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REVIEW

Analysis of interactions of immune checkpoint inhibitors with antibiotics in cancer therapy

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Abstract **The discovery of immune checkpoint inhibitors, such as PD-1/PD-L1 and CTLA-4, has played an important role in the development of cancer immunotherapy. However, immune-related adverse events often occur because of the enhanced immune response enabled by these agents. Antibiotics are widely applied in clinical treatment, and they are inevitably used in combination with immune checkpoint inhibitors. Clinical practice has revealed that antibiotics can weaken the therapeutic response to immune checkpoint inhibitors. Studies have shown that the gut microbiota is essential for the interaction between immune checkpoint inhibitors and antibiotics, although the exact mechanisms remain unclear. This review focuses on the interactions between immune checkpoint inhibitors and antibiotics, with an in-depth discussion about the mechanisms and therapeutic potential of modulating gut microbiota, as well as other new combination strategies.**

Keywords tumor immunotherapy; immune checkpoint inhibitor; antibiotics; gut microbiota; drug–drug interaction

Introduction

Cancer immunotherapy, which utilizes the body's immune system for the specific recognition and killing of cancer cells, has recently become a very active field of research. Current cancer immunotherapy strategies use different mechanisms, including immune activation with therapeutic cancer vaccines and cytokines, immunosuppressive tumor microenvironment (TME) blockade with immune checkpoint inhibitors (ICIs), and monoclonal antibodies. Research on immune checkpoints (ICs) was awarded the 2018 Nobel Prize in Physiology or Medicine. ICIs have been listed and widely used in clinical practice in China.

ICs are protective molecules in the body that normally inhibit T cell overactivation, acting as an immune "break" to prevent immune system overactivation [1] and reduce the probability of autoimmune reactions. However, many tumor cells overexpress ICs to cause T cells to enter a resting state, thereby escaping immune recognition and killing, resulting in tumor immune escape. If traditional antitumor immunotherapy is like "stepping on the accelerator while braking," then ICIs, which enhance T cell activity by blocking ICs [2], are like loosening the immune system "brake" before other treatments to improve tumor immunotherapy efficacy. Currently, programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are the most studied ICs [3].

The ICIs that have been approved by the US Food and Drug Administration include ipilimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and cemiplimab, which are mainly used to treat advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), Hodgkin's lymphoma, urothelial carcinoma (UC), and other malignant solid tumors [4]. The efficacy of ICIs is improved and their toxicity is reduced by combining ICIs with different mechanisms clinically, such as the combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab [5], which can prolong the progression-free survival (PFS) of patients with lung cancer. The emergence of dual-pathway or even three-pathway blocking therapies [6,7] provides new insights into tumor immunotherapy. In addition, new ICs, such as T cell immunoglobulin and mucin domain 3 [7], lymphocyte activation gene 3 [8,9], V-domain Ig suppressor of T cell activation [10,11], and

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adenosine A2a receptor [12,13], have received attention among clinicians, demonstrating that immunotherapy is playing an increasingly important role in future tumor treatment.

Given that ICIs can lead to serious and even life-threatening infections during tumor immunotherapy, their use in combination with antibiotics is inevitable. However, recent clinical studies have found that in most cancer patients treated with ICIs, efficacy decreases after antibiotic use. The mechanisms underlying this interaction between ICIs and antibiotics are not yet known. Here, we review and discuss the current state of combined ICI and antibiotic therapy, its mechanisms, existing challenges, and solutions, as well as emerging immune-combination therapies.

Clinical research on ICIs combined with antibiotics

ICI mechanisms

At present, PD-1/PD-L1 and CTLA-4 are the most studied ICIs (Fig. 1). PD-1, a member of the CD28 superfamily, mainly exists on the surface of activated immune cells and has two ligands, namely, PD-L1 and PD-L2 [14,15], which are B7 family proteins [16]. Healthy host cells usually do not produce substantial levels of PD-L1 on their surface, and PD-L1 is mainly expressed on tumor cells [17,18]. Studies have shown that when PD-L1 on tumor cell surface binds to PD-1 on activated T cells, cytoplasmic domain tyrosine residues are phosphorylated and protein tyrosine phosphatase (PTP) is recruited. PTP recruitment leads to dephosphorylation of signal kinases, blocking the stimulated signal transduction of CD28 and subsequent T cell activation [19]. Some studies have found that $CD8^+$ T cells show explosive growth after cancer patients receive PD-1 inhibitors [20], and PD-1/PD-L1 inhibitors can restore T cell function by blocking inhibitory signal transmission and releasing immune "brakes" to exert antitumor effects [21]. CTLA-4 is a homologous analog of CD28 [22], but compared with CD28, CTLA-4 has a stronger affinity for CD80/CD86 [16]. Thus, CTLA-4 competes to bind CD80/CD86 first. CTLA-4 also downregulates CD80/CD86 expression in antigen-presenting cells or removes it through cytoendocytosis, thereby blocking its binding to CD28 and inhibiting T cell activation [23,24]. Thus, CTLA-4 plays a negative regulatory role in immune response activation, and CTLA-4 inhibitors can block this inhibitory signal, induce T cell activation and proliferation, and restore the body's immune system function [21].

Clinical status of combining ICIs with antibiotics

Traditional chemotherapy drugs exert antitumor effects through cytotoxicity. Therefore, their adverse reactions are usually concentrated in fast-growing organs and tissues and include hair loss and bone marrow suppression [25]. By contrast, ICIs can reactivate autoreactive immune cells and tumor-specific T cells, leading to immune-related adverse events (irAEs) in almost 70% of patients [26]. These irAEs and their clinical manifestations are very similar to autoimmune diseases [27,28]. Common irAEs include lethargy, rash, pruritus, hepatotoxicity, diarrhea, colitis, hypophysitis, pneumonia, hepatitis, and endocrine lesions [29]. According to the grading standards of Common Terminology Criteria for

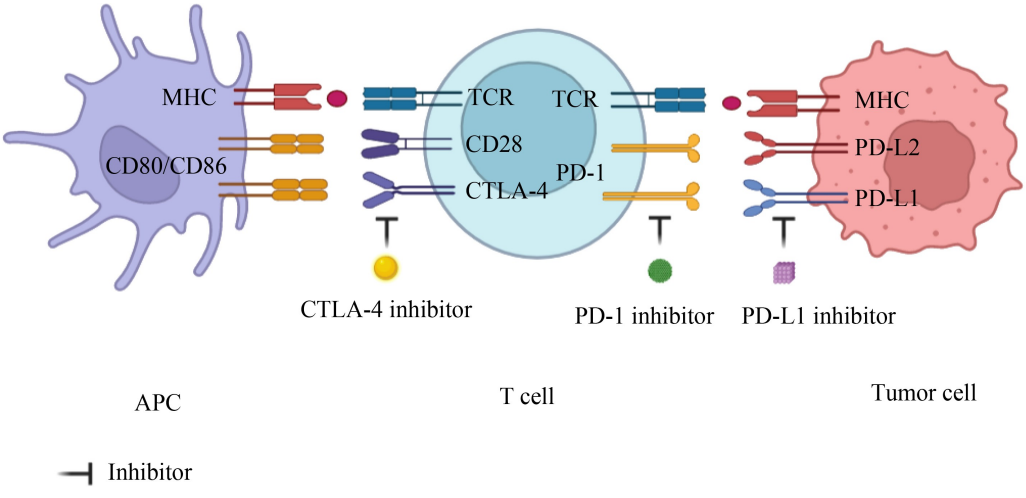

Fig. 1 ICI mechanisms. CTLA-4 on T cells binds with CD80/CD86 on antigen-presenting cells (APCs), preventing T cell activation. Blocking CTLA-4 with CTLA-4 inhibitor restores T cell function. PD-1 on T cells binds with PD-L1 on tumor cells, inhibiting T cell function and leading to tumor cell immune escape. PD-1 or PD-L1 blockade by PD-1 inhibitor or PD-L1 inhibitor releases T cell inhibition, enabling them to kill tumor cells.

Adverse Events (version 5.0), most irAEs are mild and not obvious (grade 1 or 2 adverse events), but some patients will have severe, critical, and even life-threatening irAEs (grade 3 or 4 adverse events), which require early clinical intervention [25].

IrAEs can occur throughout the whole immunotherapy process. If there is early detection and early intervention, irAEs are almost always reversible at the beginning of immunotherapy [30], but if not treated in time, they may lead to serious infection and even death [31]. IrAEs often require corticosteroids and sometimes even immunosuppressants [32]. Little is known about the safety of treating irAEs. In particular, data on infection in patients treated for ICI-associated irAEs are scarce. Castillo *et al*. [33] retrospectively underscored that serious infection occurred in 54 of 740 patients (7.3%) with melanoma who received ICIs. The main risk factors were receipt of corticosteroids and/or infliximab (an immunosuppressant). The risk of serious infection was 13.5% in patients who received either corticosteroids or infliximab but only 2% in those who did not. Karam *et al*. [32] found a higher rate (18%) of infection than that reported by Castillo *et al*. [33] and showed that infection remains the major differential diagnosis for irAEs. In their study, Ross *et al*. [34] reported that the overall incidence of severe infection was 14% (16/111) and added that the number of ICI doses administered and the use of steroids to treat patients with irAEs were strongly associated with serious infection.

Moreover, ICI therapy itself is associated with increased risk of opportunistic infections [35]. Preclinical studies have raised concerns that ICIs are directly associated with increased susceptibility to certain infections, including tuberculosis and listeriosis. In a retrospective study of NSCLC patients treated with ICIs, the majority experienced infections during or within 3 months of ICI discontinuation [36]. Fujita *et al*. [37] revealed that of a total of 167 NSCLC patients receiving ICI therapy, 32 (19.2%) experienced infectious diseases.

Furthermore, distinguishing between irAEs and infections, especially pneumonitis and colitis, is often difficult. Moreover, we cannot always establish if the episode was cured by antibiotics or immunosuppressive therapy. This is especially the case for pneumonitis because clinicians can prescribe antibiotics and steroids in grade II pneumonitis simultaneously, as suggested by Brahmer *et al*. [38]. Therefore, antibiotic therapy is unavoidable [32].

We have summarized in Table 1 the current clinical state of the combined use of ICIs and antibiotics in reference to the "Guidelines for Whole-process Pharmaceutical Care with Immune Checkpoint Inhibitors (2019 edition)" [39] and other relevant literature. Studies have reported that among NSCLC patients who received ICIs, four patients received antibiotic treatment for enteric disease recurrence, one patient received antibiotic treatment for colitis, and one patient received antibiotic treatment for urinary tract infection [40]. Another study have found that NSCLC patients treated with ICIs were given antibiotics for pneumonia, empiric fever, and urinary tract infection [41]. However, in some cases, antibiotics are clearly prohibited. For example, patients with grade 3 or higher myasthenia gravis irAEs should avoid medications that may aggravate myasthenia, such as β-blockers, quinolones, aminoglycosides, and macrolide antibiotics [42].

Antibiotics are commonly used in patients with cancer who are susceptible to infection, and studies have shown that antibiotic use can be adjusted according to neutropenia and specific manifestations [43]. When irAEs are difficult to control and secondary infection is severe or even life-threatening, the use of antibiotics in combination with ICIs is clinically recommended, but no corresponding clinical guidelines exist to guide antibiotic use. Although the role of antibiotics remains unclear and further research is needed [8], current studies have shown that antibiotics affect tumor occurrence and development through changes in gut microbiota [40].

Effects of combined ICIs and antibiotics on cancer immunotherapy outcomes

Overall survival (OS), PFS, and objective response rate/response rate are commonly used indexes to evaluate ICI therapeutic effects in clinical studies. Some clinical studies also used complete response, partial response, disease stability, and disease progression (PD) as evaluation indicators according to iRECIST criteria (modified Response Evaluation Criteria In Solid Tumors for immune-based therapeutics).

We searched PubMed and other databases for studies that involved combining ICIs with antibiotics. We have analyzed and summarized in Table 2 several recent representative clinical studies of combined ICI and

Table 1 Examples of ICIs combined with antibiotics

irAEs	Antibiotic use
Skin irAEs	Grade 3 or 4; tetracycline antibiotics have been reported to be effective replacement drugs [42]
Gastrointestinal (GI) irAEs	Grade 2, 3, or 4; use of antibiotics should be considered to prevent opportunistic infections [25]
Pneumonia irAEs	Grade 2; prophylactic use of antibiotics should be considered Grade 3 or 4; antibiotics should be added to prevent opportunistic infections [25], and broad-spectrum antibiotics are recommended [42]
Renal irAEs	Grade 2 or 3; antibiotics should be used when necessary to prevent opportunistic infections Grade 4; antibiotics are added to prevent opportunistic infections [25]

antibiotic treatment. By analyzing the survival curves and existing data, we found that many clinical studies that combined ICIs and antibiotics reduced ICI antitumor efficacy.

In a clinical study of 50 patients suffering from NSCLC, Castello *et al*. [41] found that 20 of them (40%) received ICI and antibiotic combination therapy. Their results showed that the median PFS in the antibiotics group (ICIs combined with antibiotics) was shorter than that in the no antibiotics group (ICIs without antibiotics) (4.1 vs. 12.4 months, $P = 0.004$), and the incidence of PD was significantly higher in the antibiotics group than that in the no antibiotics group according to iRECIST criteria (64.7% vs. 27.6%, $P = 0.029$). In addition, patients treated with antibiotics had a higher number of tumor metastases, which was associated with increased tumor burden and reduced antitumor effectiveness. Huang *et al*. [44] analyzed and summarized data from 2740 patients with different cancers and found that antibiotic use substantially reduced median PFS in patients treated with ICIs (hazard ratio (HR) = 1.84, 95% confidence interval (CI) = 1.49–2.26, $P < 0.001$) and was negatively associated with median OS in cancer patients (HR = 2.37, 95% CI = 2.05–2.75, $P < 0.001$). Furthermore, clinical results from Pinato *et al*. [45] and Galli *et al*. [46] showed that, after combined ICI and antibiotic treatment, the survival period of most patients was shortened and the antitumor effects of ICIs were reduced. Current studies have confirmed that antibiotics affect the occurrence and development of tumors by acting on gut microbiota, and more clinical studies have indicated that antibiotics reduce the therapeutic effects of ICIs by disrupting gut microbiota without selectivity [47]. Additionally, Hakozaki *et al*. [48] found that, compared with no antibiotics treatment, the median PFS of patients treated with β-lactam during the 30 days prior to nivolumab treatment was 1.2 versus 4.4 months, but the median OS was 8.8 versus < 8 months in a group of 90 NSCLC patients. Another study found that the combination of antibiotics and ICIs had no remarkable effect on PFS in patients with malignant tumors, but OS was shortened [49].

Sethi *et al*. [50] established a mouse model to study the effects of oral antibiotic disruption of gut microbiota abundance on tumor growth in pancreatic cancer, colon cancer, and melanoma. They found that oral antibiotic consumption not only reduced tumor growth and metastasis but also activated antitumor immunity in TME. This result suggests that such combinations are worthy of further exploration. Wei *et al*. [51] found that oral antibiotics induced gut microbiota consumption, which mediated immunogenic remodeling and T cell function activation, thereby enhancing antitumor effects.

Studies suggesting that combined ICI and antibiotic treatment can improve antitumor efficacy have indicated that antibiotics mediate this mechanism by changing gut microbiota composition, consuming "bad bacterial flora," and selectively retaining "good bacterial flora," leading to immune remodeling. However, most clinical results show that antibiotics greatly reduce ICI antitumor efficacy possibly because antibiotics cannot selectively kill "bad" bacteria, resulting in gut microbiota imbalance and inhibiting beneficial ICI mechanisms related to gut microbiota [52]. Previous studies have indicated that antibiotic use rapidly disturbed changes in microbiome composition, which depleted beneficial taxa (i.e., *F. prausnitzii*, *Alistipes* spp., and Ruminococcaceae spp.) [45,53]. Therefore, prudent clinical use of antibiotics is recommended only when there are irAEs that are difficult to control, serious, or life-threatening, and the evaluated benefits outweigh the risks.

Selecting antibiotics to combine with ICIs

ICI and antibiotic combinations are inevitable in clinical settings. Thus, the choice of which antibiotic to administer is an important factor that can influence outcomes. We summarized in Table 2 the selection of antibiotic type and timing and duration of administration from the results of recent clinical studies by analyzing relative survival curves and existing data.

From a longitudinal comparison in Table 2, we found that the majority of antibiotics used are β-lactams, quinolones, macrolides, tetracyclines, and others. As indicated by current research data, high-dose broad-spectrum antibiotics may affect the composition of gut microbiota, impair the efficacy of immunotherapy, and shorten the survival time of patients. Ahmed *et al*. [54] found that patients that used broad-spectrum antibiotics had a lower disease response rate (RR) (25% vs. 61%) than patients using narrow-spectrum antibiotics, with an HR of 2.34 (95% CI = 1.5–3.65, $P = 0.02$). Patients treated with broad-spectrum antibiotics had worse therapeutic effects. They also emphasized that narrow-spectrum antibiotic use did not affect the response to ICIs [54], whereas broad-spectrum antibiotic use reduced the ICI response rate and was associated with a greater probability of disease relapse. Pinato *et al*. [45] suggested that the reasons for this phenomenon may be that broad-spectrum antibiotics can lead to long-term ecosystem damage, which reduces the number of immune response stimulating gut microbiota, increases the number of immune response inhibiting gut microbiota, and reduces the number of cytotoxic T cells, thereby reducing ICI effectiveness [55]. Some studies have suggested that β-lactam may have the strongest effects on all kinds of cancers because they disrupt the gut microbiota by destroying Firmicutes instead of Bacteroidales; as a result, the ICI response and antitumor efficacy were reduced [56]. Another study [56] have indicated that

fluoroquinolones had the most influence on therapeutic effects in NSCLC patients, and combining fluoroquinolone with ICIs during NSCLC treatment was more effective than combinations with all other antibiotics, suggesting the possibility of precision tumor treatment with antibiotics. Therefore, we need to understand the baseline characteristics of patients using antibiotics and the dynamic changes in their gut microbes after using different antibiotics. Selection of narrow-spectrum antibiotics is recommended for the best clinical effects when combined with ICIs.

A study found that the median PFS in the antibiotics group was shorter than that in the no antibiotics group (4.1 vs. 12.4 months, $P = 0.004$) [41]. Another study obtained a similar conclusion that patients using antibiotics had shorter median PFS (HR = 1.84, $P < 0.001$) and OS (HR = 2.37, $P < 0.001$) [44]. Derosa *et al*. [57] concluded that for RCC and NSCLC patients, the median PFS and OS for those treated with antibiotics 60 days before ICI initiation were substantially longer than those treated with antibiotics 30 days before beginning ICI treatment, but both were shorter than those treated without antibiotics and the proportion of patients who developed PD increased. However, another study [58] found that using antibiotics concurrently with ICI therapy or 30 days after ICI discontinuation had better antitumor efficacy than not using antibiotics. The lower the AIER (days of antibiotics/days of ICI treatment, high AIER ⩾ 4.2%), the better the effect was [46]. This result may be due to the fact that gut microbiota takes 1 week to 3 months to return to baseline levels after antibiotic discontinuation [57], and some gut bacterial flora may even take years to recover fully [59,60], thus reducing ICI efficacy. This suggests that the impact of antibiotic use on ICI treatment depends on the relative timing of the two treatments [61]. Before immunotherapy, if infections are present, the corresponding anti-infective treatment based on bacteriological evidence must be provided to avoid the prophylactic and long-term use of antibiotics. A study reported that antibiotic use 90 days before or any time after starting ICI treatment tended to be related to favorable PFS and OS [61]. In conclusion, first, when ICI treatment is planned, it may be important to strengthen infection prevention and control measures, with antibiotic use strictly reserved for instances where it is absolutely necessary. Secondly, it may be difficult to set the optimal

Table 2 Narrative comparison of median PFS and OS between different antibiotic exposure groups based on univariable analysis

Cancer type/ patients	Antibiotic type	Antibiotic exposure	Median PFS			Median OS		
			mo vs. mo	HR	*P*	mo vs. mo	HR	*P*
NSCLC/50 [41]	β-lactams/quinolones	Antibiotics vs. no antibiotics	4.1 vs. 12.4	–	0.004	11.3 vs. 15.3	–	–
		Prior-30 vs. post-antibiotics	Similarly	–	–	Similarly	–	–
NSCLC/RCC/UC/ 2740 [44]	β-lactams	Antibiotics vs. no antibiotics	–	1.84	<0.001	–	2.37	<0.001
NSCLC/119	β-lactams	Prior-antibiotics vs. no antibiotics	–	–	–	2.5 vs. 26	9.3	<0.001
Melanoma/38		Prior-antibiotics vs. no antibiotics	–	–	–	3.9 vs. 14	7.5	<0.001
Others/39 [45]		Prior-antibiotics vs. no antibiotics	–	–	–	1.1 vs. 11	7.8	<0.001
NSCLC/157 [46]	β-lactams/quinolones/macrolides	Prior-30 vs. no antibiotics	2.2 vs. 3.3	–	–	5.9 vs. 11.9	–	–
		High vs. low AIER (during ICIs)	1.9 vs. 3.5	1.053	0.0029	5.1 vs. 13.2	1.069	0.0001
NSCLC/218 [58]	β-lactams/macrolides/quinolones	Prior-60 vs. no antibiotics	1.4 vs. 5.5	2.22	<0.01	1.8 vs. 15.4	2.61	<0.05
		c-antibiotics vs. no antibiotics	7.0 vs. 3.6	0.86	0.01	11.7 vs. 11.7	1.10	0.62
		Post-30 vs. no antibiotics	3.6 vs. 4.5	1.15	0.59	17.5 vs. 11.5	0.86	0.62
NSCLC/90 [48]	β-lactams	Prior-30 vs. no antibiotics	1.2 vs. 4.4	–	–	8.8 vs. < 8	2.02	0.19
NSCLC/60 [54]	Tetracyclines/macrolides	Prior-14 and/or post-14 vs. no antibiotics	–	1.6	0.048	6.0 vs. 22.3	1.6	0.003
	Fluoroquinolones	Broad- vs. narrow-spectrum antibiotics	–	1.895	–	–	–	–
RCC/121 [57]	β-lactams/quinolones	Prior-30 vs. no antibiotics	1.9 vs. 7.4	3.1	<0.01	17.3 vs. 30.6	3.5	0.03
		Prior-60 vs. no antibiotics	3.1 vs. 7.4	2.3	<0.01	23.4 vs. 30	1.9	0.15
NSCLC/239 [57]		Prior-30 vs. no antibiotics	1.9 vs. 3.8	1.5	0.03	7.9 vs. 24.6	4.4	<0.01
		Prior-60 vs. no antibiotics	–	–	–	9.8 vs. 21.9	2.0	<0.01
NSCLC/melanoma /102 [62]	β-lactams	Antibiotics 30+ vs. antibiotics 30−	4.3 vs. 5.8	1.43	0.1	11.7 vs. 14.5	1.53	0.1
	Fluoroquinolones	Antibiotics + vs. antibiotics −	5.8 vs. 4.4	0.69	0.1	13.3 vs. 13.8	0.98	0.9

Note: mo, month; prior-antibiotics/14/30/60, pre-therapy antibiotics, using antibiotics within 14/30/60 days prior to ICI initiation; c-antibiotics, antibiotics therapy administered concurrently ICI therapy; post-antibiotics/14/30, post-therapy antibiotics, using antibiotics after 14/30 days of ICIs withdrawal; antibiotics 30+ , antibiotics prescribed from 30 days before to 30 days after ICI initiation; antibiotics + , antibiotics prescribed at any point within the ICI treatment period; antibiotics 30− and antibiotics −, no antibiotics within the same time frame.

cutoff point for the "prior antibiotics use" considering its effect on the efficacy of following ICIs. Try best to avoid using antibiotics within 30 or 60 days before starting ICI treatment to avoid upsetting the gut microbiota. Finally, during ICI therapy, once infection occurs, antibiotics and other measures must be adopted immediately to prevent more serious consequences.

Iglesias *et al*. [62] found that long-term or multi-course use of antibiotics [55], rather than simple use within a definite time range, seemed to play a key role in ICI antitumor efficacy, and the side effects of combining antibiotics with ICIs were remarkably enhanced with cumulative antibiotic use [63]. Therefore, a feasible tumor immunotherapy strategy is to avoid repeated or long-term use of broad-spectrum antibiotics and to exploit the potential of specific antibiotics.

Huang *et al*. [44] observed that the antitumor effects of PD-1/PD-L1 inhibitors combined with CTLA-4 inhibitors were better than those of PD-1 inhibitors alone possibly because different types of ICIs synergize owing to their different mechanisms of action. Additionally, the antitumor effects of ICIs and antibiotics were not strongly related to the type of malignant tumor [45]. Some studies have found that intravenous administration had worse clinical efficacy and was less safe compared with oral antibiotic administration [55]. This may be because antibiotics are usually unstable in the liquid state. Therefore, oral antibiotic administration is mainly used in clinical treatment.

We have preliminarily concluded that curative antibiotics should be used. Preventive antibiotics should be avoided before ICI therapy. Antibiotic treatment should be based on the occurrence of infection. In summary, questions remain as to the specific relationships between ICI treatment and specific antibiotic types, timing, and durations of treatment. Current studies have offered several suggestions to improve the therapeutic response to ICIs. First, relatively short narrow-spectrum antibiotic use might not notably offset the outcomes of ICI treatment. Second, prophylactic antibiotics can be avoided as much as possible. On the basis of the comprehensive assessment of a patient's infection status and gut microbiota, the appropriate antibiotic treatment time can be selected. Moreover, repeated use of antibiotics for a long course of treatment should be avoided, and antibiotics can be administered through oral administration and others.

ICI and antibiotic interaction mechanisms

The human body has 10–100 trillion microbial cells, which mainly comprise the gut microbiota [64]. The gut microbiota is a group of microorganisms that interact with each other and includes bacteria, fungi, and viruses [65]. Owing to the gut microbiota's heterogeneity and relative stability in different individuals, it is often referred to as the "second genome" of the human body [66] and plays a very important role. The gut microbiota not only regulates the efficacy and toxicity of chemotherapy [67] but is also involved in intestinal immunity and even influences the whole body's immune system [68].

According to several studies, the gut microbiota may influence antitumor immune responses through innate and adaptive immunity, and the immune response can be improved through gut microbiota regulation [69]. The gut microbiota has received increased attention owing to its observed interactions with recent ICI cancer immunotherapies [70].

Antibiotics impact ICI antitumor effects by influencing gut microbiota composition

Studies have shown that antibiotic use can affect the composition of up to 30% of gut microbiota bacterial species [71], as well as the abundance and width of gut microbiota [41,59], leading to a loss of microbial functions that have protective effects in the host. Such changes in gut microbiota are rapid and widespread, occurring within a few days of the first antibiotic administration [72] and lasting for several months after antibiotic withdrawal [73], some even being irreversible [74].

CTLA-4 inhibitors had lower antitumor effectiveness in tumor-bearing mice fed under germ-free (GF) conditions or treated with antibiotics compared with mice fed under specific pathogen-free (SPF) conditions or not treated with antibiotics. Oral feeding of these mice with *Bacteroides* spp. or *Burkholderia* spp. restored responsiveness to CTLA-4 inhibitor treatment and, because of intestinal reconstruction, also reduced CTLA-4 inhibitor-induced colitis [75,76]. In antibiotic-treated mouse sarcoma and melanoma models, repopulation of the gut microbiota with *Akkermansia muciniphila* and *Enterococcus hirae* symbiotes restored PD-1 inhibitor responsiveness [53]. By contrast, some studies have shown that microbiome ablation using antibiotics had a protective effect on animal models of pancreatic ductal adenocarcinoma [77]. In mouse models treated with CTLA-4 inhibitors and/or PD-1/PD-L1 inhibitors, certain immune-stimulating microbiota, for example, *A. muciniphila*, *Bifidobacterium* spp. [69,78], and *Bacteroides fragilis* [75] or strains (*E. hirae*) [79], can trigger a systemic immune response and reprogram TME. Thus, disrupting the gut microbiota with antibiotics can interfere with ICI therapeutic effects.

In a clinical study of 249 patients with NSCLC (n = 140), RCC (n = 67), or uroepithelial carcinoma (n = 42) who received PD-1/PD-L1 inhibitor treatment combined with β-lactamide, fluoroquinolone, or macrolide treatment, the proportion of *A. muciniphila* in the gut microbiota of

responders was higher than that of nonresponders [53]. Another clinical study of 69 patients with RCC who received CTLA-4 inhibitors found notable differences in stool bacterial flora in patients treated with antibiotics compared with patients who received no antibiotics; some bacterial floras were overexpressed in stool samples of patients without antibiotic treatment, such as *Eubacterium rectale*, whereas other bacterial floras were overexpressed in antibiotic-treated patient stool samples, such as Erysipelotrichaceae and *Clostridium hathewayi* [80]. In a study of metastatic melanoma patients, ICI responders had a relatively high diversity of specific bacterial species in their gut microbiota, including *Faecalibacterium*, Firmicutes, Ruminococcaceae, Clostridiales, and *Bifidobacterium* [81,82]; however, the gut microbiota diversity of these bacterial taxa was lower in patients who were not responsive to ICI treatment, although the abundance of Bacteroidales was relatively high in these patients [83].

Collectively, the results of preclinical and clinical studies suggest that antibiotics affect ICI therapeutic effects by influencing gut microbiota composition. The abundance and width of gut microbiota are independent decisive factors for ICI therapeutic efficacy. If antibiotics are used in combination with ICIs at any time, then the gut microbiota will be disturbed, resulting in intestinal imbalance. Owing to the lack of antibiotic specificity, many beneficial bacterial floras that are crucial to ICI efficacy will be affected [84], inevitably leading to a reduction in ICI antitumor efficacy. These observations provide new insights into the combined use of ICIs and antibiotics. Depending on the types of ICIs used and a patient's immune characteristics, the best ICI and antibiotic combination must be determined to achieve a favorable balance between treating infection and treating the cancer.

Antibiotics impact ICI antitumor effectiveness through gut microbiota-mediated immune function regulation

Accumulating evidence suggests that gut microbiota can enhance ICI efficacy by improving the function of natural killer cells, dendritic cells (DCs), and T lymphocytes, as well as by promoting the secretion of relevant cytokine (Fig. 2) [69,75]. Thus, by destroying beneficial gut microbiota, antibiotics interfere with ICI immunotherapy.

In mouse experiments, Matson *et al*. [78] found that *Bifidobacterium* spp. supplementation increased $CD8^+$ T cells and T cells secreting IFN-γ in tumors by promoting DC maturation [75]. This increase in T cells enhanced tumor specific $CD8^+$ T cell function and restored PD-L1 inhibitor immunotherapy efficacy [69]. In addition, IFN-γ, an activator of the helper T cell 1 (TH_1) response, exerted direct cytotoxicity and upregulated class I major histocompatibility complex (MHC) in TME [85]. Another experiment showed that oral administration of *Bifidobacterium* spp. to mice treated with PD-1 inhibitors increased the aggregation of antigen-specific $CD8^+$ tumor-infiltrating T lymphocytes ($CD8^+$ TIL) and class II MHC DCs in TME, thus improving immunotherapy efficacy [69,83,86]. Furthermore, patients with high levels of *Faecalibacterium* in the gut had more $CD4^+$ and $CD8^+$ T cells in peripheral blood (PB) [83]. Studies have shown notable positive correlations between $CD8^+$ TIL levels in TME, $CD4^+$ and $CD8^+$ T cells in PB of human responders treated with PD-1 inhibitors, and the abundance of Clostridiales, Ruminococcaceae, and *Familiabacterium* [69,83,86]. When T cell quantity increases, ICI antitumor efficacy also increases. Oral administration of *A. muciniphila* and *E. hirae* was found to upregulate central memory $CD4^+$ T cells expressing small intestine-associated chemokine receptor CCR9 and/or TH_1-associated chemokine receptor CXCR3 in mouse mesenteric lymph nodes and tumor-draining lymph nodes (TDLNs) and upregulate the tumor site $CD4^+$/Foxp3 ratio, thereby enhancing antitumor efficacy. Cytokines secreted by $CD4^+$ T cells (including TH_1, Tc_1, and IFN-γ) in PB of patients treated with PD-1 inhibitors and cytokines secreted by bone marrow-derived DCs (including IL-12) were strongly related to *A. muciniphila* and *E. hirae* application [53,75,86]. *E. hirae* also promotes $CD8^+$ T cell accumulation [79], improving the tumor-killing effect. The combination of oral *B. fragilis* and CTLA-4 inhibitor treatment in a GF mouse model was found to induce DC maturation in TDLNs and further enhance the TH_1 immune response [53,75,86]. Patients with more *Faecalibacterium* and other Firmicutes were found to have a lower proportion of regulatory T cells (Tregs) in PB [87]. Bacteroidales was found to induce $CD4^+$ T cell differentiation into Tregs that secrete numerous anti-inflammatory cytokines (such as IL-10) [69,88]; this may cause tumor immune escape and TH_{17} secretion of IL-17, which play important roles in promoting an inflammatory response. Studies have also shown that patients who did not respond to PD-1 inhibitors had more Bacteroidales in their gut microbiota and an increased number of Tregs and myeloid-derived suppressor cells (MDSCs) in systemic circulation [83]. Another study found that immunosuppressive MDSC differentiation in mice rich in *B. fragilis* was also increased, which promotes colon tumor occurrence [89]. Therefore, the relationship between Bacteroidales species and ICI efficacy appears to be complicated and may be related to the specific types of ICIs and antibiotics used.

In summary, beneficial gut microbiota plays an important role in ICI efficacy by regulating immune cell and cytokine levels in MLNs, TDLNs, and PB. Antibiotics diminish ICI antitumor immune effects by disturbing the gut microbiota. Therefore, caution around antibiotic use is recommended.

Antibiotics impact ICI antitumor efficacy through gut microbiota-mediated influences on body metabolism

Smith *et al*. [90] indicated that short-chain fatty acids, gut microbiota metabolites, could impact steady-state Treg levels in mice, thus influencing mouse immune function. Xu *et al*. [91] used a microsatellite stability (MSS) type CT26 cell-induced colorectal cancer (CRC) male BALB/c mouse model under SPF conditions. They gave one group of mice with vancomycin in sterile drinking water (Vanc group) [92] and another group with colistin in sterile drinking water (Coli group) [93]. When tumor size reached 50 mm^3 (9 weeks old), the mouse were intraperitoneally injected with 250 μg mouse-PD-1 monoclonal antibody or an isotype control monoclonal antibody. They found that the Vanc group showed moderate responses, whereas the Coli group had poor responses. Other studies have found that some synthetic and metabolic functional pathways (such as glycerol phospholipid metabolism and sheath glycolipid biosynthesis) were dominant in the Vanc group but not in the Coli group, which may be related to better PD-1 inhibitor immunotherapy efficacy. Therefore, antibiotics may regulate the therapeutic potential of PD-1 inhibitors in mice bearing MSS type CRC by affecting the glycerol and phospholipid metabolic pathways. Furthermore, some antibiotics may have an inherent negative impact on the clinical process of malignant tumors by promoting carcinogenesis and metastasis [94]. At present, the mechanisms underlying antibiotic effects on ICI efficacy via gut microbiota regulation of metabolic pathways are unclear and warrant further study.

In summary, many clinical studies have investigated the combined use of ICIs and antibiotics and found that gut microbiota plays an important role [95–97]. However, the mechanisms underlying the combined effects of ICIs and antibiotics must be further clarified. Here, we have summarized only some of the possible mechanisms discussed in current research; more specific ones, such as immune and metabolic pathways, should be further explored.

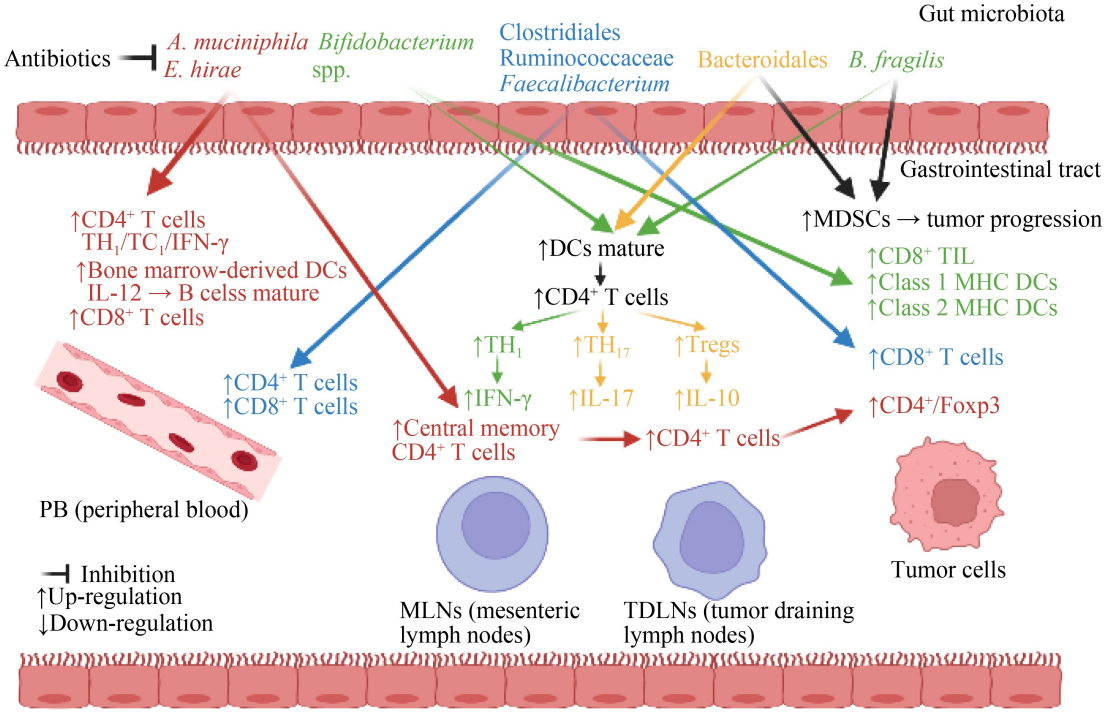

Fig. 2 Proposed antibiotic immunomodulatory mechanisms influencing ICI anticancer efficacy via the gut microbiota in animal models and patients. *Akkermansia muciniphila*, *Enterococcus hirae*, Clostridiales, Ruminococcaceae, and *Faecalibacterium* can upregulate $CD4^+$ and $CD8^+$ T cell expression in peripheral blood (PB). *A. muciniphila* and *E. hirae* can upregulate central memory $CD4^+$ T cell expression in mouse mesenteric lymph nodes (MLNs) and tumor-draining lymph nodes (TDLNs) and can upregulate the $CD4^+$/Foxp3 ratio in mouse tumors, thus enhancing antitumor efficacy. Clostridiales, Ruminococcaceae, and *Faecalibacterium* can increase $CD8^+$ T cell quantity in mouse tumors, thus enhancing antitumor efficacy. *Bifidobacterium* spp. and *Bacteroides fragilis* can induce dendritic cell (DC) maturation in TDLNs and further enhance IFN-γ secreting helper T cell 1 (TH_1) immune responses. *Bifidobacterium* spp. also upregulate $CD8^+$ T cell expression and class I and class II major histocompatibility complex (MHC) in TME. Bacteroidales can induce $CD4^+$ T cell differentiation into regulatory T cells (Tregs) that secrete numerous anti-inflammatory cytokines (such as IL-10), leading to tumor immune escape and TH_{17} secretion of IL-17, which play important roles in promoting inflammatory responses. Immunosuppressive myeloid-derived suppressor cell (MDSC) differentiation is also increased in mice rich in *B. fragilis* and Bacteroidales, which promotes colon tumor occurrence.

Creation of new ICI immunotherapy combination strategies

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT), which transfers the entire gut microbiota from one host to another, has demonstrated promising results in preclinical models. An FMT study that used an MCA-205 sarcoma mouse model treated with PD-1 inhibitors found that mice that received effective FMT from patients with a good response to PD-1 inhibitor treatment showed considerably delayed tumor growth compared with mice that received FMT from patients with no response to PD-1 inhibitor treatment [98]. Another study found that GF mice that received high-abundance FMTs had high $CD4^+$/Foxp3 T cell levels in spleen [69].

On the basis of these preclinical data, Baruch *et al*. [99] and Davar *et al*. [100] evaluated the safety and efficacy of responder-derived FMT together with anti-PD-1 in patients with PD-1-refractory melanoma. Results showed that responders exhibited increased abundance of taxa, such as Actinobacteria (Bifidobacteriaceae and Coriobacteriaceae) and Firmicutes (Ruminococcaceae and Lachnospiraceae) [53,78,83], which were previously shown to be associated with response to anti-PD-1, counteracted myeloid-induced immunosuppression to augment $CD8^+$ T cell activation in TME, and downregulated multiple circulating cytokines and chemokines associated with resistance to anti-PD-1, thereby improving the efficacy of ICI therapy. Overall, because the gut microbiota is a key factor in ICI efficacy, an FMT that remarkably improves gut microbiota composition, abundance, and width can improve ICI efficacy, and the use of this strategy may increase in clinical research.

Probiotics, prebiotics, and symbionts

Probiotics are active microorganisms that can restore or improve the gut microbiota, thus enhancing ICI anticancer efficacy [101]. Prebiotics are food ingredients that selectively promote the growth of one or several microorganisms in the intestines and are beneficial to the host's immune system health [102,103]. Hu *et al*. [104] found that feeding prebiotic supplementary food to a colorectal cancer mouse model increased the relative abundance of *Ruminococcus* and *Bifidobacterium* in the gut, which substantially reduced tumorigenesis. Symbionts are a synergistic combination of specific probiotics and prebiotics [105] that can improve immunotherapy effects. We hope to find a kind of bacterium, or a combination of microorganisms, that not only promotes antitumor therapy efficacy but also reduces immunotherapy toxicity [106]. Probiotics, prebiotics, and symbionts are widely used in the field of functional food with high safety and few side effects. Thus, their use in tumor immunotherapy has great potential.

ICI combination with tyrosine kinase inhibitors

Derosa *et al*. [80] administered different doses of tyrosine kinase inhibitors (TKIs; sunitinib, axitinib, or cabozantinib) to mice with different genetic backgrounds, BALB/c mice, and C57BL/6 mice for 3 weeks and longitudinally collected stool samples. They found that the three TKIs considerably induced gut microbiota diversity in BALB/c and C57BL/6 mice. More importantly, *Alistipes senegalensis* abundance was higher in the intestines of BALB/c mice treated with sunitinib and cabozantinib than treated with axitinib. In the intestines of C57BL/6 mice, *Eubacterium siraeum* was overexpressed in all three groups, and *A. senegalensis* and *A. muciniphila* abundance and immune response stimulation were the highest in the cabozantinib group. Overall, TKIs induced remarkable gut microbiota changes and increased immunostimulatory intestinal microorganisms, which can improve ICI efficacy in RCC patients.

New preparation technology

Li *et al*. [107] used genetic engineering to generate Gram-negative bacteria that can secrete bacterial outer membrane vesicles carrying PD-1. Nanoscale vesicles accumulated at the tumor site and bound to PD-L1 on tumor cells, blocking the binding of PD-L1 to effector T cell PD-1. This caused more effector T cells to be released, leading to less tumor cell immune escape. Thus, this method of combining tumor-targeted therapy with ICI treatment could restore immune function, demonstrating a preliminary exploratory victory. However, at present, this method is only theoretical, and potential toxic effects on normal tissue cells must be anticipated.

ICI combination with traditional Chinese medicine preparations

Previous studies have demonstrated the beneficial effects of traditional Chinese medicine on gut microbiota. In a C57BL/6J mouse model, ginseng polysaccharides (GPs) were found to enhance $CD8^+$ T cell function and decrease Treg inhibitory effects, thus increasing αPD-1 inhibitor antitumor effects by remodeling the gut microbiota [108]. The combination of GPs and αPD-1 inhibitors could provide a new strategy to improve NSCLC patients' sensitivity to PD-1 inhibitor immunotherapy. Furthermore, the combination of Gegen Qinlian Decoction (GQD) and PD-1 inhibitors could provide a new strategy for MSS-type CRC treatment. In a mouse xenograft tumor model, the combination of GQD and mouse-PD-1 inhibitor treatment was found to strongly inhibit CT26 tumor growth

and substantially increase gut *Bacteroides acidophilus* content [109]. In addition, a Shaoyao Ruangan mixture was observed to increase considerably the number of *Bacteroides* spp. in the gut [110], and curcumin was reported to increase *Lactobacillus* spp. content [111]. Given that traditional Chinese medicine preparations have mild effects, few toxic side effects, and generally play a regulatory role, they are often used in combination with other medicines in the clinical treatment of major diseases. The use of inherently immunomodulatory traditional Chinese medicine preparations could potentially reduce ICI damage to the immune system, improve antitumor efficacy as a whole, and improve overall prognosis. Chinese and Western medicines can complement each other, which could be beneficial to finding effective tumor treatments.

Lifestyle changes

One dietary study [112] reported that subjects on a high-fat diet had remarkably different gut microbiota characteristics compared with subjects on a high-fiber diet. Another study [113] found that diets rich in whole grains and dietary fiber were associated with lower cancer risk compared with diets high in meat, refined grains, and sugar. Many studies have suggested that a high-fiber diet may reduce the incidence of cancer [113–115], but none of these have described corresponding microbial changes or proposed potential mechanisms. Studies have shown that lactic acid may regulate PD-L1 expression in tumor cells [116], a decreased lactic acid concentration in TME may increase invasive immune cell number [117], and exercise reduces lactic acid concentration, thus improving cancer immunotherapy efficacy. Mouse experiments [118] have demonstrated that chronic sleep interruption changes gut microbiota composition, and other studies have shown that sleeping late may disrupt gut microbiota balance and affect the body's metabolism [119]. In short, many lifestyle factors, such as diet, exercise, and sleep [120,121], can affect cancer immunotherapy efficacy by regulating the gut microbiota. Therefore, maintaining a healthy lifestyle is necessary for cancer prevention and treatment.

Summary and perspective

In conclusion, the synergistic/reductive effects of antibiotics in immunotherapy are inconsistent, the optimal type, timing, and duration of combined antibiotics remain unclear, and the mechanisms underlying combined ICI and antibiotic treatment in tumor immunotherapy must be further elucidated. Thus, more prospective clinical trials are warranted. At present, the combination of ICIs and antibiotics is often associated with worse antitumor efficacy in clinical practice and thus, the appropriate use of antibiotics (with regard to the clinical symptoms and the risk of infection) should be encouraged. More specific clinical guidelines are needed to standardize antibiotic use during ICI treatment, clarify the relative best efficacy of different combinations, and provide solutions to serious irAEs. The combination of ICIs and antibiotics must be treated seriously in clinical settings. Investigations into the mechanisms underlying ICI and antibiotic interactions are ongoing, which will provide crucial understanding to enable blocking harmful interactions.

The gut microbiota has been shown to play an important role in the interactions between ICIs and antibiotics. Recent research has investigated how manipulating the gut microbiota can regulate the immune system and improve immunotherapy efficacy [122], as well as overcome drug resistance and adverse reactions during immunotherapy. In the future, it may be possible to positively impact cancer immunotherapy by manipulating the gut microbiota, and gut microbiome sequencing may be used to predict whether the body responds to ICIs [123]. Given that many infections that occur during cancer treatment can only be cured by antibiotics, it is not feasible to completely avoid the combination of antibiotics with ICI treatment. Therefore, appropriate methods must be developed to offset the negative impacts of antibiotics on ICI efficacy. To improve cancer survival, it is critical to accelerate research on how antibiotics affect gut microbiota, ICI and antibiotic combinations and their interaction mechanisms, and solutions for overcoming the negative effects of combining ICIs and antibiotics, as well to establish corresponding guidelines.

With the development of cancer immunotherapy, new treatment combinations have also emerged. The combinations of immunotherapy with chemotherapy, radiotherapy, or tumor-targeted therapy have generated new ideas for cancer treatment. A key next step is to further clarify how ICIs make patients vulnerable to infections and establish antibacterial prevention guidelines. Further research is needed to identify reliable biomarkers [124] that predict ICI responsiveness and guide clinical practice. Owing to gut microbiota heterogeneity and immune function differences among patients, some experts have recently proposed personalized cancer immunotherapy with the hope of minimizing toxicity and prolonging patient survival time. With greater understanding of how the gut microbiota regulates the immune system, the era of personalized medicine is rapidly approaching.

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Compliance with ethics guidelines

Yingying Li, Shiyuan Wang, Mengmeng Lin, Chunying Hou, Chunyu Li, and Guohui Li declare no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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