Microbiome Modulation as a Determinant of Cancer Therapy Response: Highlights from ESCMID 2026

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THE ROLE of the microbiome as a modulator of cancer therapy response has become a key topic in recent oncology research. At the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2026 Global Congress, emerging data highlighted how not only microbial composition, but especially microbial function, can influence outcomes in patients receiving immunotherapy and chemotherapy. In precision oncology, where treatments are tailored to tumour biology, the microbiome and diet are emerging as relevant and modifiable factors.

INTRODUCTION

Clinical outcomes in oncology remain highly heterogeneous, even among patients with similar molecular profiles. Despite major advances in targeted therapies, a significant proportion of patients do not achieve the expected benefit. This variability has led to increasing interest in host-related factors, particularly the gut microbiome, as contributors to treatment response.

This also raises a broader question: how can we reprogramme the immune system in patients with cancer beyond tumour-directed strategies? While oncology has traditionally focused on tumour-specific mechanisms, there is growing recognition that systemic factors, such as immunity, metabolism, and the microbiome, also play a key role.

The microbiome influences systemic immune responses, tumour microenvironment interactions, and drug metabolism. Importantly, its impact seems to go beyond the presence or absence of specific bacterial taxa. Functional outputs, particularly microbial metabolomic activity, are increasingly recognised as key determinants of response. Data presented at ESCMID Global 2026 reinforced this shift towards a more functional perspective.

MICROBIOME AND IMMUNOTHERAPY RESPONSE

There is now substantial evidence linking the gut microbiome to response to immune checkpoint inhibitors. Both preclinical and clinical data consistently link specific microbial profiles with improved antitumour immunity, particularly

through enhanced CD8+ T-cell activity.[1] Differences in microbial composition between responders and non-responders have been consistently described, although no single 'beneficial' microbiome signature has been universally identified.[2]

> **How can we reprogramme the immune system in patients with cancer beyond tumour-directed strategies?**

Faecal microbiota transplantation (FMT) provides some of the strongest evidence supporting a causal relationship. In patients with melanoma who were refractory to immunotherapy, transfer of microbiota from responders has led to clinical benefit in a subset of cases. The effect does not appear to depend on specific bacterial species alone, but rather on broader ecosystem characteristics.

Mechanistically, modulation of tumour immunogenicity appears relevant. Data presented by Markel et al. (Markel, unpublished data) suggested a potential link between microbiome modulation and tumour immune recognition, possibly involving pathways such as adenosine deaminase acting on RNA 1 (ADAR1)-mediated RNA editing, which may enhance T-cell recruitment and chemokine signalling. Despite these promising findings, several practical questions remain unresolved, including the optimal route of administration, the need for microbiome depletion prior to FMT, and how to maintain its effects over time.

ANTIBIOTICS AND DISRUPTION OF RESPONSE

Antibiotic use is common in patients with cancer, with up to one-third receiving antibiotics at the start of immunotherapy (often broad-spectrum agents), and rates of receiving antibiotics reach up to 31% during this period.[3,4] It is consistently associated with reduced immune checkpoint inhibitor efficacy, likely mediated through disruption of microbial diversity and function.[3,4]

Meta-analyses involving large patient cohorts have repeatedly shown worse outcomes in patients exposed to antibiotics close to the start of treatment, highlighting the importance of timing.[5,6]

These findings are further supported by large-scale analyses including over 46,000 patients across more than 100 studies, confirming worse outcomes in both immunotherapy and chemo-immunotherapy settings.[7] However, not all antibiotics have the same impact, with broad-spectrum agents and combination regimens showing the most pronounced negative effects, likely due to greater microbiome disruption (Alves, unpublished data).

In the context of antibiotic exposure, dysbiosis may promote a more tolerogenic immune environment, alter immunometabolic pathways, and disrupt key microbial networks. Changes in bile acid metabolism, expansion of less favourable taxa such as *Enterocloster* spp., and altered signalling pathways may all contribute to impaired treatment response.[8]

Microbiome-based tools, such as TOPOSCORE, are beginning to translate these insights into clinically relevant strategies, enabling stratification of patients according to their likelihood of response to immunotherapy.[9] These findings underscore the importance of careful antibiotic stewardship, favouring targeted approaches and limiting unnecessary exposure.[10,11]

BEYOND COMPOSITION: THE ROLE OF MICROBIOME FUNCTION

A key takeaway from ESCMID Global 2026 is the shift from focusing on microbial composition to understanding microbial function. While earlier studies aimed to identify specific bacterial taxa, current evidence suggests that metabolic activity may be more relevant.

This is illustrated by early-phase studies evaluating prebiotics such as camu camu, a polyphenol-rich source including castalagin.[12] Despite minimal changes in

microbiome composition, improvements in clinical outcomes were observed, accompanied by significant shifts in metabolomic profiles. These findings support the concept that function, rather than taxonomy, drives response.

Among the pathways of interest, bile acid metabolism has emerged as an important immunomodulatory axis, with microbiome-driven alterations shown to impair tumour-specific T cell responses.[13] Similarly, metabolites derived from tryptophan metabolism appear to influence treatment response.

MICROBIOME AND CHEMOTHERAPY

The microbiome also plays a role in chemotherapy, influencing both efficacy and toxicity. A key aspect is the presence of intratumoural bacteria, which challenges the traditional view of tumours as sterile environments.[14]

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In pancreatic cancer, intratumoural bacteria are thought to originate from the gut, supporting the concept of microbial translocation.[15] The microbiome can influence treatment response through several mechanisms, such as drug metabolism, immune modulation, and the production of bioactive metabolites.[16] A well-known example is gemcitabine, which can be inactivated by bacteria within the tumour that express specific enzymes, ultimately leading to treatment resistance.[17] This effect appears drug-specific and has not been clearly observed with other chemotherapies. Preclinical studies have shown that antibiotic treatment can restore gemcitabine efficacy, and this strategy is currently being explored in clinical trials such as the ongoing PRODIGE 106 PANORAMIX study.

Beyond these direct interactions, the microbiome has also been linked to tumour biology and clinical outcomes. In pancreatic cancer, both microbial signatures and metabolomic profiles have been associated with disease risk and prognosis.[18]

THERAPEUTIC MODULATION AND CLINICAL IMPLICATIONS

Therapeutic modulation of the microbiome is emerging as a promising strategy to improve cancer treatment. Among the most relevant studies reported this year, the FMT-LUMINate trial reported encouraging response rates in melanoma and non-small cell lung cancer, while in renal cell carcinoma, the randomised Phase II TACITO trial showed similar findings, supporting the potential benefit of microbiome modulation across tumour types.[19,20]

Multi-omics analyses suggest that these effects may be driven less by donor engraftment itself and more by the depletion of deleterious microbial taxa, although this requires confirmation in larger, controlled studies.[20,21] Although results vary between studies, most data suggest a role for FMT in modulating response to immunotherapy. However, its implementation in routine practice remains limited by challenges related to scalability, standardisation, and regulatory complexity.

Importantly, commonly used over-the-counter probiotics do not appear to provide benefit and may even impair microbiome recovery and treatment outcomes. These findings highlight the need for more effective strategies to preserve the microbiome, including optimising antibiotic use and reducing unnecessary polypharmacy.[22,23] In this context, antibiotic stewardship becomes particularly relevant in clinical practice. Emerging approaches, such as microbiome-sparing antibiotics like lolamicin, have shown promising results by selectively targeting pathogens while preserving microbial diversity and maintaining anti-programmed cell death protein 1 (PD-1) inhibitor activity.[24]

EXPERT PERSPECTIVE

Data from ESCMID 2026 further support the idea that the microbiome plays an important, although still not fully understood, role in shaping responses to cancer therapy. Beyond tumour-directed strategies, host-related factors, particularly microbiome function and diet, are increasingly recognised as modifiable elements that may help improve outcomes.

Across regions, including Europe and North America, current strategies are broadly aligned, with a shared interest in how the microbiome influences treatment response. There is also a clear shift towards studying microbial function rather than focusing only on taxonomy. At the same time, microbiome composition varies according to geography, diet, and environmental exposures, leading to differences across populations. While these variations are unlikely to change the underlying biological mechanisms, they may influence which microbial taxa or functions are most relevant in a given context.

> **Research is moving towards identifying functional profiles and potentially harmful microbial patterns**

Finally, it is becoming clear that there is no single definition of a 'healthy' microbiome. Instead, research is moving towards identifying functional profiles and potentially harmful microbial patterns. This more pragmatic, function-oriented approach may help address regional variability and support the development of microbiome-based strategies applicable across different settings.

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