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CRISPR-engineered probiotics for targeted production of inosine as an immunomodulatory metabolite to enhance cancer immunotherapy response: A review

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Abstract

Background: Cancer immunotherapy, especially immune checkpoint inhibitors (ICIs), has improved cancer survival but remains limited by variable response and adverse effects. Emerging evidence demonstrated that gut microbiome, particularly inosine, is a critical determinant of immunotherapy efficacy through its capacity to produce immunomodulatory metabolites that enhance T-cell activation, promote dendritic cell function, and restore anti-tumor immunity. Advances in CRISPR-Cas technology has enabled precise engineering of probiotic strains for targeted inosine production, offering a potentially safer and more effective immunomodulatory approach.

Purpose: This study aims to evaluate CRISPR-engineered probiotics for targeted production of inosine as an immunomodulatory metabolite to enhance cancer immunotherapy response.

Method: A narrative literature review was conducted using secondary data collected from online databases such as PubMed, ScienceDirect, and ResearchGate.

Results: A total of 11 studies were analyzed, showing that CRISPR-engineered probiotics can precisely enhance inosine production via targeted purine metabolic pathways. Microbiota-derived inosine promotes T-cell and dendritic cell activation through A2A receptor signaling, driving Th1 polarization, IFN-γ secretion, CD8+ cytotoxic T-cell activity, and supporting T-cell metabolism under stress. Engineered probiotics demonstrated more consistent inosine production and predictable immunomodulatory effects compared to conventional strains, potentially synergizing with ICIs to reduce tumor growth and improve antitumor immunity.

Conclusion: CRISPR-engineered probiotics for targeted production of inosine suggest potential to enhance cancer immunotherapy response.

Keywords: CRISPR-Engineered Probiotics; Cancer Immunotherapy; Gut Microbiome; Inosine; Immune Checkpoint Inhibitors

1. Introduction

Immune checkpoint inhibitors (ICIs) have transformed the field of oncology by significantly improving survival across multiple malignancies. However, this therapeutic breakthrough remains incomplete, as clinical responses to ICIs are highly variable, immune-related adverse events are frequent, and the associated economic burden remains substantial.1,2 These inconsistencies have redirected scientific attention toward host-dependent factors, particularly

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the gut microbiome, which profoundly shapes systemic immunity and influences both tumor progression and treatment outcomes.3,4

Accumulating evidence identifies the gut microbiota, particularly inosine, as a critical determinant of immunotherapy efficacy through its capacity to produce immunomodulatory metabolites that enhance T-cell activation, promote dendritic cell function, and restore anti-tumor immunity.5,6 Nevertheless, the therapeutic potential of inosine remains constrained by poor bioavailability, systemic instability, and incomplete elucidation of its mechanisms within the tumor–immune microenvironment. Therefore, developing innovative strategies for localized and controlled inosine delivery is essential to enhance the efficacy of immune checkpoint blockade.

Recent advances in clustered regularly interspaced short palindromic repeats (CRISPR) technology have enabled the precise and programmable modification of probiotic genomes, allowing for targeted in situ biosynthesis of bioactive metabolites such as inosine.7,8 Through CRISPR-mediated gene editing, probiotics can be engineered to function as living biotherapeutics capable of sensing the host environment, synthesizing, and delivering immunoregulatory molecules directly within the gut.9,10 These engineered probiotics represent a promising platform for enhancing cancer immunotherapy by enabling site-specific inosine production with reduced off-target effects and improved metabolic precision.

2. Methods

The type of research used in this study is a literature review with a narrative design, utilizing secondary data obtained from previously published research, including original studies and review articles. The literature search was carried out using online databases such as PubMed, ScienceDirect, and ResearchGate.

The inclusion criteria encompassed studies published between 2020 and 2025 that specifically investigated CRISPR-engineered probiotic strains for the targeted biosynthesis of inosine and their implications in enhancing cancer immunotherapy responses. The exclusion criteria included publications released prior to 2020, articles without full-text availability, and non-English publications.

Literature searching was conducted using the PICO (Population, Intervention, Comparison, Outcome) framework. The population (P) included patients undergoing cancer immunotherapy, particularly those treated with immune checkpoint inhibitors (ICIs) who exhibit variable or poor responses due to microbiome imbalance or immune suppression. The intervention (I) involved the administration of CRISPR-engineered probiotic strains designed for in situ inosine production within the gut microenvironment. The comparison (C) included non-engineered probiotics or standard cancer immunotherapy alone without microbial modulation. The outcome (O) focused on enhanced immune checkpoint inhibitor response, improved T-cell activation, reduced tumor growth, and better overall survival outcomes, with secondary outcomes including improved safety and microbiome balance.

3. Result

3.1. Mechanisms of Inosine Biosynthesis through CRISPR-Based Engineering of Probiotic Strains

Targeted genetic design approaches utilizing the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system offer programmable and precise strategies for engineering probiotic strains, enabling modification of the genome in live cells, including those within the gut microbiota.11 CRISPR-based engineering of probiotic strains, such as Lactobacillus and Bifidobacterium, involves a precise genome editing process using the CRISPR-Cas system to introduce, delete, or modify specific genes that enhance probiotic functionality.12,13

The process begins with designing a single-guide RNA (sgRNA) targeting a specific genomic locus and delivering the CRISPR-Cas components—typically Cas9, Cas12, or Cas13—into the bacterial cell via plasmid vectors or conjugative plasmids like TP114.14 The Cas nuclease induces a double-strand break (DSB) at the target site, which is then repaired by non-homologous end joining (NHEJ) or homology-directed repair (HDR) using a donor DNA template to enable precise genome modifications.15 Edited strains are selected using antibiotic resistance markers and verified through PCR and sequencing, followed by functional testing to confirm the desired phenotypic traits.12 The entire genome editing in probiotics is demonstrated in Figure 1.

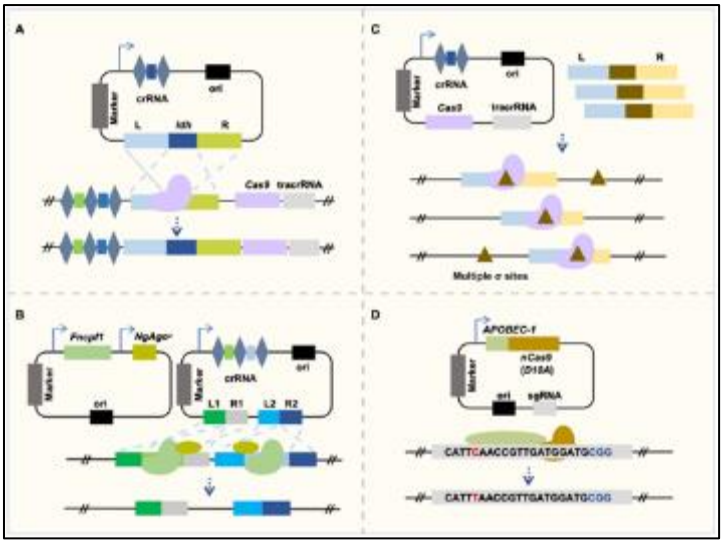

Figure 1 CRISPR-based genome editing in probiotics. (A) Integration of ldh gene into chromosome via the endogenous II-A CRISPR-Cas system in P. acetolactic. L, left arm; R, right arm; ori, replication origin; crRNA, CRISPR RNA; tracrRNA, trans-activating crRNA; marker, screening marker. (B) CRISPR/Cpf1-assisted multiple genes editing in B. subtilis. A mutation of Natron bacterium Gregory Argonauts (Ngao) was used to improve the homology recombination efficiency. (C) Gene editing based on δ sites of Ty elements in the yeast genome. (D) C·G-to-T·A amber mutation based on the CRISPR-cytosine BE in Bifidobacterium. APOBEC-1, a member of activation-induced cytidine deaminase/ APOBEC nucleic acid cytosine deaminase family.13

Advanced CRISPR systems, including the RecE/T-assisted CRISPR/Cas9 platform, improve recombineering efficiency in Lactobacillus, while TP114-DROID systems enable targeted editing and selective bacterial elimination in the gut.14,16 In the context of inosine biosynthesis, these tools can activate or enhance purine metabolic genes such as purA, purB, and purH to boost inosine yield. Hybrid CRISPR-probiotic constructs, such as Lactobacillus rhamnosus GG integrated with a CRISPR/Cas9 nanosystem (LGG-MHS), demonstrate how gene editing can enhance immunogenic responses by modulating immunosuppressive genes, a strategy applicable to inosine-producing pathways for immunotherapy enhancement.17

Naturally, probiotics such as Lactobacillus and Bacillus subtilis can synthesize inosine via purine metabolism using dietary or host-derived substrates, influencing immune and metabolic regulation.18,19 Through metabolic engineering, this process can be optimized: in B. subtilis, knockout of drm and ywjH redirects metabolic flux toward purine synthesis, while overexpression of zwf boosts precursor supply via the pentose phosphate pathway.20 Similarly, CRISPR-modified Escherichia coli Nissle 1917 expressing adenosine deaminase converts immunosuppressive adenosine into inosine under hypoxia, enhancing antitumor immunity.21 Collectively, these metabolic and CRISPR-based engineering strategies demonstrate the potential of probiotics as living biotherapeutic platforms for in situ inosine production, thereby strengthening host immune regulation and augmenting cancer immunotherapy efficacy, as shown in Figure 2.

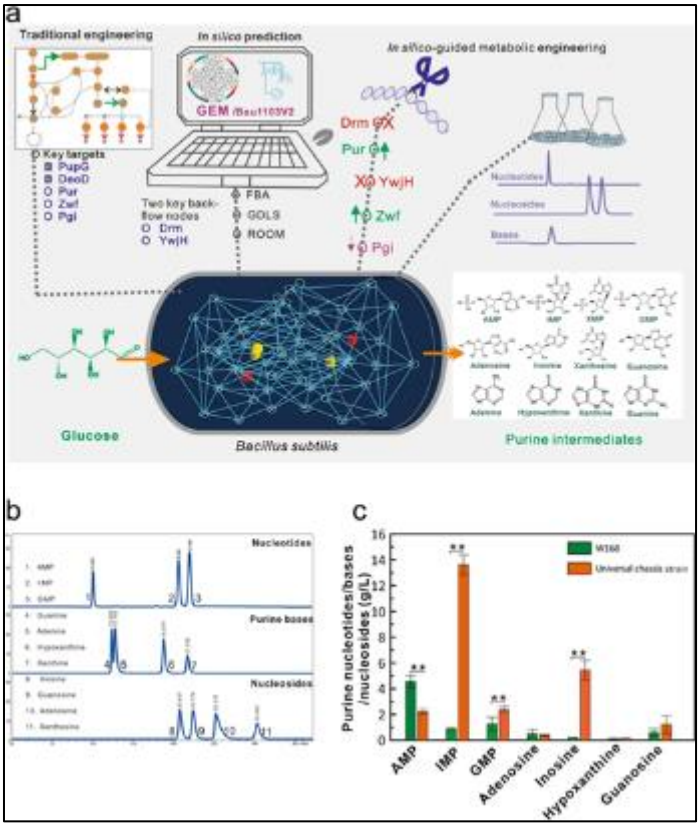

Figure 2 Construction of the general purine chassis bacterium by in silico-guided metabolic engineering strategy; (a) Schematic diagram for in silico-guided metabolic engineering strategy; (b) The retention times of purine nucleosides, bases, and nucleosides by HPLC; (c) Determination of purine nucleosides metabolites synthesized in the general purine chassis strain. All error bars indicate ± SD, n = 3. A value of P less than 0.05 was regarded to be a significant difference with the W168 strain using the T-test (*, $P < 0.05$; **, $P < 0.01$).20

3.2. Immunomodulatory Role of Inosine in Enhancing Cancer Immunotherapy Response

Inosine, a gut microbiota-derived metabolite predominantly produced by Bifidobacterium pseudolongum, has emerged as a key mediator of the microbiome–immune axis that enhances cancer immunotherapy efficacy. Inosine enhances immunotherapy response by modulating immune cell function, primarily through the activation of T cells and dendritic cells, which are essential for effective antitumor immunity. Acting as both a signaling molecule and a metabolic substrate, inosine binds to the adenosine A2A receptor (A2AR) on T cells, inducing IL-12 receptor β2 (IL12Rb2) expression and interferon-gamma (IFN-γ) secretion that promote Th1 polarization and CD8+ cytotoxic T-cell activation within the tumor microenvironment.5,22 Furthermore, inosine supports T-cell metabolism by serving as an alternative carbon source under glucose-limited conditions, sustaining effector functions during metabolic stress.18,24 Collectively, these mechanisms reduce immunosuppressive factors within the tumor milieu and enhance the efficacy of immune checkpoint inhibitors.25

Recent studies have shown that microbiota-derived inosine significantly enhances the efficacy of immune checkpoint inhibitors. Gut commensals such as Bifidobacterium pseudolongum, Lactobacillus johnsonii, and Olsenella species produce inosine that activates the adenosine A2A receptor (A2AR) on T cells, promoting IFN-γ secretion, Th1 polarization, and cytotoxic T-cell activity. This signaling leads to tumor regression and improved survival in preclinical models of melanoma, colorectal cancer, and bladder cancer. As shown in Figure 4, inosine drives Th1 differentiation via A2AR signaling only under co-stimulatory (IFN-γ) conditions, suggesting its immunomodulatory effects rely on a primed immune environment and how this antitumor activity is lost in A2AR-deficient T cells, establishing the dependence of inosine's mechanism on A2AR-mediated signaling.5

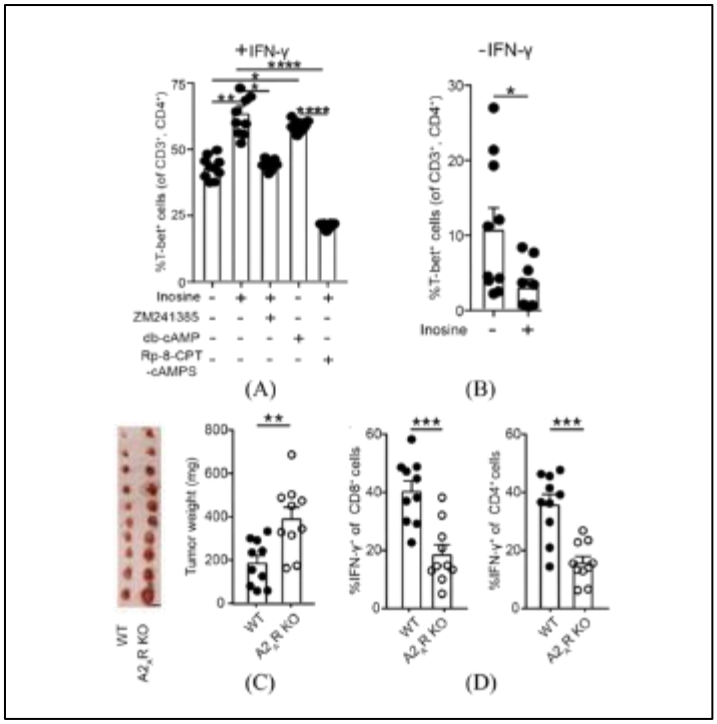

Figure 3 Inosine promotes Th1 differentiation through A2AR signaling only when co-stimulation (IFN-γ) is present and its anti-tumor effect is dependent on A2AR expression on T cells; (A) Naïve CD4+ T cells were co-cultured with bone marrow derived dendritic cells and IFN-γ. Quantification of T-bet+, CD3+, CD4+ T cells 48 hours after co-culture in the presence or absence of inosine, A2A receptor inhibitor (ZM241385), cell permeable cAMP (db-cAMP) and protein kinase A inhibitor (RP-8-CPT-cAMPS); (B) Same as (A) without IFN-γ; (C) Pictures of tumors and tumor weight are shown at day 20. Scale bars: 1 cm; (D) Quantification of IFN-γ+ in CD8+ or CD4+ T cells in the tumor are shown.5

Complementing these mechanistic insights, studies have demonstrated the therapeutic potential of inosine as an immunometabolism adjuvant. A randomized controlled trial by Zhao et al. (2024) reported that inosine supplementation resulted in a 37% reduction in disease progression risk (HR 0.63; p = 0.011) and nearly doubled the objective response rate compared to controls, underscoring its efficacy in augmenting cancer immunotherapy outcomes.26 Additionally, inosine modulates immune metabolism and epigenetic programming of CAR-T cells, promoting mitochondrial activity and enhancing effector functions.27,28

Beyond checkpoint blockade, inosine modulates immunity through the inosine–A2AR–cAMP–PKA axis, enhances CAR-T cell persistence by limiting adenosine-mediated suppression, and reprograms metabolism toward T-cell stemness and memory.24,27 Moreover, it has been shown to modulate the metabolism and epigenetic programming of CAR-T cells, shifting their bioenergetic profile toward enhanced mitochondrial function and long-term persistence, thus improving antitumor potency.27,28 These mechanisms collectively strengthen inosine's position as an immunomodulatory metabolite capable of bridging microbial signaling and host immune responses.

4. Discussion

A total of 11 studies were compiled and analyzed, involving both preclinical and clinical research on CRISPR-engineered probiotics designed to produce inosine as an immunomodulatory metabolite to enhance cancer immunotherapy efficacy.

Compared to conventional probiotics, CRISPR-engineered probiotics offer a major advantage in genetic precision, enabling specific gene deletions, insertions, or replacements to directly enhance desired functions, such as the production of immunomodulatory metabolites like inosine.12,13 This precision results in more consistent and predictable therapeutic outcomes, unlike conventional probiotics, whose effects often vary across individuals and populations due to natural strain diversity.12 Moreover, CRISPR-based probiotics can be functionally customized to improve stress tolerance, therapeutic protein production, or metabolite synthesis, depending on the clinical goal.29,30 In terms of safety, modern CRISPR systems are designed to minimize off-target effects, ensuring controlled interactions with the native gut microbiota. In contrast, conventional probiotics may exhibit unpredictable microbial interactions

that affect their efficacy.14 When it comes to metabolite production, engineered strains are optimized for stable and high-yield synthesis, while natural strains show variable production depending on environmental and host factors.31 Collectively, CRISPR technology provides a targeted, efficient, and customizable approach, making it a promising platform for next-generation microbiome-based and immunomodulatory therapies, as explained in Table 1.

Table 1 Comparison between CRISPR-engineered and conventional probiotics for precision gut microbiome outcomes

Aspect	**CRISPR-Engineered Probiotics**	**Conventional Probiotics**
Precision Targeting	Precisely targeted genetic modifications; specific gene deletions, insertions, or replacements.[12,13]	Limited to naturally occurring strains; variable effects across populations.[12,13]
Efficacy Consistency	More predictable and consistent outcomes due to defined genetic modifications.[12]	Highly variable; clinical outcomes differ among populations and strains.[12]
Functional Customization	Customizable functionalities (enhanced stress tolerance, therapeutic protein production, metabolite synthesis).[13,30]	Fixed functionalities based on natural traits.[13,30]
Off-Target Effects	Controlled; designed to minimize off-target effects on beneficial microbes.[14]	Unpredictable interactions with resident microbiota.[14]
Production of Desired Metabolites	Engineered for high-level, consistent production.[31]	Variable production levels; strain-dependent.[31]

Subsequent studies identified inosine as a key immunomodulatory metabolite that enhances checkpoint blockade efficacy. B. pedologic–derived inosine boosts anti–CTLA-4 therapy by promoting IFN-γ production, T-cell infiltration, and tumor regression, as confirmed in humanized preclinical models.22 Through the inosine–A2AR–cAMP–PKA axis, inosine also supports CAR-T cell persistence, counters adenosine suppression, and promotes T-cell stemness.24,27 Clinical data show inosine supplementation improved progression-free survival (HR 0.63) and increased IFN-γ and IL-12 without raising severe adverse effects compared to the standard cancer procedures, as demonstrated in Table 2.26

Table 2 Comparison between gut microbiome (inosine produced by probiotics) and standard procedures (chemotherapy, radiation, surgery) in their overall efficacy for cancer treatment

Aspect	**CRISPR-Engineered Probiotics**	**Conventional Probiotics**
Mechanism	Modulates immune responses, enhances anti-tumor immunity, and influences the efficacy of immunotherapy through metabolites like SCFAs, bile acids, and inosine.[28]	Relies on direct targeting of cancer cells via surgery, chemotherapy, radiation, or immunotherapy (e.g., checkpoint inhibitors).[28]
Efficacy	Can enhance the response to immunotherapy and reduce toxicity, particularly in patients with specific microbiome profiles.[28]	Efficacy varies based on cancer type, stage, and patient health.[28]
Response Rates	Can improve response rates to immunotherapy in certain patients.[25]	Varies widely; some patients may not respond to standard treatments.[25]
Long-term Impact	May support long-term immune memory and sustained antitumor effects.[24]	Often associated with temporary remission and higher relapse rates.[24]
Adverse Effects	Generally well-tolerated, with minimal side effects compared to conventional therapies.[5,26]	Often associated with significant side effects (chemotoxicity, immune-related adverse events (irAEs), checkpoint inhibitor toxicity).[5,26]

5. Conclusion

CRISPR-engineered probiotics capable of targeted inosine production represent a promising strategy to enhance cancer immunotherapy by modulating T-cell and dendritic cell activity, improving tumor regression, and supporting CAR-T cell persistence. These engineered strains offer precise, high-yield, and predictable immunomodulatory effects, providing a viable adjunct to existing immune checkpoint inhibitors. Further research on more extensive clinical trials is warranted to optimize the use of CRISPR-engineered probiotics and other microbiome-derived metabolites to enhance cancer immunotherapy efficacy and achieve broader, more consistent patient responses.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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