WHIOCE PUBLISHING PTE. LTD.
PROVIDING
FIRST-CLASS SCIENTIFIC INFORMATION
FOR TOP SCHOLARS

2026 Volume 11, Issue 2
Advances in Precision Medicine
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

Exploring Immunotherapy Strategies for Oral Squamous Cell Carcinoma Microenvironment Based on Peptide-Mediated Signal Regulation

Shengwei Bao, Sen Yang*

[1]Zunyi Medical University, Zunyi 563000, Guizhou, China.

[2]Department of Oral and Maxillofacial Surgery, Suining Central Hospital, Suining 629000, Sichuan, China

**Author to whom correspondence should be addressed.*

Abstract: Oral squamous cell carcinoma (OSCC) is a difficult therapeutic challenge, with 50–60% of patients surviving for as long as 5 years, even now after many improvements in traditional therapy. The immunosuppressive tumor microenvironment (TME) of OSCC, which is rich in regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells (MDSCs), presents a significant obstacle to effective immunotherapy. Recent studies have shown that peptide-based therapies have the potential to regulate key signal transduction pathways in OSCC TME, and they have more advantages over traditional monoclonal antibodies, such as better tissue penetration, lower immunogenicity, and easier access to intracellular targets. This summary reviews the current understanding of peptide-mediated signal regulation strategies for modulation of the microenvironment in OSCC, which include immune checkpoint regulation, metabolic reprogramming of immunosuppressive cell populations, and combinatorial approaches combining traditional therapies. Some research data show that synthetic long peptides, antimicrobial peptides with anti-cancer properties, and self-assembling peptide biomaterials can promote the reprogramming of immunologically cold OSCC TME to an immunologically active state. Clinical translation is still in its infancy, and a combination of HPV-targeted peptide vaccines and checkpoint inhibitors has shown promise in head and neck squamous cell carcinoma. In the future, research will be extended to individualized neoantigen peptide vaccines, dual-checkpoint inhibitor peptides, and peptide-functionalized nanodelivery systems responsive to tumor microenvironmental stimuli. Overall analysis will build a model to help us understand the rational therapeutic strategy of peptide-based immunomodulation for OSCC.

Keywords: Oral squamous cell carcinoma; Tumor microenvironment; Peptide-based immunotherapy; Signal transduction pathways; Immune checkpoint modulation.

Online publication: February 26, 2026

1. Introduction

Oral squamous cell carcinoma, which belongs to oral cancer and accounts for over 90 percent of such cancers, is also one of the main public health problems worldwide at present; approximately 377,000 people are newly diagnosed with this disease globally each year [1]. Although some treatments have been applied in clinical practice, including surgical resection,

radiotherapy, and platinum-based combination chemotherapy, However, compared with more than three decades ago, there has been little improvement in the cure rate. Resistance of tumors to therapy in OSCC is mainly due to the complex immunosuppressive environment in the tumor microenvironment that actively subverts anti-tumor immune responses via multiple redundant pathways [2].

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have changed the treatment paradigm for recurrent or metastatic head and neck squamous cell carcinoma, and regulatory authorities have approved pembrolizumab and nivolumab for this indication [3]. The objective response rate of checkpoint inhibitor monotherapy in some patients is only about 15-20%, which means that most OSCC patients are still lacking effective treatment approaches under such therapy that cannot overcome the multilevel immunosuppressive state within tumors, thus making it urgent to develop a combination of immunotherapy for OSCC [4]. The tumor microenvironment, which is an essential factor influencing treatment response, consists of a complex system for cancer cells, immune cells, stromal components, and extracellular matrix elements that engage in continuous cross-talk through soluble factors or cell-to-cell communication [5].

Peptide-based therapeutics have become a promising approach to precision immunomodulation in the tumor microenvironment. Compared with monoclonal antibodies, therapeutic peptides have the advantages of a smaller molecular weight (~2-50 amino acids), a high degree of penetration into tissues due to their small size, a lower production cost by synthetic chemistry rather than a biological expression system, and access to intracellular signal molecules that are not available for antibodies [6]. Peptides also have lower immunogenicity and are more readily available for rational design to modulate specific protein-protein interactions involved in immunosuppressive signaling pathways. The drug situation is that the global market for peptide drugs has grown significantly, with more than 80 peptide drugs already on the market worldwide and a predicted total market value of approximately $50 billion.

The OSCC tumor microenvironment differs from that of other solid tumors in many aspects, mainly including chronic inflammation caused by carcinogenic factors such as tobacco and betel nuts, dysbiosis of the oral microbiota with an increase in oncogenic bacteria, and specific anatomical limitations of the oral cavity [7]. In view of the differences among them, OSCC-specific therapy cannot simply be inferred from other cancer types. Recent advances in the molecular structure of OSCC have revealed that numerous peptide-targetable signaling nodes are involved, including the JAK2/STAT3/PD-L1 axis, the PI3K/AKT/mTOR pathway regulating the metabolism of regulatory T cells, NF-κB-mediated inflammatory signaling, and the TGF-β/SMAD cascade promoting the activation of Cancer-Associated Fibroblasts (CAFs) [8].

This paper carries out a comprehensive analysis of strategies for regulating the signal by peptides in targeting the OSCC tumor microenvironment, synthesizes mechanistic insight, and synthesizes clinical translation of preclinical evidence and efforts. The following sections will examine the immunosuppressive situation of OSCC, peptide-based modulation of key signaling pathways, therapeutic applications, and challenges to clinical application. By systematically reviewing relevant literature at home and abroad, this article aims to build a concept system for the rational design of peptide immunotherapy drugs for oral squamous cell carcinoma.

2 . The Immunosuppressive Landscape of OSCC Tumor Microenvironment

The tumor microenvironment of oral squamous cell carcinoma is an immunologically hostile environment that has developed through coordinated suppression of anti-tumor immune responses via multiple pathways [9]. Comprehensive immunophenotyping studies using mass cytometry and single-cell RNA sequencing have shown that OSCC tumors are primarily infiltrated by immunosuppressive cell populations rather than effector lymphocytes and thus exhibit an immunologically cold phenotype that is resistant to conventional immunotherapy. The significant cellular components that contribute to immune evasion include CD4+CD25+FOXP3+ regulatory T cells, M2-polarized tumor-associated macrophages, and MDSCs of the granulocytic and monocytic subtypes.

Regulatory T cells are one of the key obstacles to anti-tumor immune responses in OSCC, and their frequency in peripheral blood and tumors is negatively correlated with patient survival. These cells inhibit the effector T cell response

through several mechanisms, including the consumption of IL-2 by high-affinity CD25 expression, the secretion of immunosuppressive cytokines such as IL-10 and TGF-β, and the direct cytotoxicity of granzyme B-mediated effector cells. Transcription factor FOXP3 plays a central role in determining the Treg fate, and its inhibitory activity is retained via association with NFAT1, etc. Metabolic reprogramming is a hallmark of tumor-infiltrating Tregs, and the activation of the PI3K/AKT/mTOR pathway enhances their competitive fitness in the nutrient-poor tumor microenvironment. Therapeutic strategies that target Treg depletion or functional inhibition need to be avoided for systemic autoimmunity, and at the same time, they should achieve tumor-selective immunomodulation [10].

Tumor-associated macrophages are the primary type of immune cell in many OSCC samples and can be activated in different ways, such as the tumoricidal classical activation mode of M1 macrophages and the promotion of angiogenesis, tissue remodeling, and immune suppression of alternative activation mode M2 [11-14]. The IL-4 receptor and colony-stimulating factor 1 receptor send signals to keep the M2 polarization state going. STAT6, IRF4, and PPARγ drive transcriptional programs. These cells have a lot of the mannose receptor CD206, the hemoglobin scavenger receptor CD163, and the immune checkpoint ligand PD-L1. CAFs are another important part of the stroma [15, 16]. They release transforming growth factor beta, which stops dendritic cells from maturing and activating cytotoxic T lymphocytes. They also change the extracellular matrix by crosslinking collagen with lysyl oxidase. The dense fibrous stroma of OSCC makes it hard for immune cells to get in and makes it hard for therapeutic antibodies to work.

Signal transduction pathways that orchestrate immunosuppression in the OSCC microenvironment have been extensively characterized through phosphoproteomic analyses and functional genomic screens. The JAK2/STAT3 pathway has become a key factor in immune escape, and constitutive STAT3 phosphorylation was observed in more than 50 percent of the OSCC samples [17, 18]. Activated STAT3 directly transactivates PD-L1 expression in tumor cells, confers resistance to cisplatin-induced apoptosis, and promotes epithelial-mesenchymal transition. Crosstalk among the JAK2/STAT3 and MAPK/AP1 pathways amplifies immunosuppressive signals through synergistic effects. The NF-κB pathway regulates the expression of pro-inflammatory cytokines, such as IL-6, IL-8, and VEGF; recruits MDSCs; and promotes angiogenesis. The aforementioned interconnected signalling networks offer multiple targets that are susceptible to peptide-based therapeutic intervention, as outlined in the subsequent sections. These interconnected signalling networks have many intervention points that are susceptible to peptide-based therapeutic modulation, as summarized in Table 1.

Table 1. Main Signalling pathways and peptide-based interventions in the tumor microenvironment of OSCC.

Signaling Pathway	Primary Function in TME	Peptide Intervention	Mechanism of Action
JAK2/STAT3/PD-L1	PD-L1 upregulation, chemoresistance, EMT	STAT3 inhibitory peptides, JAK2-targeting peptides	Disruption of STAT3 dimerization and nuclear translocation
PI3K/AKT/mTOR	Treg metabolic fitness, survival	PI3K-selective peptide inhibitors	Selective Treg depletion via metabolic disruption
PD-1/PD-L1 checkpoint	T cell exhaustion, immune tolerance	DPPA-1, P-F4, cyclic PD-L1 blockers	Competitive inhibition of PD-1/PD-L1 interaction
FOXP3/NFAT1	Treg suppressive function	P60, FOXP3 393-403 inhibitory peptides	Disruption of FOXP3-NFAT1 protein interaction
CD206/mannose receptor	M2 macrophage polarization	RP-182 reprogramming peptide	M2 to M1 macrophage repolarization

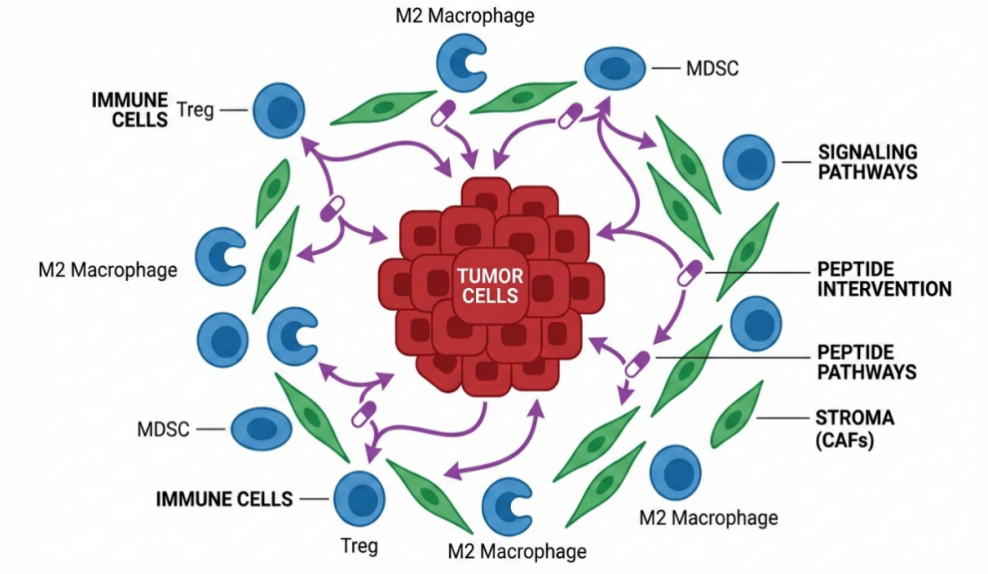

Figure 1. Schematic illustration of the OSCC tumor microenvironment and peptide-mediated immunotherapy strategies.

Figure 1 shows the complex cellular structure and signal network within the oral squamous cell carcinoma (OSCC) tumor microenvironment (TME). At the center, the red aggregated tumor cells are surrounded by a variety of stroma, mainly green spindle-shaped CAFs. The surrounding blue immune cells constitute a robust immunosuppressive niche, which includes regulatory T cells (Tregs), M2 macrophages (that promote tumor growth and suppress immunity), and MDSCs. These components have complicated crosstalk, which is mediated by a variety of signaling pathways that are depicted as purple arrows. In the peptide intervention part, a purple pill-shaped icon is placed at the site to indicate the site of peptide intervention. Therapeutic peptides can regulate specific paths in the peptide pathway to break through pro-tumorigenic signals and restore anti-tumor immune responses.

3. Peptide-Based Signal Regulation Strategies

Therapeutic peptides for OSCC tumor microenvironment regulation can be functionally divided into immune checkpoint inhibitor peptides, cell-penetrating peptides that disrupt intracellular signal transduction, antimicrobial peptides with immunomodulatory activity, and self-assembling peptide biomaterials that act as carriers [19, 20]. Immune checkpoint modulation is currently the most clinically advanced area, and a large number of peptide antagonists have been developed for PD-1/PD-L1, CTLA-4, LAG-3, and other emerging checkpoints. D-peptide DPPA-1 has a high affinity for PD-L1, and incorporation into matrix metalloproteinase-responsive nanoparticles enables tumor-selective release. Cyclic peptides targeting PD-L1 exhibit higher metabolic stability than linear ones, and macrocyclization confers resistance to proteolytic degradation while retaining binding affinity.

The peptide P-F4 binds to programmed death-1 with a dissociation constant of 0.119 micromolar and competitively inhibits the binding of PD-L1 [21]. When formulated as nanoparticles, P-F4 increased the infiltration of CD8+ T cells and simultaneously decreased the proportion of regulatory T cells in the tumor environment of murine models. One of the more creative ways is the use of dual-checkpoint inhibitory peptides, such as CSBP, which simultaneously inhibit the CD24/Siglec-10 is an innate immune checkpoint that regulates macrophage phagocytosis and the PD-1/PD-L1 adaptive immune checkpoint. Such a bifunctional peptide can be designed to link the innate immune system and the adaptive immune system, and it can also be used in conjunction with radiotherapy. The development of dual-targeting peptides is a new direction for the improvement of single-checkpoint blockade, aimed at breaking through the limitations brought about by the redundancy of immunosuppressive mechanisms in the tumor microenvironment.

Cell-penetrating peptides can regulate intracellular signal transduction pathways that have been considered undruggable using conventional antibodies. Transcription factor STAT3 is a target of OSCC that needs to be inhibited, as it participates in the regulation of many oncogenic processes. STAT3 inhibitory peptides interfere with the SH2 domain-mediated dimerization process, thereby preventing nuclear translocation and transcriptional activation. Similarly, peptides that target the FOXP3-NFAT1 interaction in regulatory T cells can also functionally inactivate these suppressor cells without requiring systemic depletion. Peptide P60 can inhibit the transcription of FOXP3, and after being conjugated with a CD28-targeted aptamer for Treg-selective delivery, it shows anti-tumor activity at concentrations 200 times lower than those of unconjugated forms. This approach has high-precision target coverage and thus reduces off-target effects and increases the safety margin of treatment.

Antimicrobial peptides are a kind of novel therapy that connects the oral microbiome-immunity pathway for OSCC. The cationic antimicrobial peptide NRC-03 selectively enters OSCC cells without harming normal oral keratinocytes, inducing apoptosis via cyclophilin D-mediated mitochondrial permeability transition pore opening and oxidative stress. Piscidin-1 is a marine-derived antimicrobial peptide that can induce both the intrinsic and extrinsic apoptotic pathways of cells, as well as inhibit angiogenesis by suppressing the migration and tube formation of endothelial cells. The human cathelicidin LL-37 has tissue-specific anti-cancer effects on OSCC and induces apoptosis by regulating the p53-Bcl-2/BAX pathway and caspase-3. Antibacterial peptides have a direct bactericidal effect on bacteria, can alter the structure of the oral microenvironment, and inhibit oncogenic bacteria such as Porphyromonas gingivalis and Fusobacterium nucleatum; they also change The state of chronic inflammation caused by specific compositions of the oral microbiota for OSCC.

Self-assembling peptide-based biomaterials can achieve precise, controlled drug release of immunotherapy drugs at the tumor microenvironment. The multidomain peptide with the sequence K2(SL)6K2 spontaneously forms nanofiber hydrogel under physiological conditions and can be used as an injectable scaffold for the sustained release of STING agonists. The STINGel platform transforms immunologically cold tumors into immunologically hot tumors by activating the cGAS-STING pathway, inducing the production of type I interferons and the maturation of dendritic cells. In a murine oral cancer model, STINGel achieved 60% long-term survival compared to 10% for free STING agonist; all survivors showed complete tumor rejection upon rechallenge, suggesting the establishment of immunological memory. The following SynerGel formulation contains the drug-mimicking peptide L-NIL-MDP, which inhibits inducible nitric oxide synthase and simultaneously releases STING agonists; by dual pathways, it achieves immunomodulation to remove immunosuppression and activate the immune system.

4. Clinical Translation and Therapeutic Challenges

The clinical translation of peptide-based immunotherapies for OSCC is still in its infancy, and among them, the most advanced programs are focused on peptide vaccines for HPV-positive oropharyngeal cancer. The ISA101 vaccine consists of 13 synthetic long peptides that cover HPV-16 E6 and E7 oncoproteins, designed to induce broad CD4+ and CD8+ T cell responses against the viral antigen. A Phase II clinical trial of ISA101 combined with nivolumab involved 24 patients with incurable HPV-16-positive cancers, primarily oropharyngeal squamous cell carcinoma. The overall response rate reached 33%, which is roughly twice that of the CheckMate-141 trial at about 16% for nivolumab monotherapy. Two patients achieved a durable complete response for more than 4.5 years, and biomarker analysis showed that proteasome pathway enrichment and interferon-γ response signatures in the baseline tumor biopsy were strongly associated with clinical benefit. These encouraging results have been granted the Fast Track designation by the US Food and Drug Administration for ISA101b in September 2021.

HPV-targeted vaccines are not the only type; some peptide vaccines are also being studied for use in head-and-neck squamous cell carcinoma. A Phase II clinical trial of multi-peptide vaccination targeting the LY6K, CDCA1, and IMP3 antigens showed that cytotoxic T lymphocyte induction rates were 85.7%, 64.3%, and 42.9%, respectively, in HLA-A24-

positive head-and-neck squamous cell carcinoma patients, and the immune response was positively correlated with overall survival. Personalized neoantigen peptide vaccines are a new frontier of research that combines whole-exome sequencing with patient-specific mutations and synthesizes customized peptide cocktails. Early studies have shown that it is feasible and immunogenic, and one Phase I trial reported a 5-year disease-free survival rate for some patients, including head and neck cancer patients. The high mutational burden of tobacco-associated OSCC makes this type of malignant tumor more suitable for neoantigen vaccination.

Although it has shown encouraging results in preclinical studies and initial clinical applications, peptide immunotherapy for OSCC is still far from being widely used in clinics. Pharmacokinetic constraints, such as quick renal excretion, protein degradation, and low oral absorption rate, are often associated with a lack of efficacy; therefore, there may be frequent dosing or complex drug delivery systems. A dense fibrous stroma and hypoxic microenvironment of OSCC are all adverse conditions for peptide penetration. There may be immunogenicity due to prolonged exposure to peptides, and neutralizing antibodies that affect the therapeutic effect are likely to be produced. Patient selection is still imperfect, and biomarkers predictive of the response to peptide immunotherapy have not been validated in prospective trials. There are still no regulatory paths clarified for personalized peptide vaccines, and standardization of production processes and quality control of patient-specific products remain unresolved issues. Combination strategies combining peptide therapeutics with other modalities or immunotherapies also need to undergo rigorous clinical trials to determine the best application sequence, dose, and target patient. To this end, interdisciplinary cooperation among peptide chemistry, immunology, pharmaceutical science, and clinical oncology will need to be realized. Selected clinical trials of peptide-based immunotherapy for OSCC/HNSCC from 2020 to 2025 are listed in Table 2.

Table 2. Selected Clinical Trials of Peptide-Based Immunotherapy for OSCC/HNSCC (2020-2025)

Trial ID / Vaccine	Phase	Target Antigen	Combination	Key Outcome
ISA101/ISA101b	Phase II	HPV-16 E6/E7	Nivolumab	ORR 33%; 2 CRs > 4.5 years
Multi-peptide (LY6K/CDCA1/IMP3)	Phase II	LY6K, CDCA1, IMP3	Monotherapy	CTL induction 85.7%/64.3%/42.9%
UV1 (hTERT peptides)	Phase II	Telomerase (hTERT)	Pembrolizumab	Ongoing enrollment
PGV001 (neoantigen)	Phase I	Personalized neoantigens	Monotherapy	5-year DFS in HNSCC subset
mRNA-4157 (neoantigen)	Phase I	mRNA-encoded neoantigens	Pembrolizumab	Safety and immunogenicity established

5. Conclusion

Peptide-mediated signal regulation is a scientific and reasonable approach to the immunosuppressive tumor microenvironment of oral squamous cell carcinoma that holds promise for clinical application. The specific advantages of therapeutic peptides, such as their ability to enhance tissue penetration, target intracellular sites, and be rationally designed, place them in a position to act as an effective supplement to traditional immunotherapy. Molecular mechanisms have identified numerous peptide-targetable signalling nodes in the OSCC microenvironment, including immune checkpoints, metabolic pathways of immunosuppressive cells, and inflammatory cascades. Preclinical research has demonstrated that peptides can effectively remold the immunologically cold OSCC tumor microenvironment by checkpoint blockade, macrophage repolarization, regulatory T-cell depletion, and innate immune activation.

Clinical translation has begun, and the HPV-targeted peptide vaccine shows encouraging efficacy signals when used in combination with checkpoint inhibitors; the response rate is higher than that of checkpoint inhibitor monotherapy, and durable complete responses have been observed in some patients. In the future, the research directions should focus on

the personalisation of neoantigen peptide vaccines for HPV-negative OSCC, the dual-checkpoint inhibitory peptides that connect innate and adaptive immunity, antimicrobial peptides that utilise the oral microbiome-immunity axis, and self-assembling peptide biomaterials for controlled immunotherapeutic delivery. In light of the pharmacokinetic limitations, by optimizing the delivery system, identifying predictive biomarkers, and establishing rational combination strategies, it is expected that the full therapeutic potential of peptide-based immunomodulation in oral squamous cell carcinoma will be fully realized.

Disclosure statement

The author declares no conflict of interest.

References

[1] Xue N, Wang Y, Wang Z, et al., 2025, Trends in Immunotherapy for Oral Squamous Cell Carcinoma. *Cellular Oncology*, 1-21.

[2] Ruffin AT, Li H, Vujanovic L, et al., 2023, Improving Head and Neck Cancer Therapies by Immunomodulation of the Tumour Microenvironment. *Nature Reviews Cancer*, 23(3): 173-188.

[3] Furukawa N, Popel AS, 2021, Peptides That Immunoactivate the Tumor Microenvironment. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, 1875(1): 188486.

[4] De Sousa LG, Rajapakshe K, Canales JR, et al., 2022, ISA101 and Nivolumab for HPV-16+ Cancer: Updated Clinical Efficacy and Immune Correlates of Response. *Journal for Immunotherapy of Cancer*, 10(2): e004232.

[5] Gan M, Liu N, Li W, et al., 2024, Metabolic Targeting of Regulatory T Cells in Oral Squamous Cell Carcinoma: New Horizons in Immunotherapy. *Molecular Cancer*, 23(1): 273.

[6] Leach DG, Dharmaraj N, Lopez-Silva TL, et al., 2021, Biomaterial-Facilitated Immunotherapy for Established Oral Cancers. *ACS Biomaterials Science & Engineering*, 7(2): 415-421.

[7] Hou D, Hu F, Mao Y, et al., 2022, Cationic Antimicrobial Peptide NRC-03 Induces Oral Squamous Cell Carcinoma Cell Apoptosis via CypD-mPTP Axis-Mediated Mitochondrial Oxidative Stress. *Redox Biology*, 54: 102355.

[8] Elmusrati A, Wang J, Wang CY, 2021, Tumor Microenvironment and Immune Evasion in Head and Neck Squamous Cell Carcinoma. *International Journal of Oral Science*, 13(1): 24.

[9] Zhang X, Wu Y, Lin J, et al., 2024, Insights into Therapeutic Peptides in the Cancer-Immunity Cycle: Update and Challenges. *Acta Pharmaceutica Sinica B*, 14(9): 3818-3833.

[10] Sui X, Niu X, Zhou X, et al., 2023, Peptide Drugs: A New Direction in Cancer Immunotherapy. *Cancer Biology & Medicine*, 21(3): 198.

[11] Wu K, Lin K, Li X, et al., 2020, Redefining Tumor-Associated Macrophage Subpopulations and Functions in the Tumor Microenvironment. *Frontiers in Immunology*, 11: 1731.

[12] Wang N, Wang S, Wang X, et al., 2021, Research Trends in Pharmacological Modulation of Tumor-Associated Macrophages. *Clinical and Translational Medicine*, 11(1): e288.

[13] Wang S, Sun J, Dastgheyb RM, et al., 2022, Tumor-Derived Extracellular Vesicles Modulate Innate Immune Responses to Affect Tumor Progression. *Frontiers in Immunology*, 13: 1045624.

[14] Hourani T, Sharma A, Luwor RB, et al., 2025, Transforming Growth Factor-β in Tumor Microenvironment: Understanding Its Impact on Monocytes and Macrophages for Its Targeting. *International Reviews of Immunology*, 44(2): 82-97.

[15] D'Arcangelo E, Wu NC, Cadavid JL, et al., 2020, The Life Cycle of Cancer-Associated Fibroblasts Within the Tumour Stroma and Its Importance in Disease Outcome. *British Journal of Cancer*, 122(7): 931-942.

[16] Xu M, Zhang T, Xia R, et al., 2022, Targeting the Tumor Stroma for Cancer Therapy. *Molecular Cancer*, 21(1): 208.

[17] Jha A, Alam M, Kashyap T, et al., 2023, Crosstalk Between PD-L1 and Jak2-Stat3/MAPK-AP1 Signaling Promotes Oral Cancer Progression, Invasion and Therapy Resistance. *International Immunopharmacology*, 124: 110894.

[18] Khatoon E, Hegde M, Kumar A, et al., 2022, The Multifaceted Role of STAT3 Pathway and Its Implication as a Potential Therapeutic Target in Oral Cancer. *Archives of Pharmacal Research*, 45(8): 507-534.

[19] Moreno-Vargas LM, Prada-Gracia D, 2024, Exploring the Chemical Features and Biomedical Relevance of Cell-Penetrating Peptides. *International Journal of Molecular Sciences*, 26(1): 59.

[20] Khonakdar H, Ehsani M, Naderi G, et al., 2025, Recent Advances in Injectable Stimuli-Responsive Hydrogels for Biomedical Applications. *Journal of Polymers and the Environment*, 33(8): 3512-3554.

[21] Tao H, Cheng L, Liu L, et al., 2020, A PD-1 Peptide Antagonist Exhibits Potent Anti-Tumor and Immune Regulatory Activity. *Cancer Letters*, 493: 91-101.