processing pipelines, and inadequately validated microbial biomarker panels plays an important role in this section (Shi et al., 2024). The regulatory bodies are endeavoring to formulate normative frameworks for the classification and approval of microbiome-related diagnostic instruments and other necessary tools which are important for this; So the significant deficiencies persist in concerning quality control treatment and clinical validation segment. (Cammarota et al., 2017)

8.2 Multi-Omics Integration in Microbiome-Guided Oncology

8.2.1 Integrating Microbial, Immune, and Tumor Signaling Networks

The Precision of oncology is increasingly emphasizing multi-omics that incorporate the microbiome and it is not only in conjunction with immunomics but also with metabolomic and their transcriptomic layers which is very necessary in this section. In the Microbial metabolites sector, for example - short chain fatty acids (SCFAs) and inosine, are very essential and sufficient mediators that are regulate immune cell response, differentiation, cytokine signaling, and epithelial repair or replace, thereby an influencing of treatment which are responses to ulcerative colitis (UC) patients and are which people who needs to treatment (Lu & Tong, 2024)

8.2.2 Computational Integration and Biomarker Discovery Pipelines

For the interpretation of high-dimensional multi-omics data it is very essential to cultivate advanced computational paradigms which are also very important for patient’s treatment. For instance, network-based modeling can be employed to delineate interactions among microbes, pharmaceuticals, and host pathways, yielding insights into therapeutic responsiveness and

potential toxicity which is necessary in the area of patient's treatment development sector and for patients improvement site (Wang et al., 2025).

Multi-"omics"-based biomarker discovery pipelines that combine microbial, metabolic, and immune signatures will be essential for developing more precise and individualized diagnostic tools. So it is easily understood about its importance (Christina et al., 2025). To substantiate the translational significance of these findings, validation through both animal studies and human observation remains a crucial step. So it should be ensured that the step is fulfilled (Shi et al., 2024).

However, confirming the real-world relevance of these findings requires validation through both animal experiments and clinical observations in humans.

8.3 Personalized Microbiome Therapeutics

8.3.1 Adaptive, AI-Guided Therapeutic Strategies

In the new therapeutic strategies which are focused on the individualization of microbiome interventions methods, incorporating long-term or continuous sampling, with AI-driven adaptations to treatment protocols that generate their effectiveness. In the diet-based manipulation of metabolism by the microbes that can also be employed to enhance the immunotherapy effectiveness or it reduces the association of their toxicities (Knisely et al., 2023). Moreover, an autologous of microbiome banking which may be promotes the normalization of function following the completion of treatment and therapy (Cammarota et al., 2017)

8.3.2 Precision FMT, Engineered Microbes, and Digital Twin Modeling

The new waves of probiotics, which include the genetically modified strains, are likely to provide immune-modulating molecules using personalized profiling of microbiome model structure (Cho et al., 2024). So we can speculate that they are targeted to be used in tailored fecal microbiota transplantation (FMT) of support to treatment responses methods. Virtual Computational Models (Digital Twin Simulations) of patient-specific gut microbiome ecosystems which have been developed to predict treatment on response, discover and optimize the therapeutic interventions while it is minimizing their toxicity in the form of utilized all kinds of their compounds and segments (Wang et al., 2025). In addition, to the personalized

postbiotic therapies in relation to the specific microbial metabolites which can be enhance the specificity and safety of their treatment area (Lu & Tong, 2024). These developments which have been profound ethical implications insofar as safety, the transfer of microbial genes therapy, and for long-term ecological concerns about it (Mousavinasab et al., 2023).

8.4 Translational Roadmap for Clinical Implementation

8.4.1 Manufacturing, Regulation, Infrastructure, and Health Economics

In the development of sellable manufacturing platforms which is likely to be necessary in order to microbiome therapies to become a standard part of cancer treatment care and ensure regulatory that it will also need to be applied in treatment if it is safe and effective, such treatments which are proved. Microbiome products, including FMT materials and engineered microbes, would have to follow the Good Manufacturing Practice (GMP) of regulation (Cammarota et al., 2017). So, the regulators like the FDA and EMA who are must be decide upon a uniform approach to categorize to such treatments which are approve them for clinical usage (Cho et al., 2024). In the Establishing of microbiome-based on clinics that will be depend on the extensive sequencing site of infrastructure, empirically designed bioinformatics platforms and good manufacturing practice (GMP) facilities for therapeutic production of it (Wang et al., 2025).

8.4.2 Workforce Training and Patient-Centered Ethics

In the order for microbiome-directed oncology to be effectively applied to training of clinicians and bioinformaticians in microbial identification methods of multi-omic analysis on host samples and the pharmacological interventions to the manipulate of the microbiomes of cancer patients that will undoubtedly be needed for it (Christina et al., 2025). Furthermore, public involvement and open communication are a prerequisite and needed to allay patient fears about privacy, data repatriation of safety related to the use of microbial interventions (Ren et al., 2025). To apply these new treatments in a clinical setting responsibly, and ethical way of people that will have to trust them and to give informed consent.

Chapter 09

Conclusion

One new field is pharmacomicrobiomics that explores the differences between microbial composition and function affect people's responses to drugs. Several have shown that one's gut bacteria have the capability to activate, inactivate, or metabolize a drug before it is even absorbed by the body. The importance of this concept has been derived in oncology because the gut microbiome was found to impact lifesaving, contemporary cancer treatment approaches such as chemotherapy, immunotherapy, and targeted therapy. Pre-clinical and clinical studies pointed out that microorganisms modulate treatment effectiveness. On its effects on the safety of treatment, bacteria enzymes influence toxicities of drugs including irinotecan. Even with advancements in oncology, the therapeutic outcomes stay inconsistent. Patients with the same genetic profiles, tumor types, and treatment processes often show different responses ranging from total remission to rapid progression or severe toxicity. Modern or traditional pharmacogenomic explanations account for only part of this variability. Today's clinical evidence suggests that gut microbiome composition has contributed significantly to these different outcomes. However, there is no proven clinical approach for understanding or modulating the microbiome in the routine cancer treatment process. This indicates the urgency for an integrated review that organizes current results and evidence and clarifies the mechanisms, clinical data, and therapeutic strategies.

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