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Oral Nano-Delivery of Gut Microbial Metabolites to Modulate HOXA5 Epigenetic Regulation and T-Cell Stemness in Oral Cancer Immunotherapy

Prakash Ramakrishnan[1]*, Mohamed Imath[2], Selvaraj Ganesh Kumar[3], Jeslin D[4], Devi M[5], S Muthulakshmi[6], Ronald Darwin Chellappan[7], Vijayakumar R[8], W Clement Atlee[9]

[1]Department of Pharmacology, Crescent School of Pharmacy, B S Abdur Rahman Crescent Institute of Science and Technology, Chennai, Tamil Nadu.
[2]DeepMolecule Drug Discovery Solutions, Chennai, 600 050, Tamil Nadu, India.
[3]Associate Professor & Head, Department of Microbiology, Centre for Biological Sciences, St. Peter Institute of Higher Education and Research, Avadi, Chennai, 600 054, Tamil Nadu, India.
[4]Associate Professor, School of Pharmacy, SBV Chennai, Sri Balaji Vidyapeeth, Pondicherry, 607 402, India.
[5]Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, Dr M.G.R Educational and Research Institute, Chennai, 600 095, Tamil Nadu, India.
[6]Assistant Professor of Psychology, School of Social Sciences and Humanities, B S Abdur Rahman Crescent Institute of Science and Technology, Chennai, Tamil Nadu.
[7]Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai, Tamil Nadu, India
[8]Department of Pharmaceutical Analysis, C. L. Baid Metha College of Pharmacy, Thoraipakkam, OMR, Chennai, 600097, Tamil Nadu, India.
[9]Professor, Department of Pharmacology, C. L. Baid C. L. Baid Metha College of Pharmacy, Thoraipakkam, OMR, Chennai, 600097, Tamil Nadu, India.

ABSTRACT: The gut microbiota shapes antitumor immunity through metabolites that act as epigenetic modulators, yet their application to oral squamous cell carcinoma (OSCC) remains largely conceptual, with no direct preclinical evidence in this tumor type. Short-chain fatty acids, particularly butyrate, and tryptophan derivatives such as indole-3-propionic acid inhibit histone deacetylases, reprogram CD8+ T-cell metabolism, and preserve TCF1-positive stem-like progenitors that sustain responses to PD-1 blockade. However, systemic exposure to these molecules is constrained by rapid absorption, short half-life, and unpredictable luminal concentrations. Orally administered nanocarriers can protect cargo from gastric degradation, release it at defined sites, and enhance mucosal uptake. In parallel, the homeobox tumor suppressor HOXA5 is frequently silenced by promoter hypermethylation in oral cancer, and demethylating agents restore its expression in vitro. This review integrates these separate bodies of evidence. We summarize microbial metabolite biology, epigenetic control of T-cell stemness, HOX dysregulation in OSCC, and oral nano-delivery platforms, and we propose a testable framework in which nanoformulated metabolites simultaneously remodel HOXA5 chromatin in tumor cells and sustain stem-like T cells. Evidence is graded to separate established findings from hypotheses. We emphasize that a direct HOXA5–T-cell axis has not yet been

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demonstrated, and we identify critical gaps, including pharmacokinetics, oral-cavity versus colonic targeting, biomarkers, and safety. Finally, we outline translational priorities: standardized metabolite quantification, organoid and humanized models, rational checkpoint-inhibitor combinations, and adaptive trial designs for head and neck cancer.

1. INTRODUCTION

Oral squamous cell carcinoma (OSCC) arises through a stepwise accumulation of genetic and epigenetic lesions driven by tobacco, areca nut, alcohol and, in some settings, viral exposure [1]. Despite advances in surgery, radiotherapy and checkpoint blockade, outcomes for advanced disease remain poor, and only a minority of patients with head and neck cancer obtain durable benefit from PD-1 inhibitors. A growing body of work links this variability to the gut microbiome: the composition of the intestinal community predicts response to anti-PD-1 therapy in epithelial tumors and melanoma [2], [3], and microbial metabolites, rather than live bacteria alone, appear to be key effectors [4], [5].

Among these metabolites, short-chain fatty acids (SCFAs) and indole derivatives act on CD8+ T cells at the level of chromatin and metabolism. Butyrate supports oxidative metabolism and memory formation in activated CD8+ T cells [6], enhances the effector function of cytotoxic and CAR T cells [7], and, in a 2025 study, was shown to induce a FOXO1-driven stemness program in tumor-specific CD8+ T cells [8]. Indole-3-propionic acid (IPA) raises Tcf7 expression through histone acetylation and expands progenitor-exhausted T cells (Tpex) in a pan-cancer setting [9]. Because Tpex cells are the subset that proliferates after PD-1 blockade, metabolite-driven epigenetic maintenance of stemness is an attractive adjunct to immunotherapy.

A second epigenetic layer is intrinsic to the tumor. Homeobox (HOX) genes are dysregulated in OSCC through locus-specific CpG methylation changes, with the HOXA and HOXB clusters particularly affected [1]. HOXA5, a tumor suppressor, shows promoter hypermethylation and reduced expression in oral cancer, and treatment of oral cancer cell lines with 5-aza-2'-deoxycytidine restores its expression and restrains proliferation [10]. Loss of 5-hydroxymethylcytosine and TET2 in OSCC further indicates a disturbed demethylation machinery [11].

The central difficulty is delivery. Native SCFAs are rapidly absorbed in the proximal gut and metabolized, so luminal and systemic exposure is hard to control, whereas oral nanotherapeutics offer protection, site-specific release and improved mucosal uptake [12]. Recent proof-of-concept studies have shown that butyrate-loaded nanoparticles can repair the gut barrier and inhibit digestive-tract tumors [13], that colon-targeted liposome–spore hybrids can raise CD8+ T-cell infiltration [14], and that an oral prodrug nano-emulsion of a microbial metabolite can expand stem-like CD8+ T cells and potentiate anti-PD-1 therapy [15].

This review therefore asks whether oral nano-delivery of microbial metabolites could be used to coordinate two epigenetic targets in OSCC: tumor-cell HOXA5 regulation and T-cell stemness. The overall concept is shown in Fig. 1. We stress at the outset that the HOXA5–T-cell connection is a hypothesis generated by combining independent literatures; it is not an established pathway. The remainder of the article is organized as follows: Section 2 reviews metabolite biology; Section 3 covers epigenetic control of stemness; Section 4 addresses HOX/HOXA5 in OSCC; Section 5 evaluates nano-delivery systems; Section 6 proposes the integrative framework; and Sections 7–9 discuss models, translational barriers and future directions.

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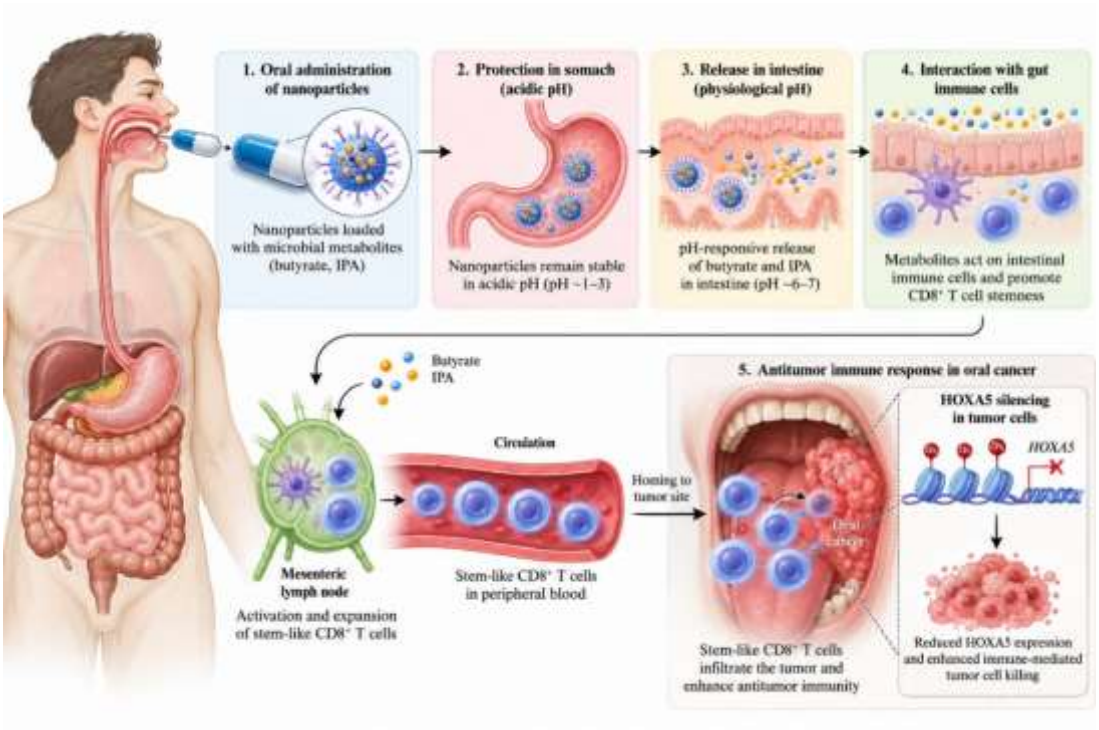

Fig. 1. Conceptual overview of the gut–oral cancer axis. Orally administered nanoparticles carrying microbial metabolites (butyrate, IPA) are protected through the stomach, release cargo in the intestine, and act on intestinal and circulating CD8+ T cells and, potentially, on tumor-cell chromatin (HOXA5). Created with BioRender.

2. MICROBIAL METABOLITES AS EPIGENETIC AND IMMUNOMETABOLIC REGULATORS

Microbial metabolites reach the host through fermentation of dietary fiber, tryptophan catabolism and secondary bile-acid metabolism. The metabolites most relevant to T-cell stemness are summarized in Table 1. Butyrate is the best characterized: it acts as an HDAC inhibitor and as an oxidative fuel, and in a 2025 report it also increased MHC-I expression through cGAS–STING activation and CD8+ T-cell recruitment through CXCL10 in colorectal cancer models [16]. Pentanoate and butyrate improved the antitumor activity of cytotoxic T cells and CAR T cells [7], and SCFA-driven histone acetylation was linked to enhanced cytotoxic CD8+ T-cell immunity in anticancer therapy [17].

Table 1. Gut microbial metabolites with reported effects on CD8+ T-cell function and stemness.

Metabolite	Principal source	Reported immune/epigenetic effect	Evidence level and ref.
Butyrate	Fiber fermentation (Firmicutes)	Promotes oxidative metabolism and memory potential; FOXO1-driven stemness program in tumor-specific CD8+ T cells; HDAC inhibition; MHC-I upregulation via cGAS–STING	Mouse in vivo and in vitro [6], [8], [16]
Pentanoate (valerate)	Gut anaerobes	Enhances CTL and CAR T-cell effector molecules and antitumor activity	Mouse, human CAR T in vitro [7], [17]
Indole-3-propionic acid (IPA)	Tryptophan metabolism (L. johnsonii, C. sporogenes)	Raises Tcf7 via histone acetylation; expands Tpex and effector T cells; sensitizes to anti-PD-1	Mouse, pan-cancer models [9], [5]
Butyrate (ex vivo-treated T cells)	Pre-treatment before adoptive transfer	Higher IFN-γ and mTOR phosphorylation, effector-memory	Mouse OT-I model [18]

		phenotype, tumor protection; lower proliferation and higher apoptosis	
Other microbial metabolites	Various	Multiple metabolites modulate chemotherapy and immunotherapy response	Review level [4], [5]

Two features of this literature deserve emphasis. First, effects are strongly dose-, timing- and context-dependent: ex vivo butyrate increased effector cytokine production yet reduced proliferation and increased apoptosis [18], indicating a narrow therapeutic window. Second, most mechanistic work derives from murine colorectal, melanoma or pan-cancer models; direct evidence in OSCC is, to our knowledge, absent. Extrapolation to oral cancer must therefore be treated as provisional.

3. EPIGENETIC CONTROL OF T-CELL STEMNESS

Stem-like (progenitor) exhausted CD8+ T cells, defined by TCF1 expression, self-renew, give rise to terminally exhausted progeny and generate the proliferative burst after PD-1 blockade. Enforced Tcf1 expression instilled a stem-like program in exhausted T cells and improved viral and tumor control, with chromatin accessibility changes at enhancers and repressors [19]. Conversely, the histone demethylase LSD1 enforces an epigenetic program that opposes TCF1-mediated progenitor maintenance and favors terminal differentiation [20]. These findings show that stemness is a chromatin-defined state that can, in principle, be pharmacologically stabilized.

Microbial metabolites could intervene at several nodes of this circuit (Fig. 2). HDAC inhibition by butyrate and histone acetylation at the Tcf7 locus by IPA [9] provide a direct route to TCF1 maintenance; metabolic rewiring toward oxidative phosphorylation supports long-lived memory [6]; and FOXO1 activation provides an additional stemness driver [8]. An important caveat is that persistent HDAC inhibition is not specific to T cells and may also alter tumor, stromal and myeloid compartments, a point that becomes central when considering the tumor-cell effects discussed in Section 4.

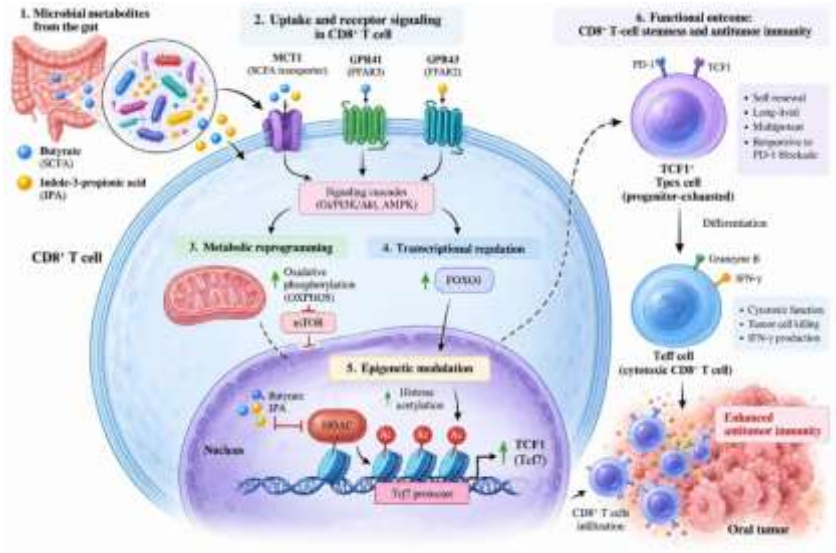

Fig. 2. Molecular routes by which microbial metabolites sustain CD8+ T-cell stemness. Butyrate and IPA inhibit HDACs and increase histone acetylation at the Tcf7 locus, activate FOXO1, and favor oxidative metabolism, supporting TCF1+ progenitor-exhausted cells that respond to PD-1 blockade.

4. HOXA5 AND HOX DYSREGULATION IN ORAL CANCER

HOX genes encode transcription factors that specify positional identity and, when dysregulated, influence cell-cycle control, epithelial–mesenchymal transition, invasion and angiogenesis [1]. A multi-omic study of premalignant oral lesions and OSCC reported locus-specific CpG methylation changes that were more prominent in the HOXA and HOXB clusters than in HOXC and HOXD, identified intronic HOXB9 methylation as a candidate discriminatory marker, and predicted that HOXA5 and HOXC9 had the strongest regulatory interactions with neighboring HOX genes [1]. Focused work on HOXA5 shows that its

promoter is hypermethylated in oral cancer and that 5-aza-2'-deoxycytidine restores expression in CAL-27, H357 and HSC-3 cells while inhibiting proliferation and spread [10]. The key evidence is summarized in Table 2.

Table 2. Evidence for HOXA5/HOX epigenetic regulation in oral cancer.

Study type	Main finding	Model/sample	Ref.
Bioinformatic and wet-lab	HOXA5 promoter hypermethylated; reduced expression; 5-Aza-CdR restores mRNA and inhibits growth	CAL-27, H357, HSC-3; oral tissues	[10]
Multi-omic (methylation capture, transcriptome)	HOXA/HOXB clusters show locus-specific CpG changes; HOXB9 intronic methylation as marker; HOXA5 and HOXC9 are highly connected nodes	Premalignant lesions and OSCC tissue	[1]
Immunohistochemistry	Loss of 5hmC and TET2, increased 5mC in OSCC versus healthy mucosa	OSCC biopsies and healthy oral epithelium	[11]

Three interpretive limits apply. First, HOXA5 behaves as a tumor suppressor in oral and breast cancer models but its role is context-dependent across tumor types, so universal claims are unsafe. Second, the cited oral cancer data on HOXA5 are modest in scale and come largely from cell lines and small tissue sets. Third, no study has yet connected tumor HOXA5 status to T-cell infiltration or stemness in OSCC. This is the principal knowledge gap that the framework in Section 6 seeks to define rather than assume.

Mechanistically, promoter CpG methylation and the TET-mediated demethylation cycle [11] set the baseline for HOXA5 silencing (Fig. 3). Because HDAC inhibitors such as butyrate act primarily on histone acetylation, they may reopen chromatin but are unlikely, alone, to erase dense CpG methylation; reactivation could therefore require combination with DNMT inhibitors or TET-supporting cofactors. This distinction is a testable prediction, not a result.

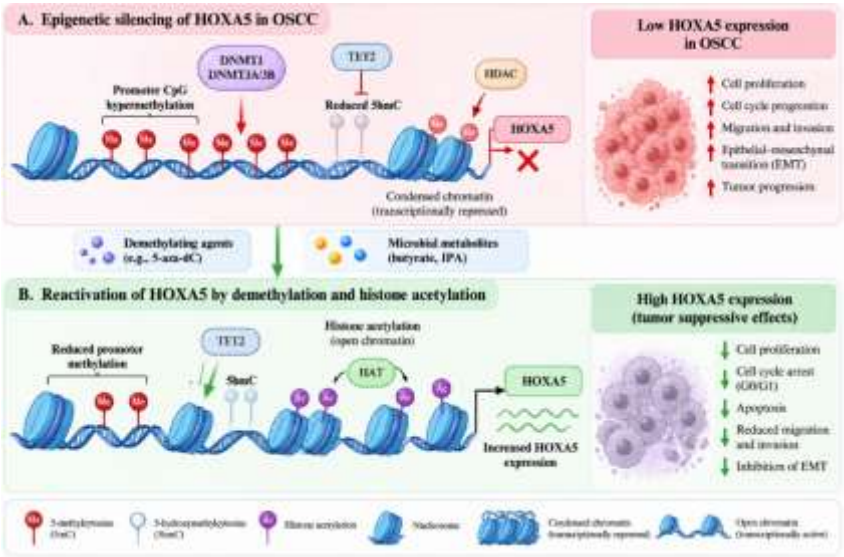

Fig. 3. Epigenetic silencing and potential reactivation of HOXA5 in OSCC. Promoter CpG hypermethylation (DNMT activity, reduced TET2/5hmC) represses HOXA5; demethylating agents restore expression, while metabolite-driven histone acetylation may increase chromatin accessibility.

5. ORAL NANO-DELIVERY PLATFORMS FOR MICROBIAL METABOLITES

SCFAs are small, polar and volatile, which complicates formulation; they are absorbed and metabolized rapidly and can produce unpleasant sensory properties. Oral nanocarriers can address these constraints by encapsulation, responsive coatings and

bioadhesion, although scale-up, cost, biosafety and pharmacokinetics remain limiting for clinical translation [12]. Representative strategies are compared in Table 3 and the delivery path is illustrated in Fig. 4.

Table 3. Oral nanocarrier strategies relevant to microbial-metabolite delivery.

Platform	Design features	Reported outcome	Ref.
Enterocyte-mimetic butyrate nanoparticles (EMBNs)	Chitosan/hyaluronic acid core loaded with butyrate; enterocyte-membrane coating adsorbing LPS and zonulin	Gut-barrier repair; inhibited growth and metastasis of digestive-system tumors	[13]
Spore–liposome hybrids	Chitosan-coated liposomes conjugated to Clostridium butyricum spores; colon colonization	Colon-specific release; enhanced CD8+ T-cell infiltration and chemo-immunotherapy in colorectal cancer	[14]
Metabolite prodrug nano-emulsion	Oral prodrug of a microbial metabolite in a nano-emulsion	Expanded stem-like CD8+ T cells; synergy with anti-PD-1 in five preclinical models	[15]
Free butyrate in drinking water (non-nano comparator)	Simple oral supplementation (1 mM in mice)	Synergy with oncolytic virus in colorectal models; illustrates dose-delivery limitations	[16]
General oral colon-targeted nanotherapeutics	pH-, enzyme- or time-responsive coatings; mucoadhesive polymers	Convenient self-administration; delivery efficiency governs benefit	[12]

For OSCC two delivery logics should be distinguished. In the gastrointestinal route, the nanoparticle delivers metabolites to the gut-associated lymphoid tissue and portal circulation to shape systemic T-cell priming, mirroring the successful colorectal models. In a local oral-mucosal route (buccal or sublingual films, mucoadhesive gels), high concentrations could be achieved at the tumor surface, but evidence that metabolite exposure there modifies HOXA5 or T-cell stemness is lacking. A hybrid approach, with swallowed carriers for systemic immunity and local carriers for tumor-cell epigenetics, may eventually prove most rational but multiplies regulatory complexity.

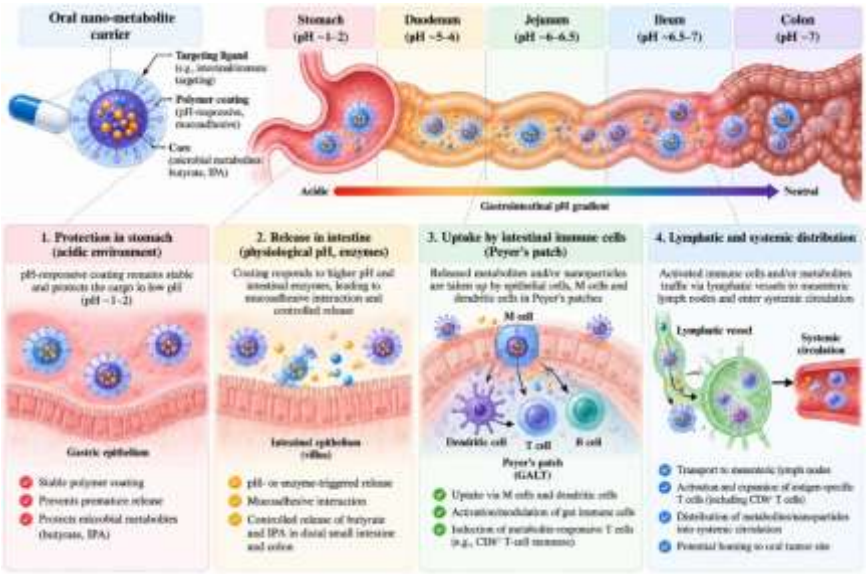

Fig. 4. Journey of an oral nano-metabolite carrier. A pH-responsive coating protects the cargo in the stomach; mucoadhesive or enzyme-triggered release occurs in the distal intestine; uptake by epithelial and immune cells follows, with possible lymphatic and systemic distribution.

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6. AN INTEGRATIVE FRAMEWORK: COORDINATING TUMOR EPIGENETICS AND T-CELL STEMNESS

We propose that a nanoformulated metabolite could act through three converging mechanisms in OSCC (Fig. 5): (i) increased histone acetylation at stemness loci such as Tcf7 in CD8+ T cells [9], [8]; (ii) enhanced antigen presentation and chemokine-mediated T-cell recruitment through MHC-I and CXCL10 [16]; and (iii) reversal of tumor-suppressor silencing, with HOXA5 as a candidate target, potentially through combination with a demethylating partner [10]. These mechanisms are not mutually exclusive, and they make distinct, falsifiable predictions summarized in Table 4.

Table 4. Testable hypotheses of the proposed framework and proposed experimental readouts.

No.	Hypothesis	Experimental test	Falsifying result
H1	Oral nano-butyrate increases TCF1+ Tpex frequency in tumor-draining lymph nodes of OSCC-bearing mice more than free butyrate	Flow cytometry, scRNA/scATAC-seq of CD8+ T cells	No difference from free butyrate
H2	Nano-butyrate increases HOXA5 promoter accessibility but not demethylation	ATAC-seq, bisulfite or methyl-capture sequencing on tumor cells	Complete demethylation without DNMT inhibitor
H3	HOXA5 restoration in tumor cells increases CD8+ T-cell infiltration	HOXA5 knock-in/CRISPRa; spatial profiling	No change in infiltration
H4	Combination with anti-PD-1 gives additive or synergistic tumor control	Orthotopic OSCC models; survival analysis	No benefit over anti-PD-1 alone
H5	Tumor HOXA5 methylation predicts response	Retrospective cohorts of PD-1-treated HNSCC	No association

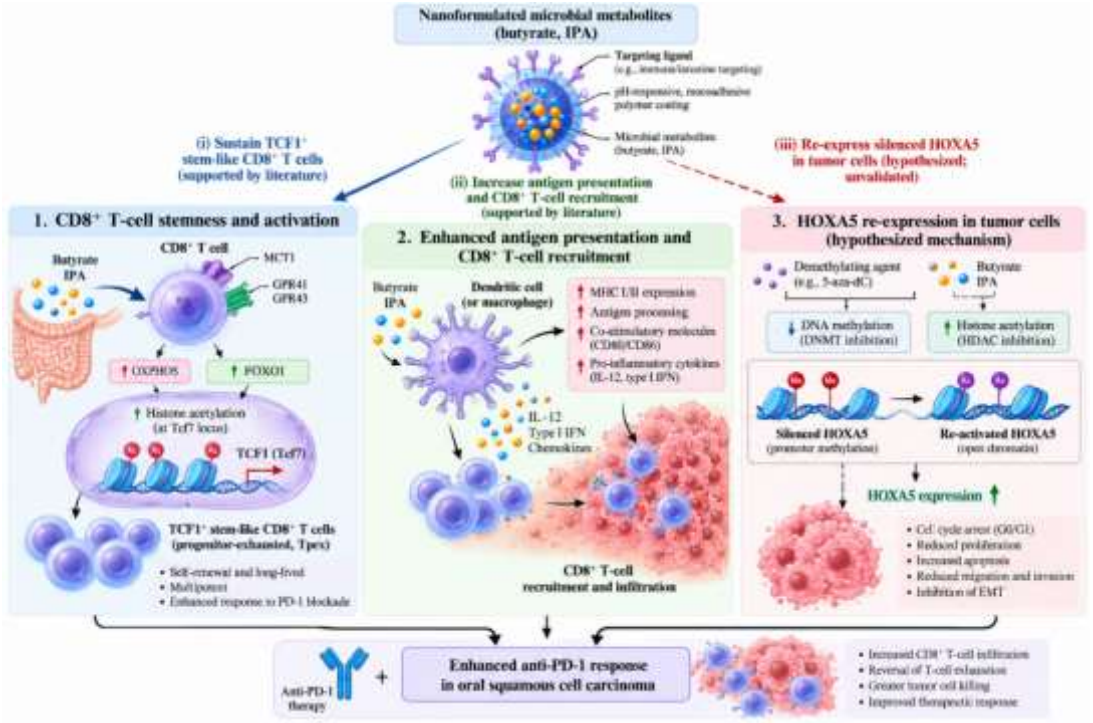

Fig. 5. Proposed integrative framework. Nanoformulated metabolites (i) sustain TCF1+ stem-like CD8+ T cells, (ii) increase antigen presentation and CD8+ T-cell recruitment, and (iii) may help re-express silenced HOXA5 in tumor cells, particularly with a demethylating partner, to improve anti-PD-1 response. Dashed arrows indicate hypothesized, unvalidated links.

7. PRECLINICAL MODELS AND BIOMARKERS

Testing the framework requires models that retain oral-cavity biology. Syngeneic orthotopic tongue or buccal models, carcinogen-induced (4-NQO) models and patient-derived organoids co-cultured with autologous T cells each address different questions; germ-free or antibiotic-treated animals are needed to distinguish the effect of exogenous metabolites from the endogenous microbiota [6]. Because ex vivo and in vivo effects of butyrate can diverge [18], dose–response and timing studies are essential. Candidate biomarkers are summarized in Table 5.

Table 5. Candidate biomarkers and models for evaluating oral nano-metabolite immunotherapy.

Domain	Biomarker/readout	Rationale	Ref.
T-cell stemness	TCF1, CD127, Tcf7 chromatin accessibility	Marks progenitor cells responding to PD-1 blockade	[19], [8], [9]
Tumor epigenetics	HOXA5 promoter methylation; 5hmC/TET2 status	Silencing and demethylation capacity	[10], [11]
HOX cluster signature	HOXA/HOXB locus-specific CpG methylation; HOXB9 intronic marker	Distinguishes premalignant from advanced lesions	[1]
Antigen presentation/chemokines	MHC-I, CXCL10, cGAS–STING activity	Metabolite-induced immunogenicity	[16]
Microbiome/metabolome	Fecal and plasma SCFA, IPA; community profiling	Baseline exposure; response prediction	[2], [3]

8. TRANSLATIONAL CHALLENGES, SAFETY AND REGULATION

Several barriers separate the concept from the clinic (Table 6). Reproducible manufacturing and cost remain unresolved for oral nanotherapeutics in general [12]. Butyrate has a narrow functional window in T cells [18], and HDAC inhibition is non-selective, creating a risk of off-target transcriptional effects. Because metabolite-based interventions are heterogeneous (small molecules, prodrugs, live biotherapeutics), regulatory classification may vary. Finally, microbiome composition differs across populations and with dietary habits, tobacco and areca-nut use, which may influence both baseline metabolite levels and response.

Table 6. Translational barriers and proposed mitigation strategies.

Barrier	Description	Proposed mitigation
Dose–response window	Butyrate improves effector function but can reduce proliferation and increase apoptosis [18]	Pharmacokinetic/pharmacodynamic modeling; controlled-release carriers
Specificity	HDAC inhibition acts on tumor, stromal and myeloid cells	Targeted ligands; cell-type-resolved single-cell readouts
Manufacturing and cost	Scale-up, batch consistency and cost limit clinical translation [12]	Quality-by-design; simple, GRAS-based excipients
Model relevance	Most evidence is in colorectal or melanoma mouse models [7], [9]	Orthotopic OSCC models, organoids, humanized mice
Patient heterogeneity	Microbiome and lifestyle exposures differ between cohorts [2], [3]	Stratified trial designs with baseline metabolomics
Evidence gap	No direct HOXA5–T-cell link demonstrated [10], [1]	Hypotheses H1–H5 (Table 4) before clinical trials

9. FUTURE PERSPECTIVES

Three priorities emerge. First, mechanistic studies should test whether tumor-cell HOXA5 status influences T-cell infiltration and stemness, since without that link the framework reduces to two parallel, independently useful interventions. Second, delivery platforms should be benchmarked head-to-head against free metabolite supplementation, with pharmacokinetic sampling in portal blood, lymph nodes and tumor tissue. Third, early-phase trials in head and neck cancer should embed

metabolomic, microbiome and epigenomic endpoints, enabling adaptive designs in which dose and combination partner (anti-PD-1, DNMT inhibitor) are refined using biomarker feedback. Emerging oral metabolite-based immunotherapies [15] and exercise- or diet-linked microbial metabolites suggest that the field is moving from correlation to engineered intervention.

10. CONCLUSIONS

Microbial metabolites such as butyrate and IPA can remodel the epigenetic and metabolic state of CD8+ T cells and preserve stem-like progenitors, while HOXA5 and related HOX genes are epigenetically dysregulated in oral cancer. Oral nano-delivery offers a plausible route to exploit both mechanisms, and early nanocarrier studies in digestive-tract cancers support feasibility. However, no study has yet linked HOXA5 regulation to T-cell stemness in OSCC. We therefore regard the concept as a hypothesis-driven research agenda, and we have specified the experiments that would confirm or refute it.

DECLARATIONS

Author Contributions (CRediT): Prakash Ramakrishnan, Mohamed Imath, Selvaraj Ganesh Kumar, Jeslin D, Devi M, S Muthulakshmi, Ronald Darwin Chellappan, Vijayakumar R, and Dr W Clement Atlee -Conceptualization; Writing – original draft; Writing – review & editing.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

All data are from the cited sources.

REFERENCES

[1] "Multifaceted regulation of the HOX cluster and its implications in oral cancer," 2025, PMC12273044. [Verify journal and volume in Zotero]

[2] B. Routy et al., "Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors," Science, vol. 359, no. 6371, pp. 91–97, 2018.

[3] V. Gopalakrishnan et al., "Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients," Science, vol. 359, no. 6371, pp. 97–103, 2018.

[4] S. Lu, C. Wang, J. Ma, and Y. Wang, "Metabolic mediators: Microbial-derived metabolites as key regulators of anti-tumor immunity, immunotherapy, and chemotherapy," Front. Immunol., vol. 15, Art. no. 1456030, 2024, doi: 10.3389/fimmu.2024.1456030.

[5] B. Ren, Y. Fang, M. Gu, L. You, T. Zhang, and Y. Zhao, "Microbiota-metabolism-epigenetics-immunity axis in cancer," Front. Immunol., vol. 15, Art. no. 1449912, 2024, doi: 10.3389/fimmu.2024.1449912.

[6] A. Bachem et al., "Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated CD8+ T cells," Immunity, vol. 51, no. 2, pp. 285–297.e5, 2019, doi: 10.1016/j.immuni.2019.06.002.

[7] M. Luu et al., "Microbial short-chain fatty acids modulate CD8+ T cell responses and improve adoptive immunotherapy for cancer," Nat. Commun., vol. 12, Art. no. 4077, 2021, doi: 10.1038/s41467-021-24331-1.

[8] [Authors: import via Zotero], "Microbiota-derived butyrate promotes a FOXO1-induced stemness program and preserves CD8+ T cell immunity against melanoma," Immunity, vol. 58, no. 11, pp. 2799–2813.e8, 2025, doi: 10.1016/j.immuni.2025.10.004.

[9] D. Jia et al., "Microbial metabolite enhances immunotherapy efficacy by modulating T cell stemness in pan-cancer," Cell, vol. 187, no. 7, pp. 1651–1665, 2024, doi: 10.1016/j.cell.2024.02.022.

[10] H. Wang, Y. Liu, J. Wu, W. Wang, H. Zhang, and C. Yi, "Bioinformatics analysis of promoter methylation and clinical significance of tumor suppressor gene HOXA5 in oral cancer," Pak. J. Zool., vol. 56, pp. 3243–3249, 2024, doi: 10.17582/journal.pjz/20230803165114.

[11] [Authors: import via Zotero], "Loss of 5-hydroxymethylcytosine and TET2 in oral squamous cell carcinoma," Anticancer Res., vol. 33, no. 10, p. 4325, 2013.

[12] L. Duan, F. Zheng, D. Merlin, H. Wang, Z. Xiao, and B. Xiao, "Editorial: Oral nanotherapeutics for colon diseases," Front. Bioeng. Biotechnol., vol. 9, Art. no. 816304, 2021, doi: 10.3389/fbioe.2021.816304.

[13] G. Xie et al., "Oral delivery of enterocyte-mimetic butyrate-loaded nanoparticles repairs the gut barrier and inhibits growth of digestive system tumors," [journal/year: verify in Zotero].

[14] M. Niu et al., "Colon-specific controlled release of oral liposomes for enhanced chemo-immunotherapy against colorectal cancer," Acta Pharm. Sin. B, 2024, PMID: 39664423.

[15] [Authors: import via Zotero], "Oral microbial-metabolite prodrug nano-emulsion expands stem-like CD8+ T cells and potentiates anti-PD-1 therapy," Nat. Nanotechnol., Aug. 2026. [Title and details to be verified from the original article; this entry was identified from a news summary]

[16] [Authors: import via Zotero], "Butyrate enhances oncolytic virotherapy (OBP-702) in colorectal cancer models," Cancer Immunol. Immunother., vol. 75, no. 1, Art. no. 10, 2025, doi: 10.1007/s00262-025-04252-4. [Verify exact title in Zotero]

[17] Y. He et al., "Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8+ T cell immunity," Cell Metab., vol. 33, no. 5, pp. 988–1000, 2021.

[18] D. A. Gaskarth, S. Fan, A. J. Highton, and R. A. Kemp, "The microbial metabolite butyrate enhances the effector and memory functions of murine CD8+ T cells and improves anti-tumor activity," Front. Med., vol. 12, Art. no. 1577906, 2025, doi: 10.3389/fmed.2025.1577906.

[19] Q. Shan et al., "Ectopic Tcf1 expression instills a stem-like program in exhausted CD8+ T cells to enhance viral and tumor immunity," Cell. Mol. Immunol., vol. 18, no. 5, pp. 1262–1277, 2021, doi: 10.1038/s41423-020-0436-5.

[20] Y. Liu et al., "LSD1 inhibition sustains T cell invigoration with a durable response to PD-1 blockade," Nat. Commun., vol. 12, Art. no. 6831, 2021, doi: 10.1038/s41467-021-27179-7.