

Recent Advances in Nanotechnology for the Prevention and Management of OSCC

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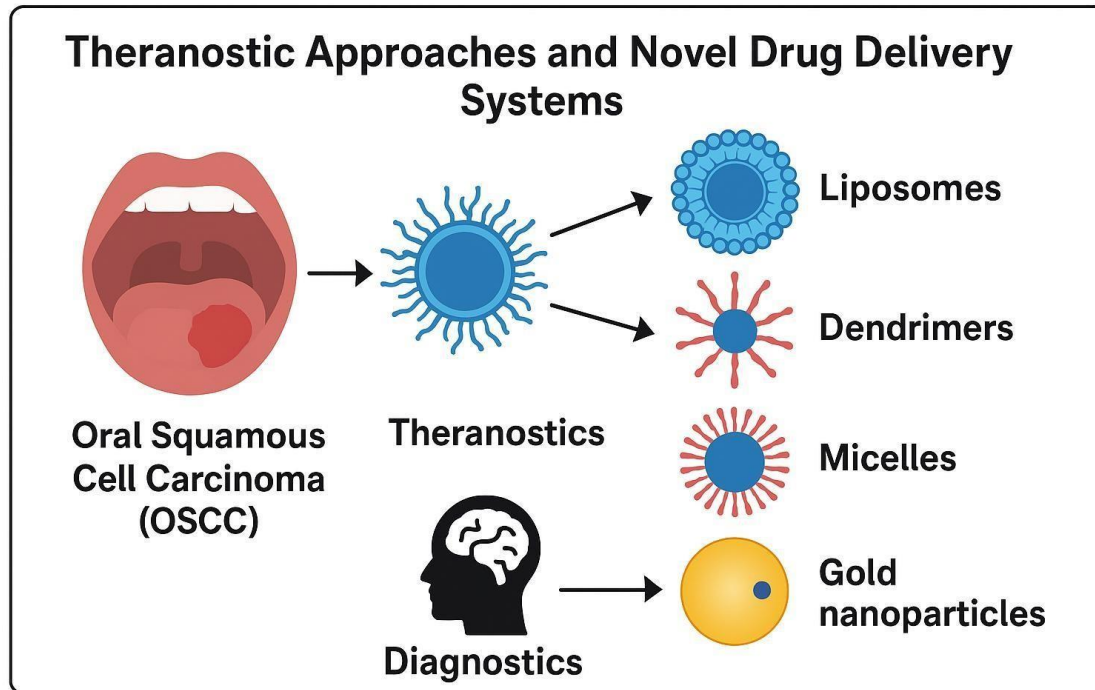
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ABSTRACT

Oral Squamous Cell Carcinoma (OSCC) is among the most common malignancies globally, contributing substantially to oral cancer-related morbidity and mortality. Traditional treatment methods, including surgery, radiation therapy, and chemotherapy, exhibit limitations such as non-specific medication distribution, systemic toxicity, and recurrence. Recent breakthroughs in nanotechnology and drug delivery technologies have resulted in the development of theranostic techniques, which provide both therapeutic and diagnostic functions within a single platform. Novel drug delivery systems (NDDS) facilitate targeted drug administration, augment bioavailability, and reduce adverse effects, ultimately enhancing patient outcomes. The shift from traditional treatment to theranostic intervention utilises nanoparticles, liposomes, dendrimers, and micelles to encapsulate anticancer drugs, facilitating controlled and localised medication release. Moreover, intelligent nanocarriers that include imaging agents provide real-time observation of drug distribution and tumour response, allowing for personalised treatment approaches. Diverse nanoplateforms, including gold nanoparticles, quantum dots, and mesoporous silica nanoparticles, have been thoroughly investigated for their multifunctionality in the therapy of OSCC. Moreover, biomimetic and stimuli-responsive drug delivery systems boost therapeutic efficacy while minimising systemic toxicity. This study underscores the transition from conventional OSCC treatments to nanomedicine-based theranostic strategies, highlighting their potential to transform oral cancer therapy. Notwithstanding significant progress, obstacles including large-scale manufacturing, regulatory approvals, and clinical implementation must be resolved for general acceptance. Future research should concentrate on enhancing nanoplateforms to attain precision oncology, hence improving prognostic and therapeutic results for OSCC patients. The amalgamation of NDDS with artificial intelligence and personalised medicine may further transform OSCC treatment, establishing theranostics as a fundamental element in oral cancer management.

Keywords: OSCC, Theranostic, Intervention, Novel Drug Delivery Systems, Nanoformulation

Graphical Abstract



Highlights

1. OSCC remains a major global health burden with limitations in traditional therapies.
2. Theranostic nanocarriers combine therapeutic and diagnostic functions for precision treatment.
3. NDDS such as liposomes, dendrimers, micelles, and nanoparticles enable targeted drug delivery.
4. Stimuli-responsive and biomimetic systems enhance efficacy while reducing systemic toxicity.
5. Integration of nanomedicine with AI and personalized medicine promises transformative OSCC management.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a common malignancy, constituting a substantial percentage of head and neck cancers globally. Although progress in standard treatments like surgery, radiation, and chemotherapy, OSCC continues to pose a significant clinical challenge due to its elevated recurrence rate, therapeutic resistance, and negative consequences linked to conventional treatment methods (Kumar, 2025). Theranostic techniques in innovative drug delivery systems (NDDS) present a promising alternative by combining diagnosis and therapy into a unified platform. This paradigm shift aims to augment the effectiveness of OSCC treatment while reducing side effects and enhancing patient outcomes (Farooq and Bugshan, 2020; S. A. Kumar et al., 2020).

Traditional therapies for OSCC frequently lead to non-specific targeting, systemic toxicity, and suboptimal therapeutic effectiveness. Chemotherapeutic drugs like cisplatin, 5-fluorouracil, and paclitaxel, although helpful in inhibiting tumours, are linked to considerable deleterious effects on healthy tissues. Moreover, radiation therapy results in consequences such as mucositis, xerostomia, and osteoradionecrosis, which negatively affect the patient's quality of life. The absence of specificity and the emergence of medication resistance create an urgent demand for more effective and focused therapies. Innovative drug delivery methods, especially those utilising theranostic tactics, have arisen as a revolutionary method to address these constraints (Morris et al., 2019; Tran et al., 2023).

Nanotechnology-based drug delivery has garnered significant interest in the treatment of OSCC owing to its capacity to augment drug bioavailability, boost tumour targeting, and diminish systemic toxicity. A variety of nanocarriers, including liposomes, dendrimers, polymeric nanoparticles, and metallic nanoparticles, have been examined for their capability to carry therapeutic medicines accurately (V. Kumar et al., 2020). Liposomal formulations, including pegylated liposomal doxorubicin, exhibit enhanced pharmacokinetics and decreased cardiotoxicity, rendering them viable options for the

treatment of OSCC. Polymeric nanoparticles have been designed to provide regulated and prolonged drug release, hence enhancing therapeutic efficacy and reducing off-target effects (Vandana et al., 2024). The amalgamation of imaging modalities with nanocarrier-based drug delivery has facilitated theranostic strategies, allowing for real-time observation of therapeutic efficacy. Theranostic nanoparticles can be modified with imaging agents, such as quantum dots, iron oxide nanoparticles, or gold nanoparticles, facilitating multimodal imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and fluorescence imaging (Manikkath et al., 2023). This real-time visualisation offers critical insights into drug distribution, tumour advancement, and therapy effectiveness, therefore enabling tailored therapeutic strategies for OSCC patients (Li et al., 2022; Viglianisi et al., 2024).

The theranostic concept, targeted medication delivery guarantees the particular concentration of therapeutic substances at the tumour site and hence reduces systemic toxicity. Designed to target particular biomarkers overexpressed in OSCC, such as epidermal growth factor receptor (EGFR), CD44, and integrins, ligand-functionalized nanoparticles (Scholtz et al., 2022; Wei et al., 2023). These nanoparticles increase cellular absorption and promote medication retention in the tumour microenvironment by including targeted moieties such as peptides, aptamers, and monoclonal antibodies. A significant problem in traditional chemotherapy, drug resistance is less likely with this focused strategy as it not only increases therapeutic effectiveness. Gene therapy-based treatments have also been investigated with regard to theranostic drug delivery systems for OSCC (Peiqi et al., 2016). Oncogenes have been silenced and tumor-suppressor pathways changed by means of RNA interference (RNAi) techniques including small interfering RNA (siRNA) and microRNA (miRNA). Nanocarriers shielding these genetic payloads from enzymatic breakdown guarantee effective intracellular delivery. Furthermore, the coupling of gene therapy with imaging techniques allows for real-time evaluation of gene expression and therapeutic response, hence improving the accuracy of OSCC treatment (Farooq and Bugshan, 2020).

The use of stimuli-responsive nanocarriers offers another interesting path in theranostic medication delivery. Designed to release its payload in reaction to particular stimuli including pH, temperature, enzyme activity, or redox potential inside the tumour microenvironment, these smart drug delivery systems For example, pH-sensitive nanoparticles take use of the acidic character of tumour tissues to activate medication release particularly at the cancer site, hence reducing systemic exposure. Likewise, enzyme-responsive nanoparticles use the overexpression of matrix metalloproteinases (MMPs) in OSCC to accomplish targeted drug activation. By lowering undesired side effects and enhancing patient compliance, these clever delivery systems provide a very controlled and exact therapeutic approach (da Costa et al., 2022).

Immunotherapy's part in OSCC treatment has attracted much interest; theranostic techniques have been crucial in improving its effectiveness. Promising outcomes in enhancing anticancer immune responses have been seen with immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies. Their therapeutic potential has been even more increased by the inclusion of nanocarriers for the directed administration of immunomodulatory chemicals (Rebaudi et al., 2023; Sami et al., 2020). Theranostic nanoparticles designed to co-deliver imaging probes and immune checkpoint inhibitors allow real-time tracking of immunological reactions, hence optimising treatment schedules for OSCC patients. Representing creative theranostic solutions, photothermal and photodynamic therapies (PTT and PDT) use light-responsive nanoparticles for cancer treatment. Extensive research has been done on gold nanoparticles, graphene-based nanomaterials, and upconversion nanoparticles for their photothermal and photodynamic qualities (Lohavanichbutr et al., 2012). These nanoparticles produce localised hyperthermia or reactive oxygen species (ROS) upon exposure to near-infrared (NIR) light, hence selectively destroying tumour cells. PTT and PDT's dual function of imaging and therapy enables exact tumour ablation while reducing injury to adjacent healthy tissues. Combining these treatments with traditional chemotherapy or immunotherapy increases the general therapeutic effectiveness against OSCC (Longo et al., 2013; Siyuan et al., 2023).

Theranostic drug delivery systems hold great promise, but several obstacles still need to be overcome for their effective clinical translation. In the evolution of nanocarrier-based therapies, biocompatibility, stability, and large-scale production stay major issues. The intricacy of the tumour microenvironment also calls for the construction of multifunctional nanocarriers able to overcome biological barriers and attain effective tumour penetration. Bringing theranostic nanomedicines to mainstream clinical practice is further made more difficult by regulatory obstacles and the requirement for thorough preclinical and clinical studies (Rizvi et al., 2024; Yang et al., 2022).

OSCC theranostic research should emphasise the creation of individualised and precision-based therapy techniques. Theranostic nanomedicine's integration of artificial intelligence (AI) and machine learning (ML) offers significant promise for optimising drug formulations, forecasting therapy responses, and customising therapies depending on particular patient profiles (Sharma et al., 2023). Furthermore, developments in 3D bioprinting and bioengineering could help to generate patient-specific tumour models for preclinical testing, hence speeding the clinical transfer of theranostic drug delivery systems (Singh, 2023). The redefining of OSCC intervention from traditional treatment methods to theranostic-based new drug delivery systems marks a major development in cancer therapy. Theranostic nanomedicine provides a revolutionary way to increase the efficacy, safety, and accuracy of OSCC management by integrating targeted medication delivery with real-time imaging and individualised treatment plans. Ongoing study and technical breakthroughs in this area have the power to transform cancer treatment and enhance results for those suffering with this aggressive cancer (Nelonda and Setiadihi, 2018; Sami et al., 2020).

The most common and dangerous types of cancer still affecting the mouth is oral squamous cell carcinoma (OSCC). Often

linked with major adverse effects, conventional treatment methods including surgery, chemotherapy, and radiation therapy have had little effectiveness in attaining total remission. Targeted, efficient, and patient-specific therapies have driven theranostic techniques using new drug delivery systems (NDDS) (Alam et al., 2021; Gnananath et al., 2017; Zafar et al., 2022). By allowing exact medication distribution, real-time monitoring, and improved treatment efficacy, theranostics a mix of therapy and diagnostics is transforming OSCC management (Kakabadze et al., 2020).

Limitations of Conventional OSCC Treatments

Traditional OSCC therapies depend mostly on systematic chemotherapy, which is non-specific and causes major damage in healthy organs. Furthermore, a major difficulty is resistance to chemotherapeutic drugs, which calls for the creation of substitute approaches. By increasing medication solubility, boosting bioavailability, and allowing targeted delivery to cancer areas while reducing negative effects, NDDS has offered a hopeful answer. Among these innovative ideas are biomimetic systems providing better pharmacokinetics and pharmacodynamics, micelles, dendrimers, liposomes, and nanotechnology-based drug carriers (Gopalakrishna Madhura et al., 2023; Husain et al., 2020).

Theranostic Approaches and Novel Drug Delivery Systems

Theranostic approaches and novel drug delivery systems (NDDS) are emerging as transformative strategies for improving the management of Oral Squamous Cell Carcinoma (OSCC). Theranostics, which combine therapeutic and diagnostic functions into a single platform, provide the dual advantage of treating cancer while simultaneously monitoring treatment response in real time. Advanced nanocarriers such as liposomes, micelles, dendrimers, solid lipid nanoparticles, and polymeric nanoparticles have been engineered to enhance drug solubility, stability, and bioavailability (Bukhari et al., 2021; Kapoor et al., 2023; Kola et al., 2023). These systems enable site-specific delivery by functionalizing nanoparticles with targeting ligands, thereby increasing drug accumulation at tumor sites and reducing systemic toxicity. Furthermore, stimuli-responsive nanocarriers release drugs in response to tumor-specific triggers like acidic pH, enzyme activity, or external stimuli such as light and ultrasound, offering precise spatiotemporal control. Integration with imaging modalities including MRI, PET, and fluorescence further enhances disease monitoring. Collectively, these theranostic and NDDS strategies promise more effective, safer, and personalized OSCC therapies, improving clinical outcomes significantly (Saeed et al., 2023; Thakur and Kutty, 2019).

Nanoparticle-Based Drug Delivery

Systems of medication delivery based on nanoparticles have become fundamental to OSCC theranostics. Engineered nanoparticles liposomes, polymeric nanoparticles, and metal-based nanoparticles among them help to encapsulate and release chemotherapeutic drugs under control. For example, liposomal drug carriers increase the stability of hydrophobic medications and enable extended circulation, hence lowering systemic toxicity. Through improved permeability and retention (EPR) effects, polymeric nanoparticles especially those functionalised with ligands targeting particular cancer cell receptors enable selective drug accumulation in tumour tissues. Metal-based nanoparticles as well, particularly gold and silver ones, have particular optical and photothermal qualities that support therapeutic and imaging (Bhattacharya, 2022; Gharat et al., 2016; Holpuch et al., 2010).

Dendrimers and Micelles

In OSCC therapy, highly branched polymeric nanocarriers known as dendrimers have attracted interest as possible drug delivery systems. Their well-defined structure and several functional groups let one combine targeted ligands, imaging indicators, and therapeutic drugs. Dendrimers are efficient theranostic platforms because of their multifunctionality, which combines diagnostic functions and medication delivery in one nanosystem (Alven and Aderibigbe, 2020; Safari and Zarnegar, 2014; Venditti, 2019). Because of their great surface functionalisation, dendrimers are perfect carriers for chemotherapeutic medicines, nucleic acids, and imaging agents. Their nanoscale size improves penetration into tumour tissues, therefore enabling focused therapy with minimal off-target effects. Dendrimers can also be designed to react to particular stimuli, such pH changes or enzyme activity, so guaranteeing controlled and site-specific drug release. In OSCC intervention, dendrimers are made more useful by these qualities since they enhance treatment results and lower systemic toxicity (Estanqueiro et al., 2015).

The theranostic strategy to OSCC treatment is significantly influenced by micelles, self-assembling amphiphilic molecules. While their hydrophilic shells increase circulation and bioavailability, these nanocarriers are made up of hydrophobic cores enclosing poorly soluble medications (Mukherjee et al., 2022). Micelles special structure lets them increase the solubility and stability of chemotherapy drugs, hence improving their therapeutic effectiveness. Moreover, micelles can be changed with targeting ligands to provide site-specific drug delivery, hence boosting accumulation at tumour sites and reducing systemic exposure. Stimuli-responsive micelles offer a regulated and continuous drug release mechanism by releasing medications in reaction to environmental cues including pH changes or enzyme activity (Estanqueiro et al., 2015). This function guarantees that therapeutic chemicals are sent exactly to malignant tissues, hence lowering adverse effects connected with traditional therapies. Micelles combination of drug delivery and imaging capabilities makes them a useful part of theranostic OSCC techniques since they allow real-time tracking of treatment response and enhance general clinical results (Safari and Zarnegar, 2014).

Biomimetic Drug Delivery Systems

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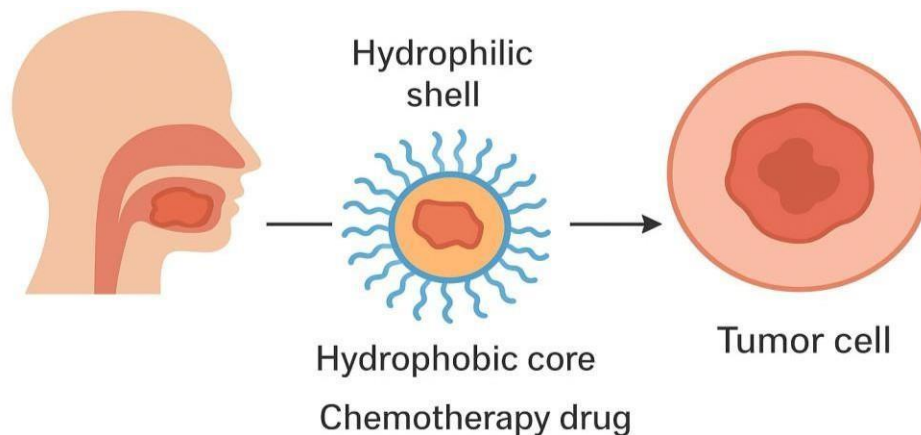


Figure 1: OSCC treatment by targeted drug delivery, improved solubility, and real-time theranostic monitoring.

Integration of Imaging and Theranostics

Theranostics also gains from NDDS's integration with imaging modalities including fluorescence imaging, positron emission tomography (PET), and magnetic resonance imaging (MRI). These imaging techniques offer insightful analysis of drug distribution, tumour development, and therapy effectiveness. For example, superparamagnetic iron oxide nanoparticles (SPIONs) can provide contrast in MRI and carry therapeutic payloads, hence allowing non-invasive tracking of drug localisation. Analogously, fluorescent nanoparticles and quantum dots help to enable precise medical strategies by means of real-time visualisation of drug release dynamics and cellular absorption (Jiao et al., 2022; Zhang et al., 2022).

Stimuli-Responsive Drug Delivery Systems

The application of stimuli-responsive drug delivery devices is another encouraging development in OSCC theranostics. These systems let out therapeutic compounds in reaction to particular tumour microenvironment triggers such pH changes, enzyme activity, or external stimuli like light and ultrasound. For instance, pH-sensitive nanoparticles take use of the acidic tumour environment to selectively activate medication release inside cancerous tissues, hence reducing systemic toxicity. Enzyme-responsive nanocarriers provide targeted medication administration by using tumor-associated proteases to destroy polymeric coverings. Moreover, light-activated nanocarriers like photodynamic therapy (PDT)-based nanoparticles provide spatiotemporal control over drug release and improve therapeutic effectiveness (Lin et al., 2021; Sun and Jiang, 2023).

Gene Therapy and RNA-Based Therapeutics

RNA-based treatments and gene therapy are also becoming more popular as theranostic methods for OSCC control. When supplied via nanocarriers, small interfering RNA (siRNA) and microRNA (miRNA) can modulate neoplastic pathways and increase chemosensitivity. By guaranteeing stability and selective absorption by cancer cells, lipid nanoparticles (LNPs) have proven to be effective carriers for nucleic acid delivery (Chawla et al., 2015). By allowing the suppression of important oncogenes and modification of tumour suppressor genes, RNA-based treatments hence preventing cancer spread and metastasis. Furthermore investigated for OSCC treatment are messenger RNA (mRNA) therapies, which enable the production of tumor-suppressing proteins to offset cancer. When combined with NDDS, CRISPR-Cas9 gene-editing technology also offers promise for exact genetic changes to fix oncogenic mutations and enhance therapy outcomes. Combining NDDS with RNA-based therapies guarantees improved bioavailability, lower immunological clearance, and higher transfection efficiency. These approaches provide a hopeful path for individualised OSCC treatment by allowing focused gene manipulation, hence opening the way for more efficient and less hazardous therapeutic procedures (Khan et al., 2022; Naaldijk et al., 2024).

FOR OSCC CONTROL

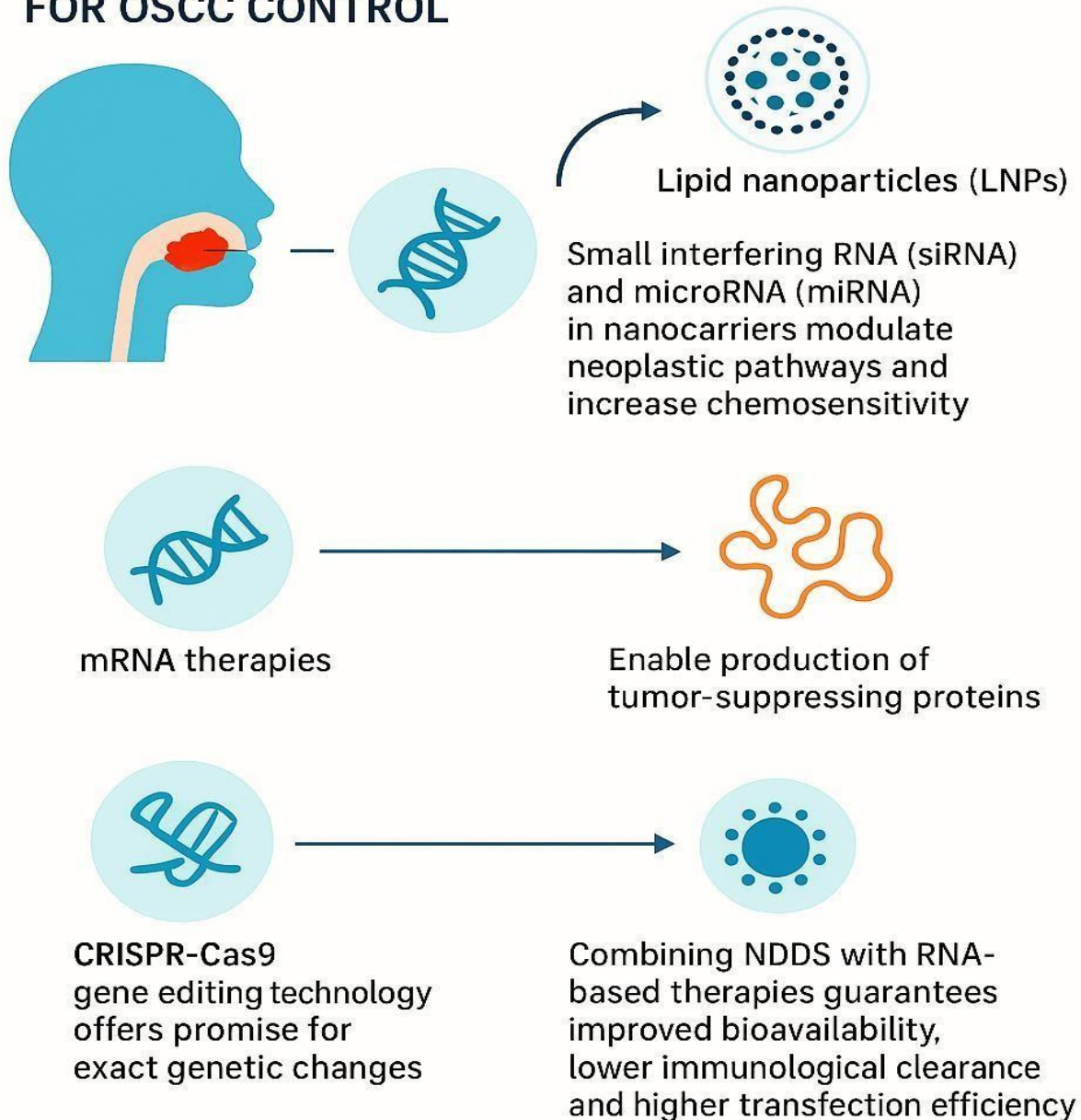


Figure 2: Illustrating RNA-based treatments and gene therapy approaches for oral squamous cell carcinoma (OSCC) control, highlighting siRNA/miRNA with lipid nanoparticles, mRNA therapies for tumor-suppressing protein production, and CRISPR-Cas9 gene editing, combined with nanocarrier drug delivery systems to enhance bioavailability, transfection efficiency, and precision-targeted cancer therapy.

Immunotherapy-Based Theranostics

Another front in OSCC treatment is immunotherapy-based theranostics. Nanocarrier-mediated delivery of cancer vaccines, cytokines, and immune checkpoint inhibitors reduces systemic toxicity and improves anticancer immune responses. Immunotherapy aims at using the immune system of the body to properly identify and destroy cancer cells (Anitha et al., 2024; Siddique and Chow, 2022). Engineered nanoparticles delivering checkpoint inhibitors like anti-PD-1/PD-L1 and anti-CTLA-4 enhance immune system activation and lower off-target effects. Cancer vaccines using nanocarriers to deliver tumor-specific antigens also promote immunological memory, so offering long-term protection against tumour recurrence (Granot-Matok et al., 2023; Rana et al., 2023; Singha et al., 2018). Cytokines such interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) can also be loaded into nanoparticles to increase the activation and recruitment of immune cells in the tumour microenvironment. Theranostic immunotherapy lets one monitor in real time immune responses and treatment effectiveness by means of imaging and therapeutic functions combined (Nadukkandy et al., 2022). Personalised treatment plans combining patient-derived immune cells and tumour antigens help to increase OSCC control even more. Although there are still difficulties in clinical translation, continuous developments in nanotechnology

and immunoengineering offer great promise in transforming OSCC treatment by means of immunotherapy-based theranostics (Cao et al., 2021).

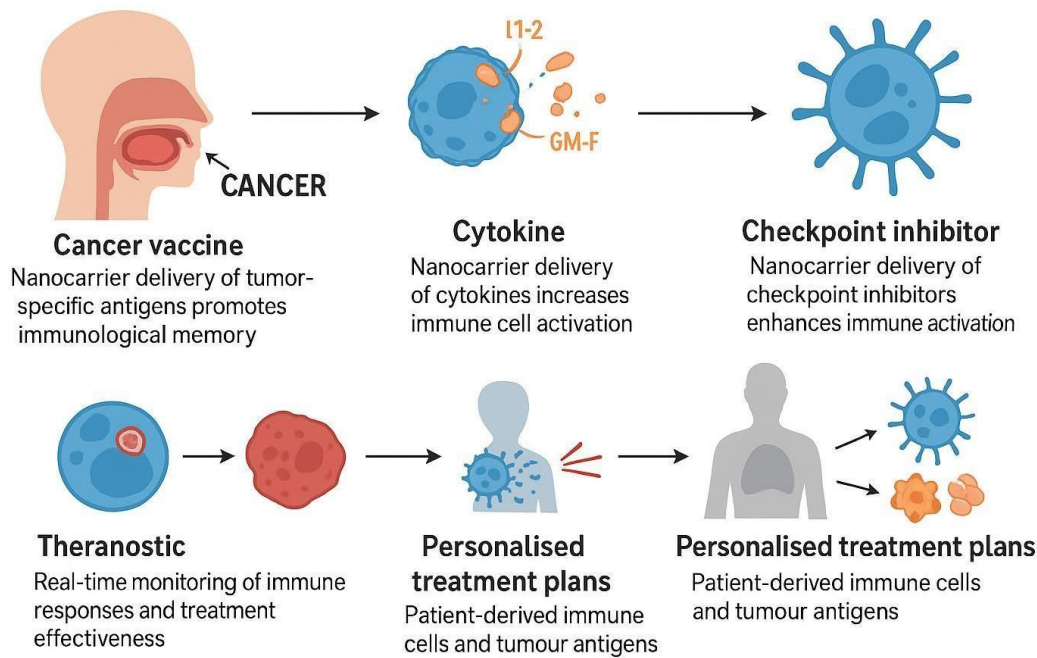


Figure 3: Illustrating immunotherapy-based theranostics in OSCC using nanocarriers for vaccines, cytokines, checkpoint inhibitors, and personalized treatment with real-time immune monitoring.

Challenges and Future Perspectives

A major worldwide health issue, oral squamous cell carcinoma (OSCC) presents great difficulties in diagnosis, treatment, and prognosis. Often resulting in major negative effects and minimal survival advantages, conventional treatment methods including surgery, radiation, and chemotherapy (Subramaniam et al., 2021; Mingming Zhang et al., 2020). Notwithstanding progress, the rates of recurrence and metastasis stay high, which calls for a paradigm change towards new drug delivery systems (NDDS) combining diagnostic and therapeutic functions a theranostic approach. Insufficient specificity and effectiveness of traditional therapies are among the main obstacles in OSCC treatment. Although they are efficient, chemotherapeutic drugs lack focused delivery, which causes general toxicity and lower patient compliance (Tomo et al., 2019). Treatment results are also made more difficult by drug resistance mechanisms include improved efflux pump activity, apoptosis evasion, and tumour microenvironment changes. Therapeutic failure is exacerbated by the heterogeneity of OSCC and the existence of cancer stem cells (CSCs), hence highlighting the need of creative approaches (Ghazi et al., 2019).

Promising substitutes that have come from nanotechnology-based medicine delivery are improved bioavailability, site-specific distribution, and lower systemic toxicity (Liu et al., 2023). The clinical translation of nanomedicine, meantime, runs against obstacles like stability, mass manufacturing, and regulatory clearances (Manikkath et al., 2023). The interaction of nanoparticles with biological barriers, immunogenic responses, and unintentional off-target effects calls for even more thorough research. Equally, the use of imaging techniques in theranostic strategies for real-time monitoring of medication distribution and therapeutic response stays underexplored in clinical environments (Bai et al., 2012).

OSCC treatment in the future will be multi-functional NDDS combining nanotechnology, immunotherapy, and gene-editing techniques like CRISPR (Hsieh et al., 2022; Nasry et al., 2018). Using biomarker-driven and AI-assisted therapy algorithms, personalised medicine has great promise for maximising therapeutic results (Harry, 2023; Mitsala et al., 2021; Vicini et al., 2022). Moreover, the use of smart biomaterials and stimuli-responsive drug carriers could transform on-demand drug release systems, hence guaranteeing exact and efficient therapy. Translating these innovative theranostic concepts from bench to bedside will depend on addressing the present constraints via multidisciplinary cooperation and comprehensive preclinical and clinical research, hence enhancing OSCC patient survival and quality of life (Choi and Kim, 2023; Pickhardt et al., 2023).

CONCLUSION

Its aggressive character, high recurrence rates, and poor survival results with current therapies keep oral squamous cell carcinoma (OSCC) a significant worldwide health issue. Though often linked with major adverse effects, non-specific targeting, and drug resistance, standard treatment methods like surgery, chemotherapy, and radiation therapy have greatly aided OSCC control. Novel drug delivery systems (NDDS) have changed OSCC intervention from traditional methods towards a theranostic paradigm combining therapy and diagnostics for precision medicine.

Drug bioavailability, stability, and targeted delivery have been greatly enhanced by the creation of NDDS, including nanoparticles, liposomes, dendrimers, micelles, and hydrogels. By allowing the encapsulation of immunotherapeutic compounds, gene therapy vectors, and chemotherapeutic drugs, these systems improve therapeutic efficacy and reduce systemic toxicity. Among these, nanotechnology-based carriers have shown extraordinary promise in overcoming multidrug resistance and enhancing medication penetration in the tumour microenvironment. Moreover, smart drug delivery systems like controlled-release and stimuli-responsive ones have allowed site-specific drug release, hence lowering off-target effects and improving therapeutic index.

The theranostic method, which integrates therapeutic and diagnostic features on one platform, is the next frontier in OSCC care. Theranostic nanoparticles including imaging chemicals like quantum dots and iron oxide nanoparticles offer real-time tracking of medication biodistribution and tumour response. This dual function guarantees accurate monitoring and helps to create individualised treatment plans depending on patient profile. Furthermore, by tackling tumour heterogeneity and immune evasion mechanisms, the inclusion of molecular-targeted treatments, RNA interference (RNAi) techniques, and immunotherapy inside NDDS increases their promise for OSCC treatment.

Notwithstanding these developments, issues including mass production, regulatory clearances, biocompatibility questions, and high manufacturing costs continue to impede the clinical translation of NDDS-based therapies. To maximise formulation techniques, evaluate long-term safety, and create uniform criteria for therapeutic uses, more study is required. Accelerating the move of theranostic NDDS from experimental investigations to ordinary clinical practice will depend on cooperative efforts among pharmaceutical companies, regulatory authorities, and multidisciplinary research teams. Redefining OSCC intervention via NDDS and theranostic strategies offers great potential to transform treatment results. These innovative approaches' promise in overcoming the constraints of traditional OSCC management is highlighted by the capacity to attain exact medication targeting, real-time monitoring, and individualised therapy. Although difficulties remain, continuous research and technical developments will be absolutely vital in determining the future of OSCC therapy, hence enhancing patient survival and quality of life.

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Conflict of interest

The authors declare no conflict of interest.

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