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REVIEW

Advancing oral cancer care: nanomaterial-driven diagnostic and therapeutic innovations

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Abstract The advent of nanotechnology has significantly advanced the diagnosis and treatment of oral cancer, offering more precise and efficient therapeutic strategies. This review presents a comprehensive overview of recent developments in the application of nanotechnology to oral cancer management. It begins with an overview of the epidemiology of oral cancer and outlines current diagnostic and therapeutic methods. The classification and advantages of various nanomaterials are then introduced. The paper thoroughly explores the use of nanomaterials as drug delivery systems (DDSs), imaging contrast agents, and therapeutic tools, with particular emphasis on multifunctional nanoplatforms that integrate diagnostics and therapy. These platforms enable real-time monitoring and immediate therapeutic response, offering innovative approaches for early detection and intervention. Despite these promising advances, several challenges persist, including issues related to biocompatibility, clearance, targeting specificity, and clinical translation. The review concludes by highlighting current limitations and proposing future directions for the clinical application of nanotechnology in oral cancer treatment.

Keywords Oral cancer · Nanomaterials · Drug carriers · Imaging contrast agents · Therapeutic drugs · Integrated diagnosis and treatment

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Overview of research background

Epidemiology of oral cancer

From 1990 to 2017, the incidence of oral cancer increased from 10 cases per 100,000 people every 4.41 years to 4.84 cases per 100,000 (Ren et al. 1990). Oral cancer is one of the most common malignant tumors worldwide, ranking second in incidence among head and neck tumors, following nasopharyngeal carcinoma. Oral and oropharyngeal cancers collectively rank as the sixth most common malignancy globally (Warnakulasuriya 2009). The incidence varies significantly across regions, with particularly high

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rates in Southeast Asia due to habits such as betel nut chewing. It is estimated that over 400,000 new cases of oral cancer are diagnosed worldwide each year, with two-thirds occurring in Asian countries, including Sri Lanka, Indonesia, India, Pakistan, and Bangladesh (Montero and Patel 2015). Due to the low early diagnosis rate and delayed treatment, the mortality rate remains high. Many patients are diagnosed at an advanced stage, leading to poor treatment outcomes. In developing countries, limited medical resources contribute to higher mortality rates compared to developed nations. The prognosis for oral cancer remains poor, with an overall five-year survival rate as low as 40%. However, early-stage detection (stage I and II) can improve survival rates to over 80% (Abati et al. 2020; Silverman et al. 2010). A major challenge in oral cancer treatment is that patients often delay seeking medical attention due to the absence of significant symptoms, resulting in late-stage diagnosis and increased treatment difficulty and mortality risks (Ilhan et al. 2021). Socioeconomic factors also play a crucial role in delayed diagnosis (Yuktha et al. 2024). Data indicate that the average diagnostic delay for oral cancer is 55.2 days, with 61.9% of patients experiencing delays exceeding 40 days. Factors associated with prolonged diagnostic delays include advanced age (> 50 years), single marital status, lower educational attainment, and lower monthly income. Additionally, delays in obtaining biopsy samples are significantly correlated with increased diagnostic delays ($p < 0.05$). Demographic and socioeconomic factors have a considerable impact on diagnostic delays in oral squamous cell carcinoma (OSCC). Targeted interventions addressing these disparities are essential for improving early detection and enhancing patient outcomes.

The risk of oral cancer is influenced by multiple factors (Fig. 1). Lifestyle habits play a critical role, with long-term smoking, betel nut chewing, and excessive alcohol consumption significantly increasing the likelihood of developing the disease. Diets high in salted, smoked, or pickled foods are also linked to elevated risk. Genetic predisposition is another contributing factor; individuals with a family history of oral cancer face a comparatively higher risk (Nagao and Warnakulasuriya 2020). Additionally, prolonged exposure to heavily polluted environments may further increase susceptibility (Petti 2009).

In recent decades, human papillomavirus (HPV) infection has emerged as a major etiological factor in oropharyngeal cancer, particularly among younger individuals (Day et al. 2020). HPV16, in particular, is responsible for the majority of cases. As HPV-related oral cancers often present without noticeable early symptoms, regular screening and HPV vaccination are essential for effective prevention and early detection (Tang et al. 2020).

The metastatic trajectory of oral cancer significantly influences treatment strategies and prognosis due to its complex anatomical spread and involvement of critical functional regions. Oral cancer primarily spreads through the lymphatic system to cervical lymph nodes, particularly the submandibular, deep cervical, and supraclavicular lymph nodes. This pattern necessitates comprehensive treatment, including surgical excision combined with radiotherapy or chemotherapy to ensure complete tumor cell eradication. Additionally, oral cancer may spread via direct invasion into adjacent tissues such as the tongue base, pharynx, mandible, or skull base, increasing surgical complexity and risks. This type of invasion can compromise essential functions such as swallowing, speech, and breathing, making it crucial to balance tumor removal with functional preservation and quality of life. In advanced cases, oral cancer can metastasize to distant organs such as the lungs and liver, shifting the treatment focus to systemic therapies such as chemotherapy, targeted therapy, or immunotherapy to control disease progression. Overall, the metastatic pattern of oral cancer necessitates a multidisciplinary treatment approach involving surgery, radiotherapy, and medical oncology. Early diagnosis and precision therapy are crucial for improving patient outcomes and reducing recurrence risk (Amoozgar et al. 2023; Liu et al. 2024).

Diagnosis and treatment methods for oral cancer

The diagnosis of oral cancer begins with a thorough evaluation of the patient's clinical symptoms, followed by the application of specialized diagnostic techniques. Histopathological examination through tissue biopsy remains the gold standard for definitive diagnosis. Tissue samples are obtained from suspicious lesions and examined microscopically to detect malignant cells (Adeola et al. 2022). For lesions located in deeper anatomical regions, endoscopic biopsy techniques may

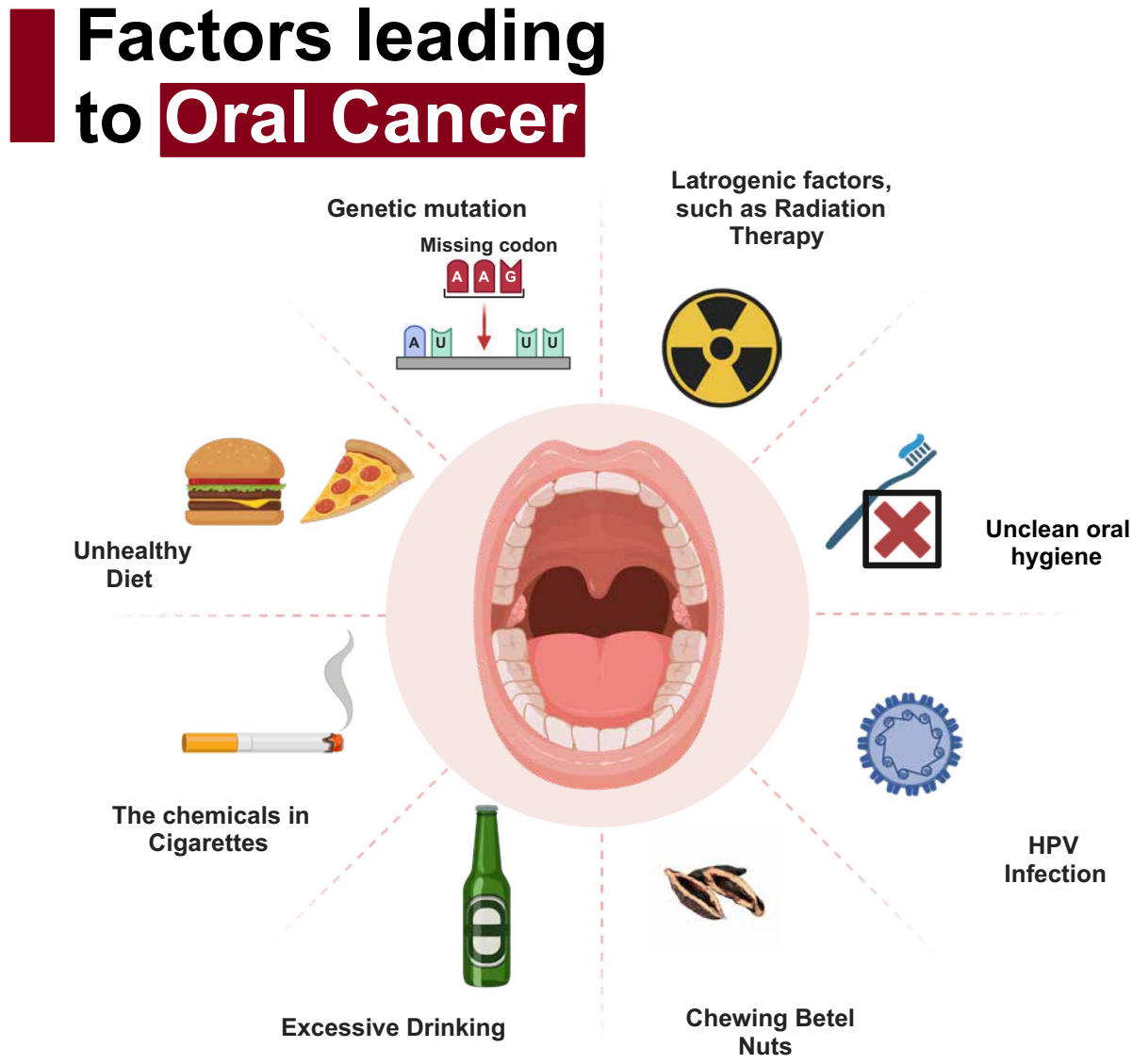

Fig. 1 Factors causing oral cancer (created by Biorender)

be employed (Zheng et al. 2004). In addition, imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) play a critical role in assessing tumor characteristics. CT enables precise visualization of the tumor's size, location, and spatial relationship with adjacent structures, whereas MRI is particularly effective in evaluating involvement of surrounding soft tissues (Burian et al. 2022). More recently, advances in molecular biology have introduced novel diagnostic approaches, providing deeper insights into tumor pathogenesis and enabling earlier detection. Molecular biomarkers play a crucial role in the early diagnosis of oral cancer. Key protein-based biomarkers include cytokeratins (CK19, CK17), epidermal growth factor receptor (EGFR), matrix metalloproteinases (MMPs), and vascular endothelial growth factor (VEGF). Genetic markers such as TP53, CDKN2A (p16), and microRNAs (miR- 21, miR- 375) are also associated with oral cancer. Through molecular analysis of patient samples, doctors can more accurately assess the malignancy and prognosis of the disease (Sasahira and Kirita 2018). Molecular diagnostics offer high

sensitivity and specificity by detecting tumor characteristics at the cellular and molecular levels. However, their widespread application is currently limited by complex sample processing, high costs, and a lack of standardization. In contrast, imaging technologies such as CT, MRI, and fluorescence imaging provide direct visualization of tumor morphology, location, and extent. These imaging modalities are particularly valuable for preoperative planning and intraoperative navigation, though they have lower sensitivity in detecting early-stage lesions and distinguishing between benign and malignant tumors. Recent advancements in molecular diagnostics, including liquid biopsy and hyperspectral imaging, have significantly improved early detection capabilities. The integration of molecular diagnostics with imaging technologies, enhanced by artificial intelligence-assisted analysis, is expected to be a key direction for future oral cancer diagnostics (Alzahrani et al. 2025; Abati et al. 2020; Dar et al. 2022).

Surgical intervention remains the primary treatment for early-stage oral cancer. The extent of surgery—such as partial or total glossectomy, mandibular resection, or other procedures—is determined based on the tumor's size and anatomical location (D'Cruz et al. 2015; Sciubba 2001). For patients who are ineligible for surgery or present high surgical risk, radiation therapy offers an effective alternative. This approach uses high-energy X-rays to damage the tumor's DNA, thereby inhibiting cancer cell proliferation (Liu et al. 2020a, b). Chemotherapy involves the administration of cytotoxic drugs to eliminate cancer cells or suppress their growth and is often used alone or in combination with surgery or radiotherapy (Sha et al. 2021). In recent years, immunotherapy has emerged as a promising treatment modality, aiming to enhance the patient's immune response to specifically recognize and attack tumor cells (Cohen et al. 2019). Traditional treatment methods for oral cancer, including surgery, radiotherapy, and chemotherapy, are often associated with significant side effects, high costs, and suboptimal efficacy. Therefore, there is an urgent need to develop novel diagnostic and therapeutic approaches.

Classification of nanomaterials and their advantages in medical diagnosis and treatment

Nanotechnology, which involves the manipulation of materials at the nanoscale (1–100 nm), has made substantial contributions to the medical field in recent years (Patra et al. 2018). Notably, several FDA-approved nano drug delivery systems (DDSs), such as Abraxane and Doxil, exceed 100 nm but are still classified as nanomedicine. At the nanoscale, materials often exhibit unique physical and chemical properties distinct from their bulk counterparts. These include enhanced mechanical strength, altered optical behavior, and increased chemical reactivity (Qi et al. 2022). The interactions between nanomaterials and biological systems are complex and highly dependent on factors such as particle size, shape, and surface characteristics, as well as the surrounding biological environment, including cellular and molecular components. For instance, nanoparticles (NPs) can readily traverse biological membranes and interact with intracellular structures (Joo and Aggarwal 2018).

Nanomaterials are generally classified into three categories: organic, inorganic, and hybrid types (Zhao et al. 2018). Organic nanomaterials, such as liposomes and polymeric NPs, are widely used in drug delivery owing to their excellent biocompatibility (Naahidi et al. 2013). In contrast, inorganic nanomaterials—such as gold NPs (AuNPs) and quantum dots—are primarily employed in biomedical imaging and therapy due to their distinctive physical and chemical properties (Erathodiyil and Ying 2011). Hybrid nanomaterials integrate the features of both organic and inorganic components, offering enhanced functionality through innovative design strategies, such as simultaneous imaging and drug delivery. Examples include silicon-based organic–inorganic NPs, metal–organic frameworks (MOFs), and lipid–polymer composites (He et al. 2015). These hybrid systems can perform multiple roles within a single platform, enabling targeted drug delivery, improved imaging contrast, and combination therapies (Park et al. 2020).

Inorganic nanomaterials possess unique advantages, including favorable morphological properties and distinct physicochemical characteristics (Kashyap et al. 2023, Xu et al. 2023, Kankala 2022, Zhu et al. 2023, Liong et al. 2008). Their unique electronic structures contribute to their rigidity and high stability in colloidal and thermal applications. These materials have been widely explored for applications such as adsorption, energy storage, optics, and catalysis. Over the past two decades, inorganic nanomaterials have garnered significant interest for biomedical

applications, including drug delivery, diagnostics, tissue engineering, biosensing, peptide enrichment, photoluminescence, and artificial enzymes (Lohse and Murphy 2012; Kankala et al. 2018; Yang et al. 2019). However, a major challenge with inorganic nanomaterials is their biocompatibility and biodegradability, which can lead to clearance issues and severe toxicity in vivo. To address these concerns, hybrid nanomaterials composed of organic and inorganic components have been developed, combining the beneficial properties of both materials. Functionalizing inorganic nanomaterials with polymers, surfactants, or small organic molecules preserves their unique physicochemical attributes while improving biocompatibility and stability (Kankala et al. 2020). These advancements have led to the creation of innovative materials with significant potential for future biomedical applications. The primary challenges in synthesizing hybrid nanomaterials include material compatibility, synthesis complexity, size control, functionalization, purification, stability, and environmental safety (Shang et al. 2023; Liu et al. 2020a, b, Quazi & Nanohydrogels 2022). These challenges increase manufacturing complexity and costs, limiting large-scale production and clinical application. To overcome these obstacles, more efficient and environmentally friendly synthesis methods need to be developed, along with optimized process parameters to enhance scalability. Furthermore, interdisciplinary collaboration across materials science, chemical engineering, and nanotechnology will be essential for advancing the industrial application of hybrid nanomaterials.

The initial application of nanotechnology in medicine has encompassed drug delivery, biomedical imaging, and tissue engineering. Nanocarriers enable precise drug delivery to specific target sites, thereby enhancing therapeutic efficacy and minimizing adverse effects (Majumder et al. 2019). Nanomaterials also improve imaging resolution and sensitivity, contributing to more accurate biomedical diagnostics (Peng and Chiu 2015). In tissue engineering, nanotechnology has introduced novel tools such as nanofibrous scaffolds that support tissue repair and regeneration (Abdollahiyan et al. 2021). Moreover, integrating nanotechnology into personalized medicine allows treatment strategies to be tailored to individual patient needs (Germain et al. 2020). Overall, nanotechnology has significantly surpassed traditional treatment methods in oral cancer management, offering several key advantages. First, nanomaterials enable precise early diagnosis through nanosensors and highly sensitive NPs, which significantly improve diagnostic accuracy and efficiency. Second, in treatment, nanodrug carriers allow for targeted drug delivery, minimizing damage to normal tissues while increasing drug concentration at the tumor site, thereby enhancing therapeutic efficacy and reducing side effects. Furthermore, nanotechnology supports innovative treatment approaches such as photothermal therapy (PTT) and radiotherapy enhancement. NPs'photothermal effects or radiosensitization properties enable precise tumor ablation or enhanced radiation therapy outcomes. Lastly, nanomaterials have shown promise in tissue regeneration, providing new hope for oral cancer patients. For example, nanohydroxyapatite-based materials promote the regeneration and repair of damaged tissues. While nanotechnology offers substantial advantages over conventional treatments, challenges remain, particularly concerning the fate and inherent toxicity of nanomaterials in biological systems. Factors such as NP size, shape, concentration, coating type, and incubation time can differentially affect various cell types, human physiology, and environmental stability, posing barriers to long-term application. Advances in green synthesis methods, such as plant-based NP synthesis, are gradually addressing these issues. The field of nanotoxicology holds significant research value in the biomedical application of nanomaterials (Talarska et al. 2021; Yata et al. 2017).

The purpose of this paper is to comprehensively review the latest developments in nanotechnology for the diagnosis and treatment of oral cancer, summarize emerging trends in its application over time (Table 1), and highlight the transition from its role as a drug carrier to an integrated diagnostic and therapeutic platform, ultimately achieving the unification of diagnosis and treatment. Additionally, it aims to forecast future developments in this field (Fig. 2). Through a detailed analysis of current progress, this review aims to offer the medical community a clear, systematic overview and valuable insights to support future clinical applications.

Table 1 Timeline of nanotechnology development in oral cancer treatment

Time Period	Major Advances and Breakthroughs	Representative Technologies/Materials
2000–2010	Initial exploration of nano drug delivery systems to enhance chemotherapy drug targeting and bioavailability	Liposomes, polymer nanoparticles
2010–2015	Development of photothermal nanomaterials for localized hyperthermia treatment of oral cancer	Gold nanorods, carbon nanotubes
2015–2020	Emergence of multifunctional nanoplatforms integrating hyperthermia, chemotherapy, and immunotherapy	Magnetic nanoparticles, nanocomposites
2020–2025	Application of nanotechnology in dynamic therapy, utilizing catalytic generation of reactive oxygen species (ROS) to kill cancer cells	Enzyme-mimicking catalytic nanomaterials, sonocatalytic nanomaterials
2025 and beyond	Development of smart nanorobots and nanosensors for precise diagnosis and treatment	Nanorobots, nanobiosensors

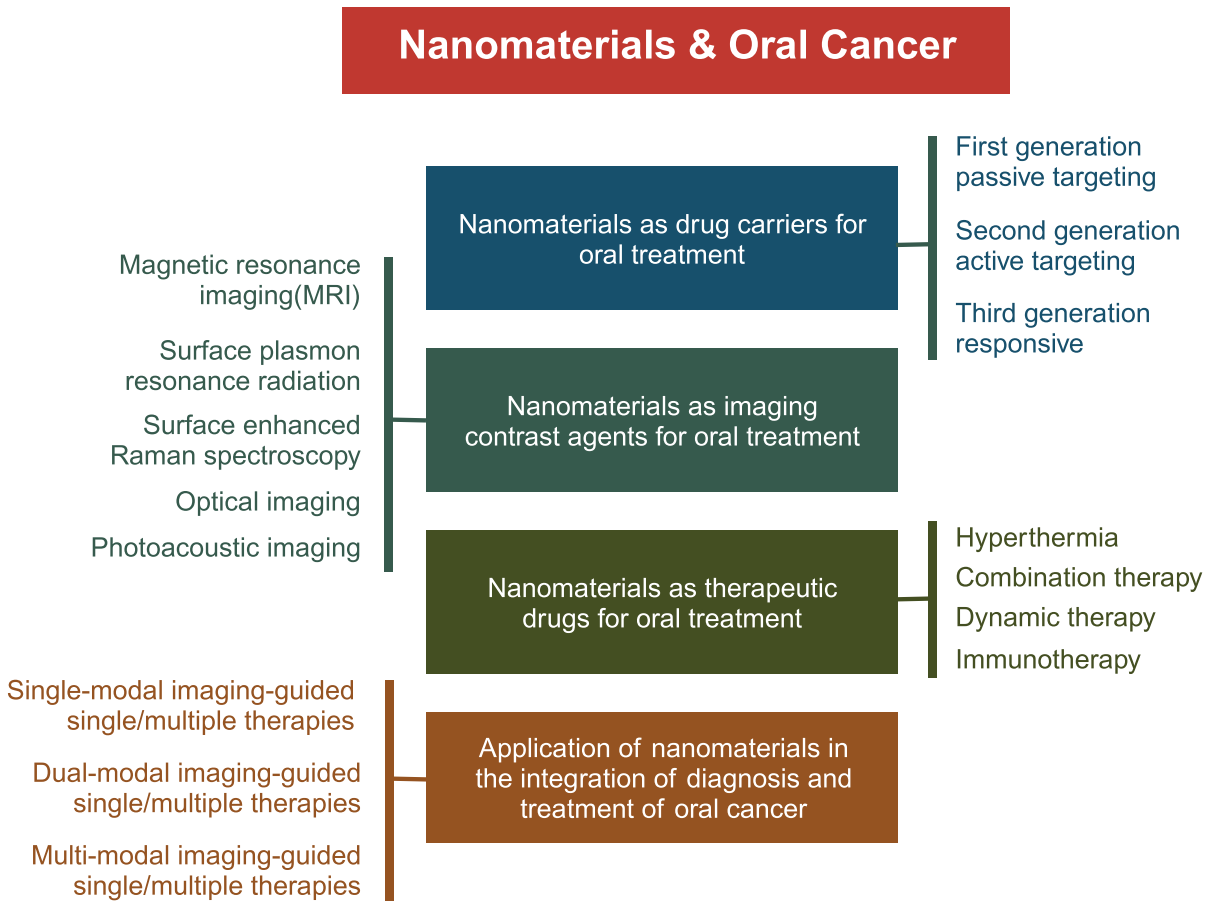

Fig. 2 A schematic diagram illustrates the structure of this review (created by Biorender)

Nanomaterials for oral cancer treatment

Nanomaterials as drug carriers for oral cancer treatment

Due to the unique anatomical characteristics of oral cancer, drug delivery faces significant biological barriers. Physical barriers include the dense extracellular matrix (ECM) and high interstitial fluid pressure.

The ECM in the tumor microenvironment (TME) of oral cancer is rich in collagen and hyaluronic acid, while the high interstitial fluid pressure prevents NP penetration. Biochemical barriers also impact drug delivery. Various enzymes in the oral environment may degrade nanodrugs, while the acidic nature of the TME may affect NP stability and drug release behavior. Additionally, the mononuclear phagocyte system (MPS) can capture and clear nanodrugs, reducing tumor targeting efficiency. The immunosuppressive TME, characterized by regulatory T cells (Tregs), may further diminish the therapeutic efficacy of nanomedicine. Nanomaterials as drug carriers demonstrate immense potential in overcoming these treatment barriers. They enhance drug solubility, improve targeting efficiency, extend circulation time, enable controlled release, overcome biological barriers, and reduce toxicity. For example, poorly soluble drugs such as paclitaxel show increased solubility and bioavailability when formulated into nanoemulsions (Wei et al. 2014). Furthermore, surface-modified NPs with antibodies or ligands exhibit improved cellular uptake and prolonged circulation time (Surface-modified lipid-based nanocarriers as a pivotal delivery approach for cancer therapy: application and recent advances in targeted cancer treatment). Nanomaterials also facilitate drug transport across physiological barriers, enhancing drug concentration in different compartments. These studies strongly support the potential of nanomaterials in drug delivery for oral cancer.

Nanomaterials have shown significant promise as drug carriers in the treatment of oral cancer. This paper reviews the classification and evolution of third-generation nanomaterials for drug delivery (Fig. 3). The first generation of nanocarriers utilizes passive targeting mechanisms, primarily relying on the enhanced permeability and retention (EPR) effect. This effect arises from the abnormal vasculature of the TME, which allows NPs to preferentially accumulate in tumor tissue (Park et al. 2019). The second generation introduces active targeting strategies, in which nanocarriers are functionalized with specific ligands or antibodies that recognize tumor-associated receptors. This approach enhances binding affinity to tumor cells and improves drug localization (Dutta et al. 2021). The third generation features stimulus-responsive nanocarriers that release therapeutic agents in response to specific cues within the TME (e.g., pH, enzymes) or external triggers (e.g., light, heat). This design allows for on-demand, site-specific drug release, enhancing both efficacy and safety (Yi et al. 2022). These three generations represent a clear evolutionary trajectory—from exploiting tumor physiology, to achieving molecular specificity, and ultimately enabling intelligent, responsive drug delivery. Together, they provide increasingly efficient, precise, and safe therapeutic strategies for oral cancer.

Passive targeting drug delivery nanomaterials and their applications in oral cancer

Passive targeting nanomaterials exploit the EPR effect to facilitate drug delivery to the TME. The abnormal vasculature and impaired lymphatic drainage associated with tumor angiogenesis allow nanoscale drug carriers to penetrate and accumulate within tumor tissues more readily (Park et al. 2019). For instance, graphene-based nanomaterials exhibit significantly higher accumulation in tumor tissues compared to normal tissues, thereby increasing local drug concentrations (Ou et al. 2020). It is important to note that Warren C. W. Cha et al. (Sindhwani et al. 2020) suggested that transcytosis rather than the EPR effect may be the primary mechanism of NP accumulation in tumors. Their study demonstrated that while transcytosis is a dominant mechanism for NP penetration into solid tumors, their research only examined three sizes of AuNPs. The contribution of the EPR effect to tumor accumulation was 12% for 15 nm AuNPs, 3% for 50 nm AuNPs, and 25% for 100 nm AuNPs. This indicates that additional complex mechanisms may influence the EPR effect for 50 nm particles, requiring further investigation.

Local drug administration represents a form of passive targeting in which anticancer agents are directly applied to the oral cavity. This approach enables precise drug delivery to tumor sites, minimizes systemic toxicity, and prolongs drug retention in the affected area. The regenerative capacity of the oral mucosa further supports the safety and practicality of this method (Hearnden et al. 2012). Studies have shown that encapsulated chitosan NPs can deliver ellagic acid to oral cancer cells (Arulmozhi et al. 2013). In 2020, Chaiyakarn Pornpitchanarong et al. successfully developed catechin-modified chitosan/hyaluronic acid NPs (Cat-NPs) for the efficient delivery of

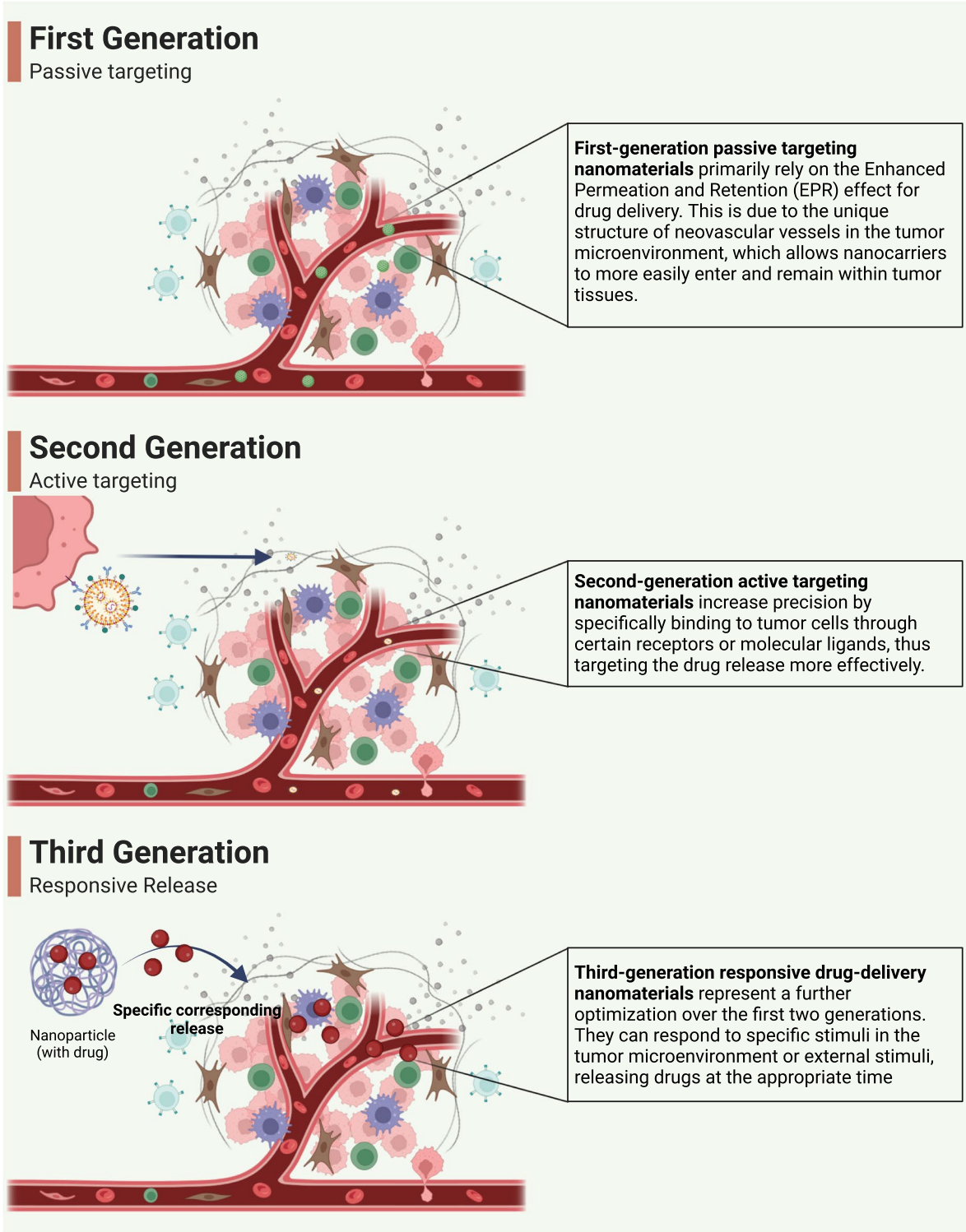

Fig. 3 Third-generation nanomaterials as drug carriers for oral cancer treatment (created by Biorender)

Doxorubicin (DOX) to oral cancer cells. These Cat-NPs exhibited excellent adhesiveness and were able to release DOX on the oral mucosa. The Cat-NPs prepared through ion gelation were negatively charged, spherical, with a size of approximately 160 nm, and demonstrated high DOX loading capacity (DOX-NPs) of 250 µg/mg and sustained release properties. The DOX-NPs effectively inhibited the growth of OSCC cells and exerted broader effects on cellular uptake, accumulation, and apoptosis induction, outperforming free DOX. These findings highlight the potential of Cat-NPs as a clinically viable platform for oral cancer therapy; however, further in vivo studies are necessary to confirm their therapeutic efficacy (Pornpitchanarong et al. 2020).

The passive delivery of plant-derived chemotherapeutic agents for oral cancer has been a major research focus. Numerous epidemiological and clinical studies have confirmed the anticancer potential of phytochemicals extracted from various herbs, attributed to their antioxidant and free radical scavenging properties (Cai et al. 2004; Stankovic et al. 2011). However, their clinical translation has been hindered by poor water solubility, rapid metabolism, low bioavailability, and fast excretion. To address these limitations, poly(lactic-co-glycolic acid) (PLGA) NPs have been employed to deliver docetaxel, a radiosensitizer, to oral cancer cells (Gupta et al. 2018). In 2019, Arokia Vijaya Anand Mariadoss et al. successfully synthesized quercetin (QCT)-loaded chitosan biopolymer NPs (PhCsNPs) using TPP as a crosslinker. These particles displayed uniform spherical shapes with sizes ranging from 80–100 nm and exhibited stable drug release. They demonstrated anticancer effects against oral cancer through induction of enhanced mitochondria-mediated cell apoptosis (Mariadoss et al. 2019a, b). In the same year, PhCsNPs were proven to possess strong antioxidant and anticancer properties in a 7,12-dimethylbenz(a) anthracene -induced oral cancer animal model (Mariadoss et al. 2019a, b). QCT, a natural antioxidant flavonoid, is widely recognized for its significant anticancer properties. In 2023, Puja Das et al. prepared QCT-loaded chitosan NPs (QCT-CSNPs) using chitosan NPs as the drug carrier. QCT-CSNPs exhibited higher toxicity against oral cancer cells, and their improved anticancer effects were confirmed through induction of enhanced cell apoptosis, inhibition of colony formation, suppression of cell migration, and chromatin condensation. Furthermore, mitochondrial dysfunction and increased ROS generation further indicated that QCT-CSNPs could mediate mitochondrial damage in oral cancer cells (Das et al. 2023). Additionally, crosslinked Zn NPs (ZFH) containing hyaluronic acid and fucoidan have also been developed for loading QCT and subsequently used for the treatment of oral cancer (Moustafa et al. 2023).

Overcoming multidrug resistance and discovering novel therapeutic agents remain significant challenges in oral cancer treatment (Lin et al. 2019). Dandan Wang et al. successfully developed a novel NP, MSNP-PEI-DOX/MDR1-siRNA, capable of delivering both MDR1-siRNA and DOX to cancer cells to overcome multidrug resistance (Wang et al. 2017a, b). Similarly, Xiao-Lei Shi et al. effectively loaded and delivered MTH1 inhibitor TH287 and MDR1 siRNA into oral cancer cells (Fig. 4). The results showed that hyaluronic acid-assembled mesoporous silica NPs exhibited excellent performance in controlling drug release and internalization in CAL27 cancer cells, with high cytotoxicity and pro-apoptotic ability (Shi et al. 2019). Additionally, the presence of cancer stem cells (CSCs), self-renewal capabilities, drug efflux, and efficient DNA repair mechanisms contribute to their resistance to conventional chemotherapy. To address this issue, Shakti Ranjan Satapathy et al. formulated hybrid NPs (QAuNP) using quinacrine and gold and investigated their anti-angiogenic and

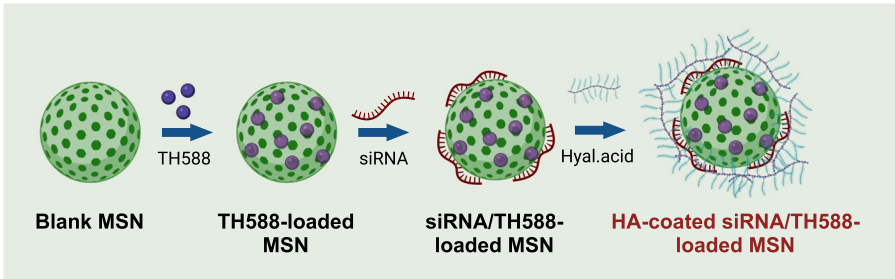

Fig. 4 Schematic diagram illustrating the preparation of mesoporous silica NPs assembled with hyaluronic acid, loaded with TH287 and siRNA (created by Biorender)

anti-metastatic effects on oral CSCs. QAuNP not only inhibited crucial angiogenic markers, such as Ang- 1, Ang- 2, and VEGF but also depleted MMP-2 in a p53 and p21-dependent manner. Furthermore, QAuNP reduced mitochondrial membrane potential by inducing the production of ROS and NO in oral CSCs. Ultimately, QAuNP significantly inhibited the proliferation of oral CSCs and induced their apoptosis, demonstrating marked disruption of angiogenesis and tumor regression in a xenograft mouse model (Satapathy et al. 2018).

The primary advantage of passive targeting lies in its simplicity, as it does not require complex surface modifications or specific ligand-receptor interactions. It is broadly applicable across various nanocarrier systems and tumor types. However, its effectiveness can be limited by factors such as tumor type, size, location, and interpatient variability (Bazak et al. 2014; Bai et al. 2021). In cases involving small-molecule drugs or deeply located tumors, the EPR effect may be insufficient, leading to poor targeting efficiency. Therefore, while passive targeting presents a promising strategy for tumor therapy, it often requires combination with other approaches to achieve optimal therapeutic outcomes.

Second-generation active targeted drug-loaded nanomaterials and their application in oral cancer

Actively targeted nanomaterials are specially engineered nanocarriers functionalized with ligands that bind selectively to tumor-specific receptors or molecules, such as EGFR, folate receptor alpha (FRα), or monoclonal antibodies (Dutta et al. 2021). This strategy leverages the overexpression of receptors or unique enzymatic profiles on tumor cell surfaces to achieve precise localization and selective binding, thereby enhancing drug accumulation at the tumor site. Compared to passive targeting, active targeting allows for more localized drug release, minimizing off-target effects on healthy tissues and improving overall therapeutic efficacy. The primary advantages of actively targeted nanocarriers include high specificity and selectivity, which significantly reduce systemic toxicity and side effects (Dutta et al. 2021). Additionally, active targeting can enhance cellular uptake of drugs, thereby increasing intracellular drug concentrations. HN- 1 is a 12-amino acid peptide with a molecular weight approximately 1% that of a typical antibody. It was initially identified through phage display screening of human head and neck squamous cell carcinoma (HNSCC) tumor cells. HN- 1 specifically binds to and efficiently internalizes within HNSCC cells, demonstrating strong cell-penetrating activity. Consequently, it has recently been recognized as a novel cell-penetrating peptide for targeted drug delivery. For example, in 2017, Yue Wang et al. synthesized polyethylene glycol (PEG)-conjugated doxorubicin (PD) by linking DOX with double amino-terminated PEG via succinimide coupling and then surface-modified PD NPs with HN- 1 using an improved nanoprecipitation method to form HNPD NPs for penetration and drug delivery in oral cancer cells (Wang et al. 2017a, b). HN-targeting significantly improved cellular drug delivery efficiency (Bao et al. 2009; Potala and Verma 2010; Un et al. 2012). Sasidharan Swarnalatha Lucky et al. developed near-infrared (NIR) excitable upconversion NPs (UCN) and modified them with EGFR for specific targeting of oral cancer cells overexpressing EGFR (Lucky et al. 2016). Other EGFR-targeting NPs have also demonstrated efficacy in oral cancer treatment (Lucky et al. 2016; Ling et al. 2022).

FRα has garnered significant attention as a therapeutic target due to its overexpression in various cancers (Scaranti et al. 2020), including clinical samples from different stages of OSCC patients (Cao et al. 2022). Capitalizing on the elevated FR expression in oral cancer cells, Bhattacharya et al. developed a glucose-derived carbon nanosphere (CSP) system functionalized with a folic acid (FA)-based cationic lipid (FA8) and loaded with the chemotherapeutic agent DOX. This CSP-based nanocarrier demonstrated efficient cellular uptake and potent cytotoxicity against tumor cells. Receptor-blocking experiments confirmed that drug internalization was predominantly FR-mediated, occurring primarily in cancer cells. In vivo studies further showed that this targeting mechanism led to prolonged drug retention and robust induction of tumor apoptosis (Bhattacharya et al. 2023).

In a related study, Jong Hyun Lee developed FA-conjugated Pluronic to non-covalently functionalize nanographene oxide (nGO) sheets for active targeting of oral cancer (Figure S1A). To regulate ligand density on the nGO surface, varying ratios of FA-conjugated Pluronic and unmodified Pluronic were blended to coat the sheets. As the proportion of

FA-conjugated Pluronic increased, the surface density of targeting ligands rose linearly. Correspondingly, cellular uptake by oral cancer cells also increased with ligand density. However, in vivo experiments using a mouse xenograft model did not reveal a proportional enhancement in tumor targeting. No significant accumulation was observed at 25% FA coverage, whereas 50% FA coating produced tumor targeting comparable to that achieved with 100% FA (Lee et al. 2015a, b). Additionally, another study demonstrated that graphene oxide (GO) loaded with tumor-targeting peptides and anticancer drugs effectively facilitated drug delivery (Li et al. 2021a, b, c).

Despite the promise of active targeting strategies, several key challenges remain, including the identification of precise molecular targets and the maintenance of NP stability in vivo. A major limitation is receptor heterogeneity among patients, which can lead to inconsistent targeting efficiency and the potential development of drug resistance during treatment. One of the key factors affecting the reliability of active targeting nanomaterials is the variability in receptor expression. Active targeting relies on the specific binding between ligands functionalized on the NP surface and receptors expressed on target cells. However, receptor expression levels can vary significantly among individuals, tissues, and even different regions of the same tumor. This variability may result in inconsistent targeting efficiency. For instance, in patients or tumor regions with low receptor expression, NPs may fail to bind effectively, reducing therapeutic efficacy. Conversely, in areas with high receptor expression, excessive NP accumulation could lead to increased local toxicity. Additionally, receptor expression may dynamically change during treatment (e.g., upregulation or downregulation in response to therapy), further impacting the long-term reliability of active targeting NPs. To enhance the reliability of active targeting nanomaterials, it is essential to account for receptor heterogeneity during design. Strategies such as multi-targeting approaches, biomarker-based ligand optimization, and real-time monitoring technologies can help dynamically adjust treatment regimens and improve therapeutic outcomes. Cancer biology research has revealed some cancer cell-specific antigens, such as carcinoembryonic antigen and galectin- 3, which play a crucial role in homotypic cell adhesion in tumors (Glinsky et al. 2001; Chen et al. 2016). Therefore, Lang Rao et al. attempted to encapsulate NPs in a layer of cancer cell membrane to achieve the homotypic targeting properties of biomimetic NPs (Figure S1B). The researchers coated patient-derived tumor cells (PDTC) on gelatin NPs (GNPs), creating PDTC@GNPs. In a patient-derived xenograft (PDX) model, PDTC@GNPs exhibited efficient targeting towards similar tumor cells and tissues, and the targeting effect was significantly enhanced when the source cell membrane of PDTC@GNPs matched the host cells; conversely, when the source cells and the host were mismatched, the targeting effect was weaker. Furthermore, the study demonstrated that when the cell membrane of PDTC@GNPs, loaded with the anticancer drug cisplatin (Pt), was applied through autologous isolation and administration in a subcutaneous tumor mouse model, the tumor almost completely disappeared, and it effectively suppressed tumor recurrence (Zhang et al. 2023a, b). The translation of this biomimetic NP into clinical practice provides a simple, safe, and effective strategy for personalized cancer treatment. While active targeting improves drug delivery precision, it may also trigger immune responses, posing a significant challenge in clinical applications. The targeting ligands (e.g., antibodies, peptides, or small molecules) and the nanomaterial itself may be recognized as foreign substances by the immune system, leading to immune activation. For example, NPs can be captured by the MPS, leading to rapid clearance by the liver and spleen, which reduces their accumulation at the target site. Certain ligands may induce specific immune responses, such as the production of anti-drug antibodies, which can impair targeting efficiency and potentially cause allergic reactions or autoimmune disorders. Surface modifications, such as PEGylation, can reduce immune recognition to some extent. However, repeated administration may still lead to accelerated blood clearance phenomenon. Therefore, designing immune-evasive NPs requires careful selection of materials, surface coatings, and ligands while integrating immune modulation strategies to improve biocompatibility and therapeutic efficacy.

Passive targeting and active targeting represent two distinct drug delivery strategies, each with its advantages and limitations. Passive targeting relies on the physicochemical properties of NPs (e.g., size, surface charge, and hydrophobicity) to facilitate tumor accumulation through the EPR effect. However, passive

targeting lacks specificity, leading to non-specific accumulation in normal tissues, which can cause side effects.

Active targeting enhances tumor specificity by functionalizing NPs with ligands (e.g., antibodies, peptides, or small molecules) that selectively bind to receptors or biomarkers on cancer cells. This strategy significantly improves NP accumulation at the target site while reducing off-target effects. While active targeting offers superior specificity and efficiency, passive targeting is simpler to manufacture and apply. In clinical practice, hybrid strategies combining both approaches are often employed to maximize therapeutic efficacy.

Third-generation responsive drug-loaded nanomaterials and their application in oral cancer

Responsive drug-delivery nanomaterials are nanoscale carriers engineered to release therapeutic agents in response to specific biological or external stimuli (Yi et al. 2022). These stimuli can be classified as endogenous—such as the acidic pH, elevated reactive oxygen species (ROS), overexpressed enzymes, or redox gradients within the TME—or exogenous, including light, magnetic fields, or ultrasound. Responsive nanomaterials are designed to release their drug payloads selectively upon encountering these stimuli, thereby enabling site-specific drug delivery. This smart release mechanism enhances therapeutic precision and efficacy while minimizing systemic toxicity and off-target effects (Moradi Kashkooli et al. 2020).

The acidic pH of the TME is a commonly exploited trigger in the design of responsive nanomaterials. For instance, co-assemblies composed of pH-sensitive molecules, malachite green methylene blue, and liposomes have been used to facilitate efficient DOX release in oral cancer cells (Liu et al. 2014). Oxygen-loaded NPs coated with polyethyleneimine polymers modified with ethyl glucuronide spontaneously release oxygen in response to decreased pH within the TME (Song et al. 2019). Polymer–upconversion NP (UCNP) hybrid nanocomposites have also demonstrated effective inhibition of oral cancer cell growth through folate receptor-mediated endocytosis and selective pH-responsive drug release (Tawfik et al. 2018). In a study by Saiyin et al., hydrophobic DOX is attached to hydrophilic and pH-responsive hyperbranched polyacrylamide (HPAH), resulting in DOX-conjugated HPAH (HPAH-DOX). Due to the amphiphilicity of HPAH-DOX, it can self-assemble into nano micelles in an aqueous solution. During self-assembly, the autophagy inhibitor LY294002 (LY) is further loaded into HPAH-DOX nanomicelles, forming the polymer micelle (PM) system (Fig. 5A) (Saiyin et al. 2014). PMs, derived from the self-assembly of block copolymers, are widely used in drug delivery due to their small size, high solubility, excellent biocompatibility, and ease of preparation. In this case, a pH-labile acyl hydrazone bond is used to link DOX to the PM. Once the nanocarrier reaches the tumor site, the acidic intracellular pH triggers bond cleavage, leading to DOX release. Additionally, exposure to acidic conditions induces protonation of the PM, reducing the hydrophobicity of its core and resulting in micelle swelling and subsequent release of the encapsulated autophagy inhibitor. Notably, LY is released more rapidly than DOX, which sensitizes tumor cells to DOX by inhibiting autophagy, thereby enhancing its cytotoxicity, preventing proliferation, and promoting apoptosis in oral cancer cells (Saiyin et al. 2014). MOFs are also commonly used as pH-triggered drug carriers due to the protonation of ligands and changes in metal–ligand coordination bonds in acidic environments (Wang et al. 2020; Zhou et al. 2021, Wu et al. 2017). Tan et al. integrated MOFs with thermosensitive hydrogels and loaded Dox and celecoxib (Cel) into the integrated system for localized oral cancer treatment (Dox/Cel/MOFs@Gel) (Fig. 5B). This drug delivery integrated system exhibits a high drug loading capacity and stably releases both drugs under pH conditions, resulting in enhanced cytotoxic effects against oral cancer cells in vitro. Furthermore, it demonstrates excellent tumor inhibition effects in vivo, inducing tumor apoptosis and suppressing tumor angiogenesis. Moreover, this localized treatment leads to significantly lower systemic toxicity without apparent damage to other organs (Tan et al. 2020).

Under physiological conditions, ROS play essential roles in regulating protein function, cellular signaling, and immune defense. However, elevated ROS levels have been observed during various cancer-related processes, suggesting that high ROS concentrations can serve as a trigger for targeted drug delivery. Nanocarriers incorporating ROS-sensitive linkers, such as organic boron-based or

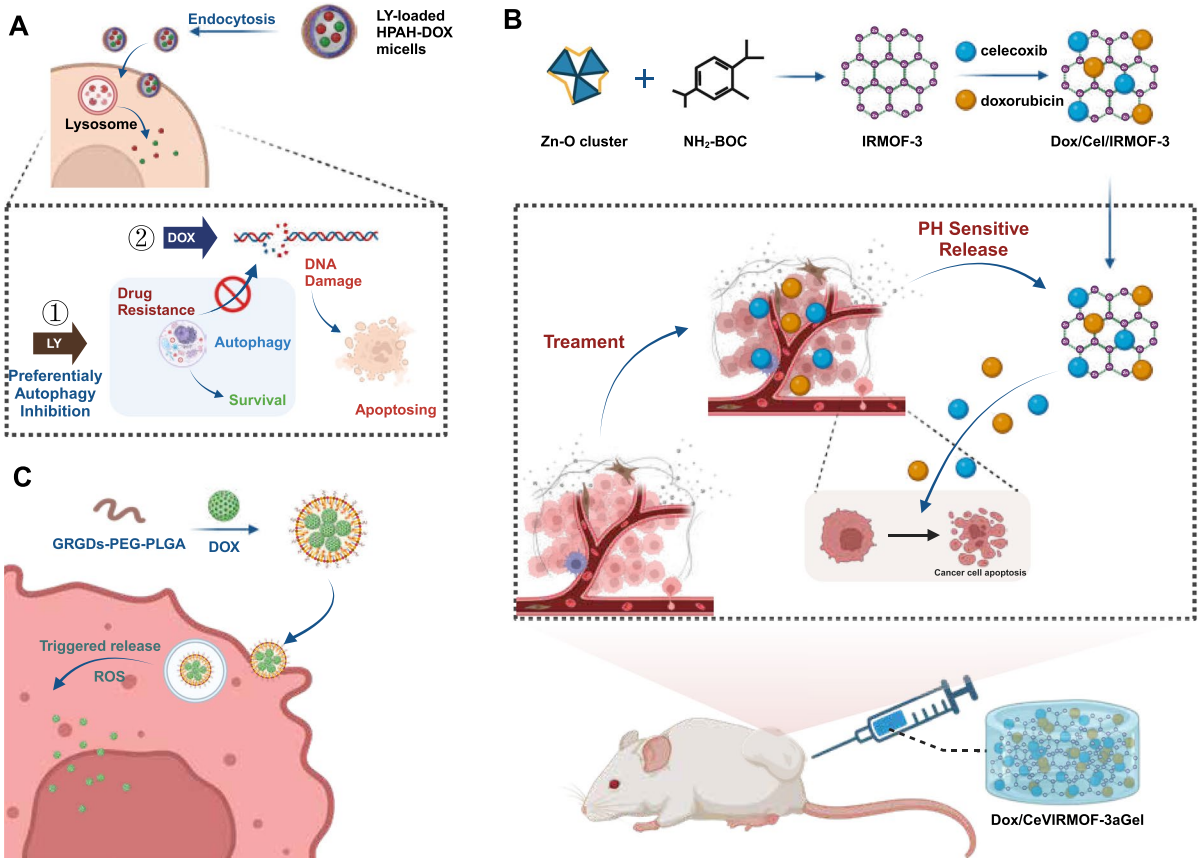

Fig. 5 Application of TME-responsive drug-loaded nanomaterials for oral cancer treatment (created by Biorender). **A** Illustration of nanomicelle-based LY/DOX delivery strategy inducing effective cell death; **B** Schematic diagram of Dox/Cel/MOFs@Gel as a novel injectable MOF and thermosensitive hydrogel for local dual drug delivery in oral cancer treatment; **C** Self-assembly of ROS-responsive polymer NPs loaded with DOX based on RGD-PEG-TK-PLGA

sulfur-containing groups, have been employed for ROS-responsive drug release (Saravanakumar et al. 2016). Thiol ether groups represent a type of sulfur-containing linker that can be degraded through oxidation, leading to the activation of ROS-mediated drug release. Qing Li et al. constructed a novel targeted and ROS-triggered drug delivery nano-platform (Fig. 5C) prepared from RGD-PEG-TK-PLGA polymer, where the ROS-sensitive TK linker is connected to PEG and PLGA, and RGD is used to target cancer cells. This nano-platform exhibits high stability, excellent targeting ability, remarkable ROS sensitivity, and outstanding biocompatibility (Li et al. 2016b, a). Additionally, another commonly used FA-modified TK-linked nano-particle has been prepared for selective internalization by cancer cells and ROS responsiveness (Wang et al. 2019a, b, c, d).

Within the TME, cancer cells must counteract oxidative stress and maintain intracellular redox homeostasis. Elevated levels of glutathione (GSH) play a critical role in neutralizing oxidative pressure, thereby supporting cancer cell survival and proliferation (Poprac et al. 2017; Sosa et al. 2013). The aforementioned ROS-triggered strategies have also been employed to respond to high GSH levels within tumor tissues. Lei Fan et al. developed a GSH-sensitive NP DDS for the delivery of paclitaxel, named FA-PEG-S–S-PCL@PTX. Here, FA mediates active targeting of the NPs to oral cancer tumors, and the disulfide bond is cleaved under high concentrations of GSH, enabling the precise release of paclitaxel at the tumor site through redox reactions, thus achieving an anti-tumor effect. In in vivo experiments, FA-PEG-S–S-PCL@PTX exhibited high accumulation at the

subcutaneous tumor site and demonstrated significant therapeutic efficacy (Fan et al. 2020a, b).

Light at specific wavelengths—such as ultraviolet (UV), visible, and NIR—has been widely utilized in tumor research as an external stimulus due to its non-invasive nature and precise spatiotemporal control (Pan et al. 2021). Among these, NIR light is particularly favored for its deeper tissue penetration and minimal damage to healthy tissues (Roy et al. 2023). In photoresponsive nanomaterial delivery systems, photoreactive moieties such as aromatic compounds, porphyrin derivatives, and azo compounds are often incorporated to enable structural transformations that trigger drug release (Li et al. 2020a, b). Xing et al. synthesized UCNs loaded with DOX and containing a spiropyran ring, in which the spiropyran amphiphilic groups can convert into hydrophilic groups under NIR irradiation, leading to detachment from the copolymer carrier and subsequent DOX release (Fig. 6A). This delivery system exhibited significant targeting effects on oral cancer cells (Xing et al. 2015). In addition, photothermal conversion materials can release heat upon NIR irradiation, inducing structural disruption in polymer carriers and enabling drug release—an alternative and effective strategy. Xie et al. prepared NPs co-loaded with indocyanine green (ICG) and cisplatin, in which NIR-induced photothermal effects from ICG cleave coordination bonds, thereby releasing cisplatin (Wang et al. 2019a, b, c, d). A novel electronic acceptor, 3-(dicyanomethylene)− 2,3-dihydrobenzo[b] thiophene- 1,1-dioxide (DTM), has been designed to develop aggregation-induced emission (AIE) characteristics and NIR-II (1000 nm) light-responsive therapeutic agents (Yu et al. 2024). Due to its AIE properties and DTM receptor, TSDNP effectively generates strong type I ROS and exhibits a high photothermal conversion efficiency (45.3%), significantly inducing immunogenic cell death (ICD). This process activates cytotoxic T lymphocytes (CTLs) and transforms the immunosuppressive TME into an immune-supportive microenvironment. Moreover, TSDNPs upregulate PD-L1 expression in OSCC cells, thereby enhancing the therapeutic efficacy of αPD-L1 immune checkpoint blockade (ICB) therapy. The results demonstrate that the combination of TSDNPs and αPD-L1 effectively eradicates OSCC tumors without causing adverse effects on normal tissues, representing a novel and effective strategy for OSCC treatment. DDSs based on magnetic NPs (MNPs) can respond to an external magnetic field to release drugs. As an externally controlled anti-tumor drug delivery carrier, it can achieve targeted drug enrichment (Li et al. 2021a, b, c). Zhang et al. developed hollow mesoporous MNPs loaded with bleomycin, which can target the lesion area under an external magnetic field and achieve sustained drug release (Fig. 6B) (Zhang et al. 2020). Researchers have developed biocompatible silica-coated magnetic iron oxide NPs (Legge et al. 2019), which were functionalized with αvβ6 integrin-targeting antibodies, a biomarker for OSCC. By leveraging the heat-generating properties of MNPs, exposure to an AMF induces hyperthermia-mediated tumor ablation, specifically targeting αvβ6-negative or overexpressing tumor cells. Compared to normal tissues, OSCC biopsy samples exhibit upregulated αvβ6 integrin expression. Functionalizing silica-coated NPs with anti-αvβ6 antibodies enables selective tumor targeting, and the combination with hyperthermia significantly enhances tumor cell destruction. This antibody-functionalized MNP-based hyperthermia therapy represents a promising targeted treatment strategy for OSCC. Furthermore, the enhanced targeting capabilities of third-generation nanomaterials provide significant advantages over first- and second-generation materials. For instance, researchers have developed: A CRISPR-Cas9 system targeting the Ptpn2 gene (Cas9-Ptpn2), utilizing a negatively charged hyaluronic acid shell electrostatically adsorbed onto a positively charged core. Mitochondria-targeting dihydroporphyrin e6 NPs for tumor-selective therapy. Through active and passive tumor targeting, these NPs accumulate in tumor tissues, enabling in vivo gene editing. The Cas9-Ptpn2 system selectively disrupts the Ptpn2 gene, enhancing IFN-γ and TNF-α signaling, and promoting $CD8^+$ T cell proliferation, thereby sensitizing tumors to immunotherapy (Yang et al. 2020). Despite extensive research, only a limited number of nanomedicines have been approved for clinical use or are currently in clinical trials (Maier-Hauff et al. 2010). One notable example is Hensify (NBTXR- 3), a hafnium oxide NP activated by ionizing radiation, developed by Nanobiotix for treating lung, prostate, head and neck, liver, and esophageal pancreatic tumors. NBTXR- 3 is currently under evaluation in three phase 1/2 trials and one phase 2/3 trial. Intratumoral administration of NBTXR- 3 has demonstrated safety and efficacy in enhancing radiotherapy outcomes for locally advanced sarcomas (Bonvalot et al. 2019).

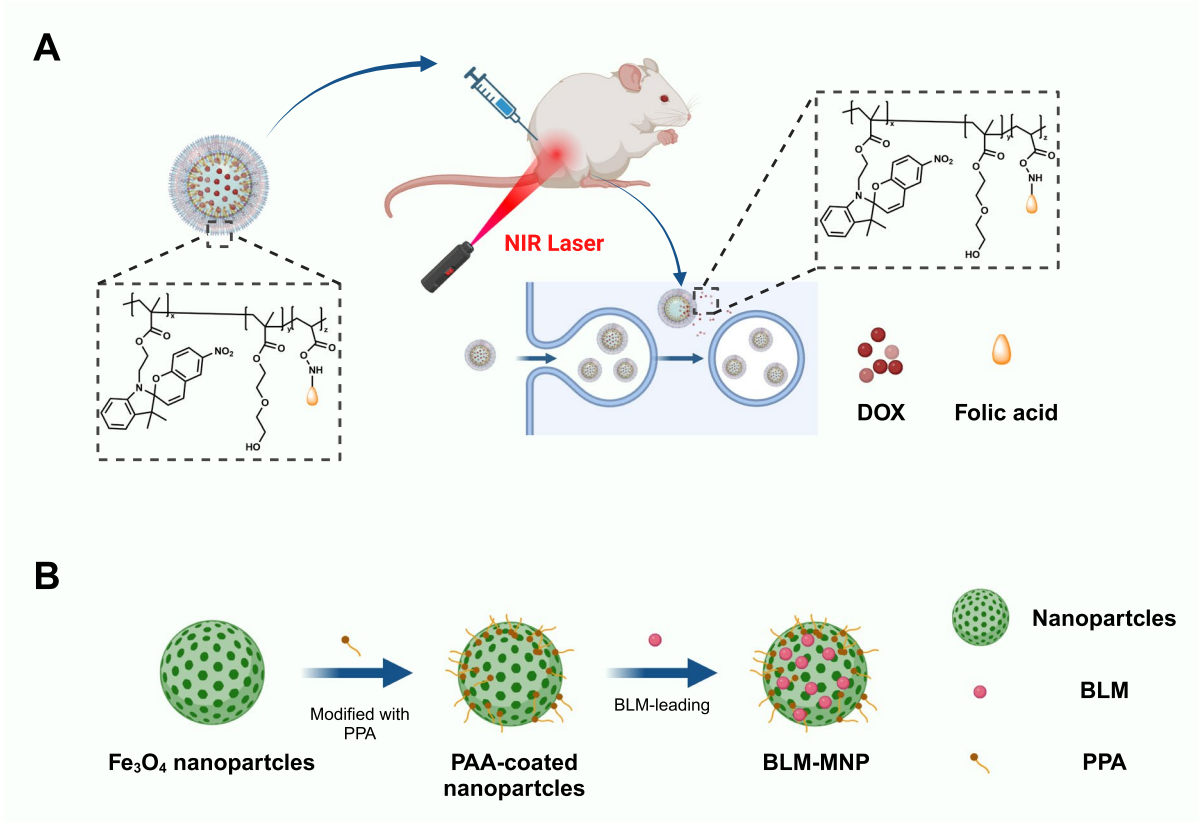

Fig. 6 Third-generation stimulus-responsive drug-loaded nanomaterials and their application in oral cancer (created by Biorender). **A** Schematic diagram of UCN/polymer multi-functional nano-composite material and NIR light-triggered drug release; **B** Schematic diagram of MNPs with outer decorated polyacrylic acid (PAA) and bonding with BLM molecules for drug delivery NP system

However, responsive nanomaterials still face some challenges. First, it is necessary to ensure that the response is rapid, reversible, and sufficiently specific to release drugs only at the target site. Second, due to the heterogeneity of the TME, combining multiple response mechanisms to achieve the optimal therapeutic effect has become a hot topic in subsequent research. Secondly, reproducibility and in vivo stability remain major limitations currently faced in the application of responsive nanomaterials. First, the issue of reproducibility primarily arises during the synthesis of nanomaterials. Minor variations in synthesis conditions, such as temperature, pH, and reaction time, can lead to differences in NP size, shape, and surface properties, ultimately affecting their responsiveness and therapeutic efficacy. This batch-to-batch variability presents challenges for large-scale production and clinical translation. Second, in vivo stability is another critical concern for the practical application of responsive nanomaterials. In complex physiological environments, nanomaterials may be affected by protein adsorption, enzymatic degradation, or clearance by the immune system, resulting in structural disruption or loss of function. For instance, certain pH- or redox-responsive materials may prematurely activate in the bloodstream, preventing effective drug release at the target site. Additionally, the long-term accumulation of nanomaterials in the body may pose potential toxicity risks or trigger immune responses. To improve the reproducibility and in vivo stability of responsive nanomaterials, it is necessary to optimize synthesis techniques, develop more stable material systems, and enhance biocompatibility and targeting efficiency through surface modifications such as PEGylation or biomimetic coatings. Furthermore, integrating advanced characterization

techniques and conducting systematic evaluations in both in vitro and in vivo models are essential approaches to overcoming these limitations.

Nanomaterial-based modifications for oral cancer therapy

Hydrogels have emerged as promising in situ delivery platforms for encapsulating nanomaterials in oral cancer treatment. Advanced bioresponsive multifunctional hydrogels exhibit unique advantages, allowing their use in drug delivery, diagnostics, vaccination, and immunotherapy (Advanced Bioresponsive Multitasking Hydrogels in the New Era of Biomedicine). Hydrogels possess a three-dimensional network structure, providing hydrophilicity and elasticity, resembling soft tissue environments. These characteristics confer biocompatibility, reducing immune rejection while serving as ideal carriers for nanomaterials. Due to their nanoscale dimensions, nanomaterials exhibit size-dependent effects, high surface area, and quantum confinement properties, enabling precise tumor targeting. They can be loaded with chemotherapeutic agents, gene therapy vectors, or photothermal and photodynamic therapy (PDT) agents, effectively inducing tumor cell destruction. For instance, some NPs carry high concentrations of chemotherapeutic drugs, ensuring controlled and sustained release at tumor sites, thereby increasing local drug concentration while reducing systemic toxicity. When hydrogels encapsulate nanomaterials, they complement each other: Hydrogels enable in situ formation and adaptive filling, ensuring precise tumor localization. The sustained release properties of hydrogels extend NP retention at the tumor site, improving therapeutic efficacy. During treatment, hydrogel-encapsulated nanomaterials can exert therapeutic effects through multiple mechanisms: Direct cytotoxicity—NPs deliver therapeutic agents to destroy tumor cell structures and functions. Physical barrier effects—Hydrogels prevent tumor cell migration and metastasis, buying more time for treatment. Studies in oral cancer animal models have shown that hydrogel-based nanomaterials significantly suppress tumor growth, reduce tumor volume, and improve survival outcomes, while minimizing side effects compared to conventional therapies. With continued research advancements and technological improvements, hydrogel-encapsulated nanomaterials may transition from laboratory research to clinical applications, offering new hope for oral cancer patients. In the future, hydrogels are expected to play a pivotal role in integrated cancer therapy, regenerative medicine, and the treatment of inflammatory, degenerative, genetic, and metabolic diseases. Biomimetic NPs, inspired by cell membrane camouflage strategies, have gained attention in oral cancer research (Alimohammadvand et al. 2024). These bioinspired delivery systems enhance immune evasion and improve tumor-targeted drug delivery. By mimicking cancer cell membranes, red blood cell (RBC) membranes, or leukocyte membranes, biomimetic NPs evade immune clearance, enhancing their accumulation at tumor sites via EPR effects, acidic pH, or tumor-specific enzyme activity. For example: Biomimetic NPs loaded with chemotherapeutic drugs, photosensitizers, or immunomodulators can efficiently target tumors after intravenous injection. Surface modifications with tumor-specific ligands (e.g., antibodies, peptides) further enhance targeting specificity, reducing systemic toxicity. Combining photothermal, photodynamic, or immunotherapy, biomimetic NPs represent a multi-modal approach for effective oral cancer treatment.

Niosomes, composed of nonionic surfactant-based vesicles, serve as versatile nanocarriers for oral cancer therapy (Sun et al. 2023). Niosomes protect drugs from premature degradation, extending therapeutic efficacy. Their unique structure enhances tumor targeting through EPR effects and endocytosis mechanisms. Upon reaching tumors, niosomes release drugs intracellularly, inducing apoptosis while minimizing systemic toxicity. Through precise tumor-targeted drug release, niosomes enhance the efficacy of chemotherapy and targeted therapy, providing a safer and more effective treatment option for oral cancer patients.

Emerging circulating nanocarriers, such as exosomes and miRNAs, exhibit immense therapeutic potential (Omrani et al. 2023; Moshrefiravasjani et al. 2024; Amoozgar et al. 2023). Exosomes provide biocompatibility and intrinsic tumor-targeting properties, while miRNA-loaded NPs regulate oncogenic pathways, suppressing tumor progression. Integrating circulating NPs into nanomedicine strategies represents a promising avenue for improving oral cancer treatment and patient prognosis. Exosomes, as naturally secreted nanovesicles, offer low immunogenicity and high biocompatibility, making them ideal drug delivery carriers. Leveraging their homing ability,

exosome-based therapies enable precise recognition and targeting of oral cancer cells. miRNAs, as endogenous non-coding RNAs, regulate gene expression and play key roles in cancer progression. miRNA-based therapeutics delivered via NPs can effectively suppress tumor cell proliferation, migration, and invasion. NPs serve as ideal carriers for exosomes and miRNAs, ensuring: Stable circulation in the bloodstream to resist enzymatic degradation and immune clearance. Efficient delivery to tumor sites, where exosomes fuse with cancer cells, releasing therapeutic cargo intracellularly. Multi-faceted anti-cancer effects, including growth suppression, apoptosis induction, and TME remodeling. This circulating NP-based drug delivery strategy represents an innovative and highly effective approach for oral cancer therapy, with the potential to significantly improve treatment outcomes and patient survival.

Utilizing the intrinsic properties of nanomaterials for oral cancer therapy

Nanomaterials have gained increasing applications in cancer therapy due to their unique physicochemical properties. Hyperthermia therapy employs localized heat to kill cancer cells, and nanomaterials serve as ideal carriers due to their high thermal conversion efficiency and targeting capability. Kinetic therapies, including nanozymes and sonocatalytic nanomaterials, demonstrate high efficacy and low toxicity, primarily catalyzing the production of ROS or gas molecules, thereby inducing cancer cell apoptosis. Recent research explores combination therapies integrating multiple therapeutic approaches for oral cancer treatment.

Hyperthermia therapy (Magnetic and PTT)

Nanomaterial-based hyperthermia therapy offers new strategies for oral cancer treatment. Hyperthermia involves localized heating to induce apoptosis in cancer cells, with nanomaterials providing high thermal conversion efficiency, targeting specificity, and synergistic effects. With advancements in technology, nanomaterial-mediated hyperthermia is expected to become a key treatment modality for oral cancer, improving therapeutic outcomes and quality of life.

Magnetic hyperthermia therapy (MHT) uses magnetic-sensitive nanomaterials to generate heat in alternating magnetic fields (AMF), increasing localized tumor temperatures and promoting cancer cell apoptosis. Studies indicate that MHT can also be effective in metastatic oral cancer (Di Corato et al. 2015; Li et al. 2016b, a). Christopher J. Legge et al. developed biocompatible silica-coated magnetic iron oxide NPs functionalized with αvβ6 integrin-targeting antibodies for oral cancer targeting. These MNPs efficiently induced tumor ablation via hyperthermia (Legge et al. 2019). Meng-Tsan Tsai et al. modified iron-gold bimetallic NPs (FeAu NPs) with MMP- 1 antibodies to achieve superparamagnetism and tumor-targeting ability. Under magnetic stimulation, these MMP-1 FeAu NPs raised the culture medium temperature to 45 °C, effectively inhibiting tumor growth (Tsai et al. 2021). PTT employs light-sensitive nanomaterials to convert light energy into heat, generating localized high temperatures to induce cancer cell apoptosis (Chen et al. 2019; Gao et al. 2021). AuNPs are among the most widely used materials in cancer diagnosis and therapy. Moustafa R.K. Ali et al. utilized gold nanorods (AuNRs) to trigger apoptosis via photothermal effects (Ali et al. 2016). HER2-conjugated gold–silica nanoshells demonstrated potential as PTT agents for oral cancer therapy (Sheikholeslami et al. 2011). Elena Navarro-Palomares et al. designed a high-affinity protein ligand (ShTxB) targeting globotriaosylceramide (GB3), which is overexpressed in precancerous and malignant oral cancer cells (Figure S2A). Functionalized ShTxB-AuNRs efficiently accumulated in GB3 + cells, inducing apoptosis (Navarro-Palomares et al. 2022). Lingling Cai et al. identified SERPINH1 as a key gene in oral cancer progression and developed SERPINH1-targeted gold nanostars for photothermal-assisted therapy, achieving promising results (Cai et al. 2022). Juanjuan Su et al. engineered an injectable hydrogel network composed of negatively charged proteins, chitosan molecules, and Ag3 AuS2 NPs, exhibiting high biocompatibility and photothermal conversion efficiency (Figure S2B). In an in situ oral cancer model, a single photothermal treatment eradicated tumors and prevented recurrence (Su et al. 2021). Metastasis is the leading cause of cancer-related mortality (Zhang et al. 2019; Ganesh and Massagué, 2021). AuNPs have been shown to inhibit cancer cell migration and prevent metastasis (Yin et al. 2023a, b; Huang et al. 2020). Moustafa R.K. Ali et al. developed Arg-Gly-Asp (RGD) peptide-functionalized AuNRs to target integrins and suppress migration. Controlled 808

nm NIR irradiation induced mild hyperthermia, disrupting cytoskeletal remodeling and reducing migration (Ali et al. 2017). GO NPs, known for their two-dimensional structure, high stability, superior photothermal sensitivity, and excellent biocompatibility, have garnered research interest (Taheriazam et al. 2023; Sharma and Mondal 2020). Functionalized GO NPs exhibit reduced toxicity and expanded biomedical applications (Sharma and Mondal 2020). Geyun Chen et al. synthesized amino-functionalized graphene oxide (AGO) NPs, significantly enhancing photothermal efficiency (Fig. 7A). Positively charged

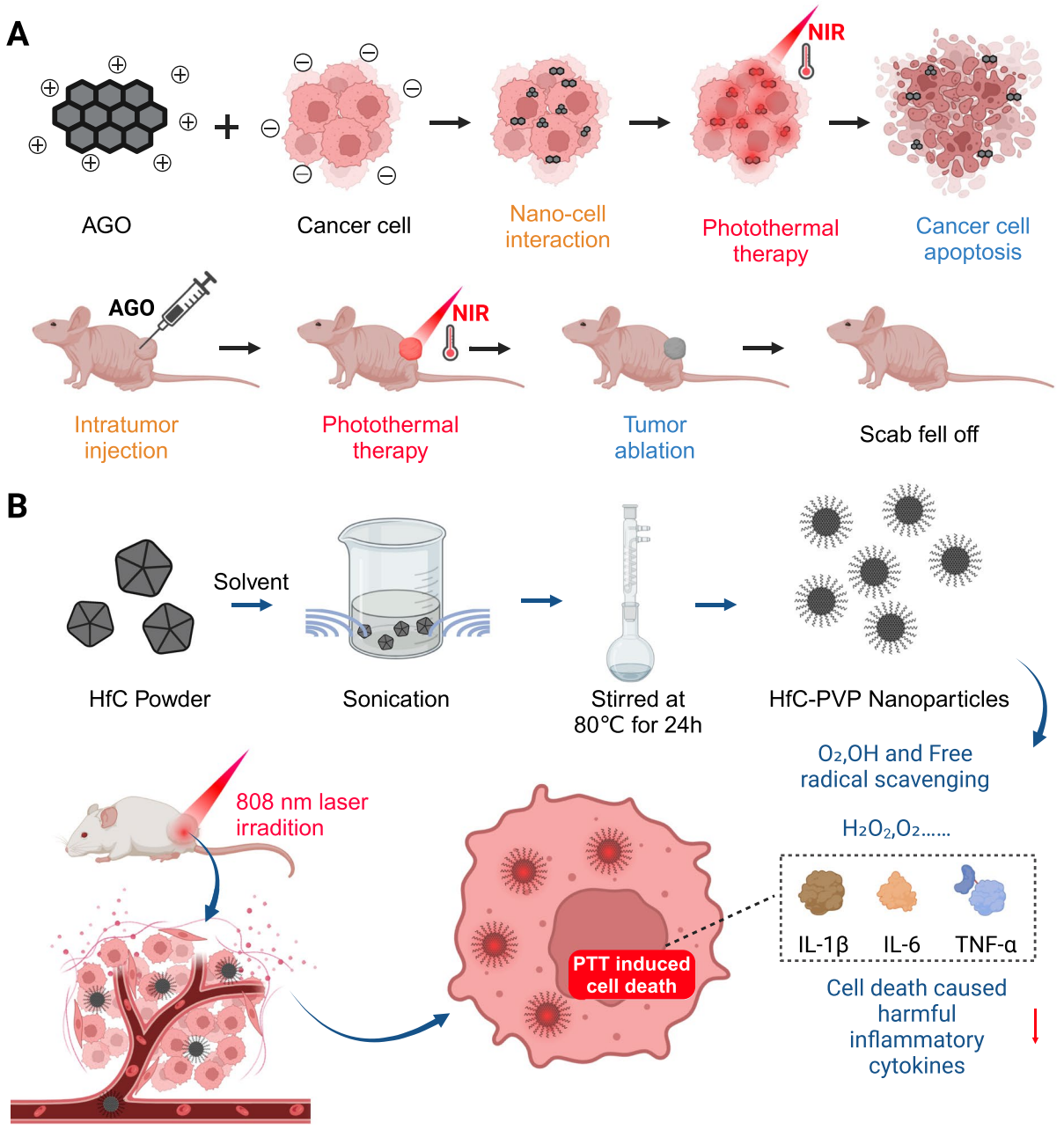

Fig. 7 Applications of Carbon Nanomaterial-Mediated PTT in Oral Cancer Treatment (created by Biorender). **A** Schematic illustration of the strong interaction between amino-modified AGO and cancer cells, along with the PTT effects under NIR irradiation; **B** Schematic of the preparation of HfC NPs and their application in non-inflammatory PTT for tumors

AGO efficiently interacted with tumor cells, accumulating in tumor tissues. Under NIR irradiation, AGO completely eradicated tumors in oral cancer-bearing mice (Chen et al. 2023a, b). In addition to the pure carbon monolayer structure, carbides formed by the combination of carbon with other elements (typically metals or metalloids) generally exhibit excellent chemical and thermal stability, making them more stable under specific therapeutic conditions. Yan Ma et al. and Haibin Mu et al. have respectively developed hafnium carbide (HfC) and silicon carbide (SiC) for PTT in oral cancer (PMID: 37540929; 34137419). Among them, hafnium carbide features a large surface area and inherent redox-active sites (Fig. 7B). Beyond its application in PTT, hafnium carbide also demonstrates outstanding anti-inflammatory properties due to its antioxidant capabilities and superoxide dismutase (SOD)-like enzyme activity (Ma et al. 2023). Additionally, silicon carbide with carbon defects, which possesses NIR absorption properties, not only prevents bacterial infections but also exerts an antibacterial effect on wounds (Mu et al. 2021), making it highly relevant for mitigating inflammation and infections associated with oral cancer. Organic nanomaterials have also emerged as a research hotspot in tumor PTT. For instance, small-molecule NPs (ITIC) based on a donor–acceptor-donor (D-A-D) structure have exhibited remarkable cytotoxicity against oral cancer cells and effective tumor ablation in vivo (Cai et al. 2019). Jianchuan Ran et al. constructed organic photothermal NPs (PBDB-TNP) using the photosensitizer PBDB. Their mild photothermal therapy (mPTT) not only synergistically enhances tumor elimination but also induces strong ICD, thereby triggering tumor-specific immune responses (Fig. 8A). During the mPTT-induced ICD process, a temperature-dependent release of damage-associated molecular patterns (DAMPs) was observed. Compared to conventional high-temperature hyperthermia, controlled rhythmic mPTT enhances anti-tumor effects and promotes abundant DAMP generation, achieving optimal immune activation. Experimental results demonstrated that rhythmic mPTT, combined with tumor ablation and ICD, exerts strong anti-cancer effects (Ran et al. 2022).

One of the significant advantages of organic nanomaterials over inorganic nanomaterials is their high modifiability, allowing researchers to integrate various additional functionalities (Zhang et al. 2018). For example, in 2021, Hongying Chen et al. developed a dual-targeted biomimetic DDS, Asp8(H40-TPZ/IR780@(RBC-H)), by modifying a mixed membrane composed of WSU-HN6 oral cancer cells (H) and RBC with an aspartate octapeptide (Asp8). This system was designed for bone metastasis and cancer targeting (Fig. 8B). The biomimetic NPs exhibit a typical core–shell spherical structure, allowing them to evade immune recognition, be selectively taken up by cancer cells, and primarily localize to bone sites invaded by oral cancer, enabling precise anti-cancer therapy during bone invasion (Chen et al. 2021a, b). In the same year, Zimu Li et al. designed a pH-responsive charge-reversible nanomaterial for oral cancer treatment. The researchers used dopamine-modified black phosphorus nanosheets (BP NSs), which possess photothermal conversion capabilities, as the base material. The surface was then modified with a polyacrylamide hydrochloride-dimethylmaleic acid (PAH-DMMA) charge-reversal system. In blood circulation, this material remains negatively charged; however, under the weakly acidic conditions of the TME, the cleavage of dimethylmaleic amide results in a positive charge, enabling strong electrostatic interactions with negatively charged oral cancer cell membranes. This enhancement in cellular uptake significantly increases the killing efficiency against oral cancer cells (Li et al. 2021a, b, c). Current clinical trials also highlight the potential of hyperthermia therapy. Ultrasound, CT, and MRI are commonly used imaging techniques to guide radiofrequency ablation probes during hyperthermia treatment and to evaluate therapeutic outcomes (Bortot et al. 2023; Solomon and Silverman 2010). As the field of medical imaging continues to evolve, new approaches for hyperthermia guidance are being explored, although some options have yet to demonstrate sufficient translational potential. Additionally, the biodegradability and long-term safety of nanomaterials are critical factors for their successful clinical application. Biodegradability ensures that nanomaterials can be naturally metabolized or excreted from the body after completing therapy, preventing potential long-term toxicity. For instance, biodegradable magnesium oxide (MgO) NPs have demonstrated excellent heat transfer properties in laser-based hyperthermia. However, the long-term safety of nanomaterials requires further investigation, particularly regarding the metabolic pathways of their degradation products, their effects on the

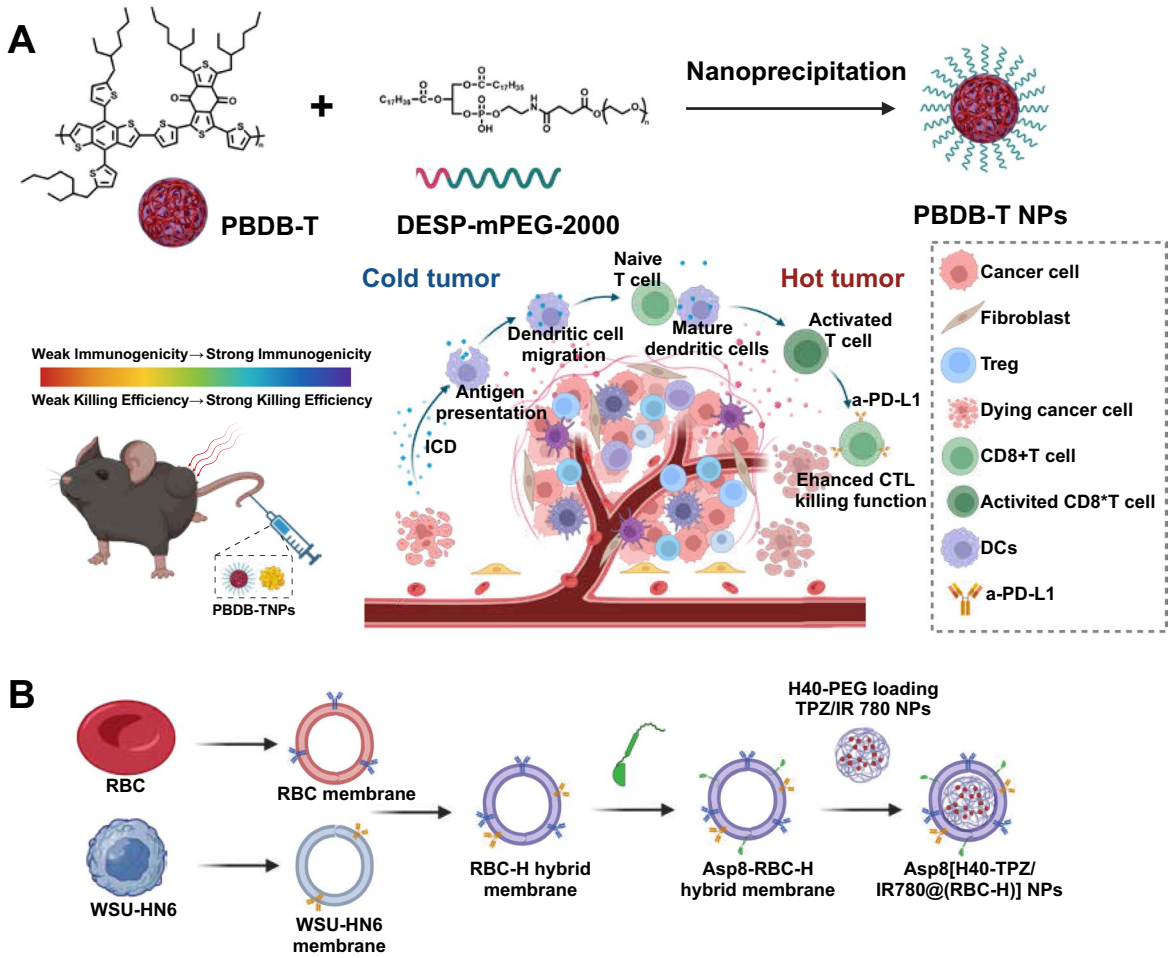

Fig. 8 Applications of Organic Nanomaterial-Mediated PTT in Oral Cancer Treatment (created by Biorender). **A** Schematic representation of the enhanced anti-tumor activity and immune activation induced by rhythmic mPTT; **B** Schematic diagram of the preparation of a dual-targeted nanobiomimetic drug delivery carrier Asp8(H40-TPZ/IR780@(RBC-H))

immune system, and potential accumulation-related risks. Establishing standardized evaluation frameworks and ensuring quality control in large-scale production are essential for the safe clinical application of these materials.

Kinetic therapy (PDT/CDT/sonodynamic therapy (SDT))

Kinetic therapy is an advanced medical treatment approach that includes PDT, CDT, and SDT. These therapies combine specific light, chemical, or sound wave sensitizers with corresponding external stimuli to induce therapeutic effects (Hu et al. 2021; Son et al. 2020; Gao et al. 2023). During the treatment, the sensitizer is first introduced into the patient's body and accumulates in the diseased site. Subsequently, specific light or sound waves activate the sensitizer, leading to the generation of highly reactive species or free radicals. These active substances cause localized tissue damage, achieving therapeutic effects.

PDT utilizes specific wavelengths of light in combination with photosensitizers to induce the production of ROS, leading to cell death (Zhou et al. 2016). Researchers have discovered that loading cisplatin (CDDP) into liposomes to form lipid-platinum-chloride NPs (LPC NPs) enhances the anti-cancer effects in tumor models. Based on this, Eka-Putra Gusti-Ngurah-Putu et al. further explored the application of LPC NPs combined with photosensitizers in PDT

for oral cancer treatment. Results indicated that PDT + LPC significantly reduced tumor volume and prolonged tumor growth inhibition, thereby reducing the frequency of chemotherapy (Gusti-Ngurah-Putu et al. 2019). However, traditional photosensitizer nanomaterials often suffer from fluorescence quenching due to molecular aggregation, reducing ROS generation efficiency. To address this, Wenbo Wu et al. designed AIEPS5, which exhibits AIE in the FR/NIR range and efficiently generates singlet oxygen (1O2) under 532 nm laser irradiation. To enhance its water solubility, researchers modified AIEPS5 with PEG, forming AIEPS5-PEG2000 (Figure S3A). Through hydrophobic interactions, AIEPS5-PEG2000 self-assembled into NPs and was further conjugated with anti-Her- 2 nanobodies for targeted oral cancer therapy (Wu et al. 2021). The results showed that the prepared AIEPS5-NPs-NB had a higher ability to generate 1O2, demonstrating superior therapeutic efficacy compared to the clinically approved photosensitizer Hemoporfin.

CDT utilizes Fenton or Fenton-like reactions to convert hydrogen peroxide (H_2O_2) into hydroxyl radicals (•OH), which damage lipids, proteins, and DNA, ultimately inducing cell apoptosis or necrosis (Cao et al. 2021). In 2023, Jiaqi Chen et al. designed intelligent drug-delivery NPs, Co-Fc@HCQ, which are composed of cobalt-ferrocene-based MOF materials (Co-Fc) loaded with the autophagy inhibitor hydroxychloroquine (HCQ). Co-Fc NPs exhibit strong Fenton reaction capabilities, generating hydroxyl radicals locally to kill tumor cells. Additionally, since tumors can maintain internal stability by removing foreign substances via autophagy, HCQ was incorporated to inhibit the fusion of autophagosomes with lysosomes, thereby reducing autophagic activity in tumor cells.

To enhance the tumor-targeting effect of CM@Co-Fc@HCQ NPs, researchers extracted oral cancer cell membranes to create biomimetic NPs with homotypic targeting and immune evasion properties. Results demonstrated that CM@Co-Fc@HCQ exhibited excellent tumor specificity, biocompatibility, and therapeutic efficacy (Chen et al. 2023a, b).

SDT utilizes sonosensitizers in combination with ultrasound waves to induce mechanical damage, leading to cancer cell death (Lin et al. 2020). In 2020, Lei Sun et al. developed an engineered mesenchymal stem cell (MSC)-based sonosensitizer, M/LPV/O_2 (Figure S3B), designed to optimize non-invasive SDT for oral cancer. M/LPV/O_2 consists of a liposomal formulation encapsulating perfluorocarbon (an oxygen carrier) and the sonosensitizer verteporfin, further coated with a functionalized MSC membrane. This system not only prolongs circulation time and enhances tumor targeting but also provides supplemental oxygen to overcome hypoxia-induced drug resistance in oral cancer. Experimental results demonstrated that even under hypoxic conditions, M/LPV/O_2 effectively stimulated ROS generation, significantly inducing oral cancer cell death. In vivo studies further revealed that, upon ultrasound stimulation, M/LPV/O_2 exhibited excellent tumor penetration and accumulation, effectively suppressing and eradicating tumors, thereby extending survival time (Sun et al. 2020a, b).

Finally, although dynamic therapy has shown potential in cancer treatment, its clinical application still faces numerous challenges. First, the therapeutic efficacy of SDT is highly dependent on the targeting ability of sonosensitizers and the specificity of the TME. However, the uneven distribution and insufficient targeting efficiency of sonosensitizers in vivo may limit treatment effectiveness. Second, SDT has limited penetration depth, particularly in deep-seated tumors or complex anatomical structures, where ultrasound attenuation and scattering may reduce therapeutic outcomes. Additionally, the safety of SDT requires further validation, as both sonosensitizers and ultrasound waves may induce adverse effects on normal tissues, such as inflammatory responses or tissue damage. Finally, the clinical standardization and large-scale application of SDT face technical bottlenecks, including the manufacturing process of sonosensitizers, optimization of treatment parameters, and synergistic effects in multimodal therapies. Addressing these limitations will require further fundamental research and clinical trials to advance the widespread clinical application of SDT.

Immunotherapy

The TME refers to the collection of immune-related cells, molecules, and mechanisms within tumor tissues that play a crucial role in tumor growth, progression, and metastasis (Binnewies et al. 2018). In many cancers, the TME can be manipulated into a tumor-favorable state, preventing immune cells from effectively recognizing and eliminating tumor cells.

For instance, tumor cells may release signaling molecules to recruit Tregs and myeloid-derived suppressor cells (MDSCs), thereby creating an immunosuppressive microenvironment that supports tumor growth (Lei et al. 2020). In oral cancer, immune checkpoint inhibitors (ICIs), such as PD- 1/PD-L1 inhibitors, are a major immunotherapy strategy. These drugs block the immune evasion mechanisms of tumor cells, enhancing the immune system's ability to recognize and attack cancer cells. Notably, pembrolizumab and nivolumab have shown improved survival outcomes in patients with recurrent or metastatic HNSCC, including oral cancer. Additionally, combining immunotherapy with chemotherapy or radiotherapy has demonstrated synergistic therapeutic effects. Emerging immunotherapeutic approaches, such as CAR-T cell therapy, are also being explored for oral cancer. However, the complexity and dynamic nature of the TME pose significant challenges for NP-based targeting of oral cancer cells. These challenges include: Abnormal tumor vasculature and complex hemodynamics, which affect NP transport and distribution. Dense ECM, hindering NP diffusion. Immune suppression, leading to rapid clearance of NPs by immune cells. Tumor heterogeneity, making it difficult for a single type of NP to effectively target all cancer cells (Azizi et al. 2023; Baghban et al. 2020). ICB therapy is a significant advancement in cancer immunotherapy. Its core principle is to block negative regulatory pathways of the immune system, thereby enhancing the anti-tumor immune response (Benci et al. 2016; Hassel et al. 2017). However, low tumor immunogenicity and the immunosuppressive TME are major barriers to achieving widespread ICB responses (Phuengkham et al. 2019). To address these challenges, Wen Su et al. combined TME-responsive nanoprodrugs (MPNPs) with oncolytic herpes simplex virus- 1 (OVs) to enhance immunotherapy through pyroptosis induction in oral cancer cells. MPNPs facilitate NP accumulation within tumors, reduce the CSC-like properties of tumor cells, and boost anti-tumor immune responses. Meanwhile, OVs enhance tumor penetration and induce pyroptosis, effectively reshaping the TME by converting "cold" tumors (immunologically inactive) into "hot" tumors (immune-active). This approach activates T cell-dependent anti-tumor immunity and enhances the efficacy of ICB therapy in controlling local tumor recurrence and lung metastasis (Figure S4) (Su et al. 2023). However, not all patients respond to immunotherapy, and some may develop severe immune-related side effects. Additionally, for tumors with highly immunosuppressive TMEs, single-agent ICB therapy may be insufficient, necessitating combination strategies with other treatment modalities.

Growing evidence suggests that malignant tumors are driven by a subpopulation of cancer cells with stem-like properties, known as CSCs. These cells are responsible for cancer relapse, drug resistance, and metastasis. Recent advancements in nanomedicine have paved the way for developing targeted therapies to eliminate CSCs, offering new hope for cancer treatment (Doustmihan et al. 2023).

The integration of artificial intelligence (AI) and nanoinformatics is enabling the identification of novel drug targets and facilitating the design of NPs for CSC-targeted therapies. Future nano-drug formulations will be tailored based on newly discovered molecular targets associated with cancer stemness, employing novel therapeutic compounds specifically designed to combat CSCs. NPs designed to target CSCs should possess: Optimized circulation stability to enhance tumor accumulation and penetration. Efficient cellular internalization for enhanced drug delivery. Controlled drug release mechanisms to maximize therapeutic effects. Endosomal escape capabilities to ensure intracellular drug activation.Specific targeting aptamers for CSC recognition. By incorporating these characteristics, intelligent NP-based therapies offer a promising avenue for overcoming CSC-mediated resistance and improving treatment efficacy.

Nanomaterials play a crucial role in enhancing ICI therapy, significantly improving both efficacy and precision: Targeted Drug Delivery: Nanomaterials can serve as drug carriers, facilitating precise delivery of PD- 1/PD-L1 inhibitors to tumor sites via surface-modified targeting ligands (e.g., antibodies or peptides). This reduces systemic drug exposure and minimizes adverse effects. TME Modulation: NPs can regulate the tumor immune microenvironment by: Releasing immune-stimulatory factors. Inducing ICD, thereby activating T cells for enhanced tumor eradication. Multimodal Therapy: Combining PTT or SDT with ICIs amplifies the immune response, forming a synergistic anti-tumor effect. Despite these advantages, challenges remain, particularly concerning NP immunogenicity and long-term safety. Further research is needed to ensure their widespread clinical application. In summary, nanomaterials

present innovative strategies for optimizing ICI therapy through targeted drug delivery, immune modulation, and combination therapy. By improving tumor targeting, reshaping the immune microenvironment, and integrating multimodal treatment, NPs offer a promising pathway to enhance the efficacy of ICIs.

Combination therapy

Combination therapy has long been an effective approach for cancer treatment, particularly the integration of thermal therapy, PDT, and other treatments such as radiotherapy and chemotherapy. These combination strategies are widely studied to enhance therapeutic outcomes and overcome treatment resistance.

Thermal therapy-based combination treatment A major research focus is the use of photosensitizers in PDT, which generate ROS upon exposure to specific wavelengths of light. Additionally, PTT can be achieved by converting light energy into thermal energy. For example: Beike Wang et al. utilized Rose Bengal and AuNRs for combined therapy (Wang et al. 2014). Wenzhi Song et al. developed ICG-gold nanocomposites for oral cancer treatment (Song et al. 2017). Given the malignant transformation risk of oral leukoplakia (OLK), clinical attention to its treatment has increased. In 2022, Lin Lin et al. designed ITIC-Th NPs (ITIC-Th NPs), an organic photosensitizer with high photothermal conversion efficiency and ROS generation under 660 nm laser irradiation (Figure S5A). In a precancerous oral cancer model, ITIC-Th NPs significantly inhibited OLK malignancy (Lin et al. 2022). To enhance catalytic therapy through PPT, Min Qian et al. introduced molybdenum diphosphide nanorods (MoP_2 NRs). These nanorods demonstrated peroxidase-like catalytic activity, breaking down H_2O_2 into hydroxyl radicals (•OH) to induce tumor cell and bacterial death under 808 nm laser irradiation (Qian et al. 2021). PTT has also shown significant potential in overcoming drug resistance in oral cancer. Long-term chemotherapy often induces drug resistance, leading to reduced efficacy. PTT, using AuNRs, carbon-based materials, or palladium-based nanomaterials, generates localized hyperthermia under NIR light, directly destroying tumor cells while bypassing traditional drug resistance mechanisms. Additionally, PTT induces ICD, releasing tumor antigens and activating an immune response, thereby enhancing anti-tumor immunity. Studies indicate that PTT combined with chemotherapy or immunotherapy significantly improves treatment efficacy against resistant oral cancer. For instance, nanocarriers co-delivering PTT agents and chemotherapy drugs can enhance synergistic effects, improving treatment outcomes. Thus, PTT not only provides a strategy to overcome drug resistance but also opens new avenues for multifunctional nanoplatforms.

Radiotherapy and chemotherapy remain common treatments for oral cancer. Standard chemotherapy regimens often include platinum-based drugs (e.g., cisplatin, carboplatin). The TPF regimen (paclitaxel + cisplatin + fluorouracil) and other platinum-based combinations with paclitaxel, fluorouracil, or cetuximab are frequently used. Additionally, EGFR-targeted therapy (e.g., nimotuzumab) has been combined with chemotherapy to improve treatment outcomes. However, chemotherapy and radiotherapy often face challenges such as toxicity, resistance, and variable sensitivity to radiation. PTT can mitigate these limitations (Lee et al. 2015a, b; Hao et al. 2022; Alamzadeh et al. 2020; Li et al. 2023). Ronghua Jin et al. developed a nanocomposite (PDA-SNO-GA-HA-DOX, PSGHD) that enhances chemotherapy through PTT (Jin et al. 2020). Xingyong Yin et al. (2023a, b) constructed DOX-loaded polymeric NPs (DOX/H_2O-PLA@PDA NPs) modified with H_2N-PEG-FA for targeted oral cancer therapy. The PDA component provided high photothermal conversion efficiency, significantly improving chemotherapy response under NIR irradiation (Yin et al. 2023a, b). In another study, Qiang Sun et al. developed cancer cell membrane-coated AuNRs (GNR@Mem) (Figure S5B). Under NIR and X-ray irradiation, these nanorods raised tumor temperatures and generated ROS, effectively damaging tumor DNA while minimizing systemic toxicity (Sun et al. 2020a, b). Similarly, thermal therapy was explored for radiotherapy enhancement (Neshastehriz et al. 2017). Maoru Zhao et al. designed polymer-modified tantalum NPs (Ta@PVP NPs) with high X-ray deposition ability, oxidative stress regulation, and efficient photothermal conversion to improve tumor oxygenation and enhance radiotherapy sensitivity. To optimize tumor retention, researchers introduced dopamine-alginate-based hydrogels (Ta@PVP-DAA) for TME-responsive gel formation. Results demonstrated

that photothermal-assisted radiotherapy using Ta@PVP-DAA hydrogel significantly inhibited oral cancer growth without facial deformities or damage to surrounding tissues (Zhao et al. 2023). Nanomaterials have great potential in combining chemotherapy with gene therapy for oral cancer, overcoming the limitations of traditional treatments while offering precise and effective therapeutic strategies. By encapsulating chemotherapy drugs and gene therapy agents (e.g., siRNA, miRNA, or plasmid DNA) in nanocarriers, synergistic effects can be achieved. Nanocarriers (e.g., liposomes, polymeric NPs, and exosomes) protect nucleic acid drugs from degradation, enabling controlled drug release. Multimodal strategies combining PTT/PDT further enhance efficacy. RNA-cleaving DNAzymes (DZ) hold great promise in RNA interference (RNAi) therapy due to high stability, biocompatibility, and specificity. MOF-coated MnO_2 nanosheets were developed for the co-delivery of DZ survivin inhibitors and DOX, demonstrating enhanced tumor suppression through a combination of DZ-mediated gene silencing, chemotherapy, and ROS generation (Nie et al. 2020). Both in vitro and in vivo studies have demonstrated that nanoplatforms significantly enhance anti-tumor efficacy. The improved tumor suppression was attributed to the combined effects of DOX-mediated chemotherapy, DNAzyme (DZ)-induced survivin gene silencing, and manganese (Mn^{2+})-facilitated ROS generation. This study presents an innovative strategy to overcome the key limitations of DZ in RNAi applications, allowing for its on-site activation and integration with other therapeutic modalities.

Despite the multiple advantages of PTT, heat shock responses within cancer cells often counteract the therapeutic effects. To overcome this, Bei-Ke Wang et al. designed a AuNR-siRNA nanocomposite for targeted BAG3 gene silencing to enhance PTT efficacy in immunotherapy. BAG3 inhibition effectively blocks heat shock responses, thereby increasing cancer cell sensitivity to PTT. Both in vitro and in vivo results confirmed that GNR-siRNA nanocomposites significantly downregulated BAG3 expression, leading to improved PTT-induced tumor destruction (Wang et al. 2016). A similar approach was adopted by Lin-Lin Bu et al., who utilized GNPs as carriers. These GNPs are degradable by MMPs, which are highly expressed in tumors. They were co-loaded with the photosensitizer ICG and STAT3 inhibitor NSC74859, achieving synergistic PTT-immunotherapy for oral cancer (Bu et al. 2021). A novel"ion-interference therapy"has been reported as an effective combination strategy with PTT. Chunxu Lv et al. synthesized GO-coated MOF NPs (ZIF- 8 NPs). These BSArGO@ZIF- 8 NS nanocomposites (Figure S5C), reduced with ascorbic acid and functionalized with bovine serum albumin (BSA), lead to intracellular Zn^{2+} overload. This overload activates autophagy pathways, disrupts cellular homeostasis, and induces mitochondrial damage, ultimately synergizing with GO-based PTT for effective oral cancer cell destruction (Lv et al. 2022).

Combination therapy facilitates multi-targeted interventions for oral cancer. PTT/PDT/chemotherapy-based combination strategies typically consist of a nanocarrier, a photosensitizer capable of both PTT and PDT, and a chemotherapeutic agent. Tingsheng Yan et al. developed a biodegradable, pH-responsive hollow mesoporous silica NP (HMSN-GM-CS-FA), which features controlled particle size and a larger internal hollow core, allowing it to co-load the photosensitizer pheophorbide a (PA) and the chemotherapeutic drug DOX to form HMSNs-GM-CS-FA@DOX/PA (Figure S6A). After FA-mediated targeting to oral cancer cells, the pH-dependent swelling effect of the coating facilitates the precise release of DOX and PA. Upon laser irradiation, the system effectively integrates PTT, PDT, and chemotherapy for synergistic anti-oral cancer treatment (Yan et al. 2020). The cysteine-rich secreted acidic protein receptor is overexpressed in various tumors, where it binds to human serum albumin (HSA) and facilitates its endocytic uptake. Yuxin Wang et al. utilized HSA as a carrier to load the photosensitizer ICG and the chemotherapeutic drug cisplatin for NIR-triggered PTT/PDT/chemotherapy (Wang et al. 2019a, b, c, d). Additionally, a dumbbell-shaped titanium dioxide (TiO_2)/AuNR composite (AuNRs-TiO_2@mS) with a mesoporous silica shell (mS) loaded with methotrexate (MTX) has been reported. In this system, MTX serves as the chemotherapeutic agent, TiO_2 acts as the PDT photosensitizer generating cytotoxic ROS, and AuNRs function as the PTT photosensitizer converting light energy into heat (Dash et al. 2023). Carrier-free nanosystems have also been explored. For instance, the anti-angiogenic drug sorafenib and the photosensitizer chlorin e6 can self-assemble into nanostructures for synergistic PTT/PDT and anti-tumor angiogenesis therapy (Wei et al.

2019). The combination of phototherapy, chemotherapy, and immunotherapy achieves tumor eradication through three complementary mechanisms. In 2023, Jun Zhou et al. developed a carrier-free DDS (DDS-IFNα1b-ICG-DOX, IID) through a simple one-step self-assembly process using three widely used clinical drugs: interferon-α1b (IFNα1b), the photosensitizer ICG, and the chemotherapeutic agent DOX (Figure S6B). IID exhibits high safety and, upon exposure to the acidic TME and NIR light, triggers the responsive release of therapeutic agents, achieving a synergistic PTT/PDT/chemotherapy/immunotherapy effect (Zhou et al. 2023). When the nano DDS enters the acidic tumor environment, its surface charge becomes positive and the NP size increases, leading to the release of DOX. Additionally, upon NIR irradiation, these larger particles rapidly decompose, releasing the remaining DOX, IFNα1b, and ICG, further enhancing the therapeutic effects and ultimately achieving potent tumor eradication.

Photodynamic combination therapy PDT is often combined with other treatment modalities to enhance therapeutic efficacy. For example: Hao Dai et al. developed a PDT-based system using MOF PCN-224 as a carrier for chloroquine (CQ), an autophagy inhibitor. The oral cancer cell membrane was coated on the MOF surface, enabling tumor targeting. Under laser irradiation, the system produced ROS to induce apoptosis, while the released CQ further inhibited protective autophagic flux, enhancing ROS-induced tumor cell death (Dai et al. 2022). Shurui Shi et al. combined PDT and chemotherapy, designing a ROS-responsive nanodrug system for targeted oral cancer therapy. They synthesized a thioether-linked PEG prodrug of DOX (RPTD) modified with cRGD peptides, and encapsulated the photosensitizer hematoporphyrin (HP) within RPTD, forming RPTD/HP NPs. Upon laser irradiation, ROS were generated, leading to tumor cell destruction and cleavage of the thioether bond, thereby releasing DOX in a controlled manner. This synergistic PDT-chemotherapy approach effectively inhibited oral cancer growth (Shi et al. 2018). Combining PDT with immunotherapy is another promising strategy. For instance, a system combining 5-aminolevulinic acid PDT (ALA-PDT) with MTHFD1L shRNA was developed, using chitosan/tripolyphosphate (CS-TPP) as a carrier for oral cancer treatment (Wang et al. 2021). Since PDT requires oxygen to generate ROS, its efficacy is often limited by the hypoxic TME. To address this, in 2022, Jia-Ying Zhou et al. developed a hypoxia-adaptive photodynamic immunotherapy nanosystem (TiO_2@Ru@siRNA). This system consisted of rhodium-modified titanium dioxide NPs loaded with hypoxia-inducible factor- 1α (HIF- 1α) siRNA (Figure S7). Under visible light irradiation, TiO_2@Ru triggered PDT-induced lysosomal damage. The HIF- 1α siRNA suppressed hypoxia-induced signaling, enhancing oxygen generation and further boosting PDT efficacy. Additionally, TiO_2@Ru@siRNA downregulated key immunosuppressive factors, upregulated immune cytokines, and activated $CD4^+$ and $CD8^+$ T lymphocytes, effectively remodeling the immune microenvironment and inhibiting oral cancer growth (Zhou et al. 2022).

Potential toxicological impacts of combination therapy While nanomaterial-based combination therapies (e.g., PTT and chemotherapy) show remarkable synergistic anti-tumor effects, their potential toxicological impacts warrant attention. NPs may accumulate in the body, triggering immune or inflammatory responses. Some NPs are captured by the MPS, leading to hepatic or splenic toxicity. PTT generates high temperatures, which can damage surrounding healthy tissues, especially when NP distribution is uneven. Controlled Release and Biodegradation of Nanocarriers While nanocarriers improve targeted chemotherapy, their release kinetics and degradation products must be strictly regulated to avoid toxicity to healthy tissues. Certain degradation products may be cytotoxic or induce oxidative stress. Further research indicates that NP toxicity depends on size, shape, surface modifications, and degradation properties. Additionally, NP exposure pathways (e.g., inhalation, skin contact, or injection) can influence their toxicological behavior. Strategies to Reduce Nanotoxicity To minimize the potential toxicity of nanomaterial-based therapies, researchers are exploring several strategies: Surface modification to reduce immune recognition. Development of biodegradable nanomaterials to limit long-term toxicity. Application of machine learning and high-throughput screening to optimize NP design, balancing therapeutic efficacy and safety. Overall, while nanomaterial-based combination therapies significantly improve anti-tumor outcomes, they also pose complex toxicological

challenges. Future studies should optimize material design, develop novel safety assessment methods, and promote interdisciplinary collaboration for clinical translation.

Nanomaterials as imaging contrast agents for oral cancer diagnosis

The integration of nanomaterials into medical imaging has opened new avenues in the diagnosis of oral cancer, driving transformative advances in imaging technologies. As contrast agents, nanomaterials significantly enhance imaging resolution and sensitivity while enabling the development of multimodal imaging platforms (Jiang et al. 2023; Smith and Gambhir 2017). Nanomaterials have demonstrated immense potential in the field of imaging due to their high sensitivity, resolution, and excellent targeting ability. As technology progresses, various advanced imaging techniques such as MRI, surface plasmon resonance scattering (SPRS), surface-enhanced Raman spectroscopy (SERS), optical imaging, and photoacoustic imaging (PAI) are being adopted for the diagnosis of oral cancer, each with its unique advantages and characteristics. In the following sections, we explore the integration of these imaging techniques with nanomaterial-based contrast agents, highlighting key breakthroughs and innovations that are reshaping the landscape of oral cancer diagnosis.

MRI

MRI is a noninvasive diagnostic technique that utilizes a strong magnetic field and radiofrequency pulses to induce nuclear magnetic resonance in hydrogen atoms within the body. By detecting these resonance signals, high-resolution two- or three-dimensional images of internal tissues can be reconstructed (Kuhl 2019). Nanomaterials play multiple roles in MRI diagnostics, primarily as contrast agents that enhance image contrast, thereby improving the identification of lesion areas (Busquets et al. 2015). Wu et al. developed modularly assembled, targeted NPs by functionalizing nanomaterial surfaces with self-assembled targeting moieties. The resulting RGD4 C-Fe_3O_4 NPs exhibited strong targeting capabilities and provided high-resolution molecular imaging contrast in both oral cancer cell models and animal models with elevated $\alpha v\beta_3$ integrin expression (Wu et al. 2008). In another study, Shanavas et al. encapsulated FA-chitosan conjugates onto PLGA NPs co-loaded with paclitaxel and superparamagnetic iron oxide NPs (SPIONs) (Figure S8A). FA was used for active targeting, and the coated protonated amine groups endowed the material with sensitivity to acidic pH (Figure S8B). Although polymer encapsulation and FA-chitosan coating slightly reduced the magnetic properties of SPIONs, the core aggregation of SPIONs effectively shortened the overall T_2 relaxation time, thereby enhancing NP relaxivity and improving in vitro MRI performance (Shanavas et al. 2017).

However, in current clinical practice, MRI procedures are relatively time-consuming, often requiring patients to remain motionless for extended periods, which contributes to higher operational costs. Moreover, MRI is contraindicated in certain patient populations, such as those with implanted metal devices or pacemakers. Although nanomaterials improve MRI contrast, their sensitivity may still be insufficient for detecting small or early-stage lesions, increasing the risk of missed diagnoses or misinterpretation.

SPRS

SPRS is an optical imaging technique that leverages the localized surface plasmon resonance (LSPR) effect of metal NPs. When light interacts with the surface of these NPs, it induces collective oscillations of surface plasmons, resulting in pronounced scattering and absorption peaks (Priest et al. 2021). In SPRS, nanomaterials are primarily employed as scattering-enhancing agents to amplify signal intensity and improve imaging sensitivity (Philip and Kumar 2022).

Studies have shown that conjugated NPs tend to aggregate more readily than their unconjugated counterparts, leading to significantly enhanced SPRS signals (Katsutoshi and Katsuhisa 1985). AuNPs exhibit unique optical properties and hold considerable promise as biosensors for live-cell imaging (Hua et al. 2021).Ivan H. El-Sayed and colleagues conjugated colloidal AuNPs with monoclonal antibodies targeting the epidermal growth factor receptor (anti-EGFR) and acquired SPRS images and absorption spectra in cultured cells using a simple and cost-effective approach. Within the cytoplasm, these NPs can

exist in either dispersed or aggregated states. While malignant cells may exhibit nonspecific uptake of NPs, they still enable detailed intracellular labeling. Notably, AuNPs conjugated with anti-EGFR antibodies demonstrate strong specificity for cancer cell surfaces, significantly enhancing binding affinity. This targeted interaction results in narrower surface plasmon resonance (SPR) absorption bands and pronounced redshifts. These findings suggest that SPRS imaging and SPR absorption spectroscopy using antibody-conjugated AuNPs may serve as valuable tools for molecular biosensing in both in vivo and in vitro applications related to oral cancer diagnosis and research (El-Sayed et al. 2005).

However, a key limitation of nanomaterial-mediated SPRS lies in its reliance on optical imaging principles, which inherently restrict imaging depth and resolution, limiting its suitability for in vivo imaging and real-time monitoring of oral cancer.

SERS

SERS is a highly sensitive spectroscopic technique that exploits the electromagnetic enhancement effect generated by metal nanostructures to amplify molecular Raman scattering signals (Mandal and Tewari 2022). Its underlying principle is based on the significant increase in Raman signal intensity when target molecules are adsorbed onto rough metallic surfaces or nanostructures. By utilizing inelastic scattering of light—typically in the visible, NIR, or near-UV range—SERS enables the differentiation of normal, precancerous, and malignant oral tissues (Katsutoshi and Katsuhisa 1985). In normal tissue, Raman scattering signals tend to be relatively uniform, whereas in malignant tissues, the signals are heterogeneous, reflecting distinct chemical compositions and molecular structural alterations associated with pathological changes (Sharma et al. 2023).

SERS-active metal NPs significantly enhance the temporal resolution and imaging quality of Raman-based techniques, enabling the acquisition of detailed dynamic cellular information and monitoring of cellular responses to potential therapeutic agents (Shen et al. 2021). Jeon Woong Kang et al. developed a method for high-speed, high-resolution live-cell Raman imaging by employing small spherical AuNPs featuring narrowly spaced nanogap structures responsive to NIR excitation, in combination with high-speed confocal Raman microscopy. Three distinct Raman-active molecules embedded within the nanogaps generated strong and uniform Raman signals in solution, allowing rapid acquisition of high-resolution single-cell images without inducing substantial cellular damage. Moreover, the resulting Raman images clearly delineated the intracellular distribution of AuNPs at specific sites such as the cytoplasm, mitochondria, and nucleus, thereby facilitating real-time monitoring of morphological changes associated with cell death processes (Kang et al. 2015).

However, obtaining highly sensitive SERS signals requires the design of complex nanostructures with precisely controlled and uniformly distributed nanogaps. These stringent design parameters necessitate high-precision synthesis and fabrication techniques, which can significantly increase the development and production costs of SERS-based contrast agents. Moreover, although SERS offers molecular-level resolution, NPs introduced into complex biological environments—such as the oral cavity—may interact nonspecifically with various biomolecules. Consequently, SERS contrast agents must exhibit high selectivity and specificity to accurately distinguish target lesions from surrounding healthy tissues.

Optical imaging

Optical imaging refers to the acquisition of images through the interaction of visible or NIR light with biological tissues. This technique encompasses fluorescence imaging, two-photon imaging, optical coherence tomography (OCT), and other modalities (Wu et al. 2019). In this context, nanomaterials are employed as contrast agents to enhance image brightness and contrast, thereby improving visualization and diagnostic accuracy (Padmanabhan et al. 2016). For instance, quantum dots (Chen et al. 2021a, b; Li et al. 2022b, a), AuNPs (Fan et al. 2020a, b), and dye-loaded NPs are all known for their excellent fluorescence or scattering properties.

OCT is an imaging modality that employs infrared light to generate cross-sectional images of subsurface tissues. It offers high-resolution imaging comparable to histopathological analysis, with resolution levels surpassing those of conventional imaging techniques such as MRI and ultrasound (Dauerman 2023). Moreover, OCT enables the visualization of microstructural features, including

intercellular architecture, which is critical for the early detection of oral cancer (Heidari et al. 2019). In a clinical study involving 28 oral cancer patients, optical scans of tumor margins were performed in the immediate ex vivo stage. The average epithelial thickness at tumor-free margins was 360 μm, whereas tumor-infiltrated margins exhibited an average thickness of 567 μm. These findings indicate that tumor invasion can be identified by structural alterations and epithelial thickening (Hamdoon et al. 2016). In 2018, researchers prepared responsive plasma gold nanoclusters as contrast agents for OCT to detect early oral cancer. Plasma AuNPs assembled into Au NC via acid-cleavable linkers, which decomposed into individual AuNPs under weakly acidic tumor environments (Figure S9A), reducing SPR effects and enhancing Brownian motion. OCT imaging with Au NC allowed for the visualization of tissues, displaying decreased scattering intensity and increased Doppler variance in abnormally proliferating cancerous tissue (Kim et al. 2018).

Fluorescence imaging is a biomedical technique that utilizes the fluorescence properties of molecules or fluorescent probes. These fluorophores absorb light at specific wavelengths and emit light at longer wavelengths upon excitation (Li et al. 2020a, b). In cancer research and therapy, fluorescence imaging is widely employed to detect tumor location, size, and therapeutic response—particularly during interventional procedures—thereby facilitating more precise tumor localization and resection (Koch and Ntziachristos 2016). Its major advantages include high contrast, molecular or cellular specificity, and a non-invasive or minimally invasive profile, making it well-suited for real-time monitoring and repeat imaging. In a clinical study involving 156 patients with oral cancer, those who underwent fluorescence-guided surgical resection exhibited a significantly lower three-year local recurrence rate. These findings underscore the utility of fluorescence imaging in guiding surgical margin decisions and highlight its role in reducing local recurrence in early-stage oral cancer (Poh et al. 2016).

However, nanomaterial-based optical imaging is primarily constrained by its limited tissue penetration, restricting its application to superficial lesions. Additionally, intrinsic tissue autofluorescence and light scattering can interfere with imaging accuracy. To address these limitations, the development of nanomaterials with extended absorption and emission wavelengths represents a promising strategy for achieving clearer localization and delineation of oral cancer lesions.

PAI

PAI is an emerging medical imaging modality that employs laser or other light sources to illuminate biological tissues. The uneven distribution of light-absorbing molecules induces localized thermal expansion, generating acoustic waves that are detected and reconstructed into images (Lin and Wang 2022; Zhao et al. 2022; Fu et al. 2018). By integrating the high contrast of optical imaging with the deep tissue penetration of ultrasound, PAI enables non-invasive, radiation-free imaging (Choi et al. 2023). This technique has been successfully applied to the diagnosis of various deep-seated tumors, including lung cancer (Lucero and Chan 2021; Jung et al. 2019), liver cancer (Yu et al. 2019), and colorectal cancer (Bi et al. 2021).

Jun Xiong et al. developed multifunctional, targeted polymeric NPs co-loaded with the photosensitizer ICG and DOX for PAI–guided photothermal ablation of oral cancer (Figure S9B). These NPs were conjugated with stromal cell-derived factor 1 (SDF- 1) and tumor-specific antibodies via carbodiimide chemistry, enabling active targeting through interactions with overexpressed CXCR4 and SDF- 1 receptors on tumor cells. Upon NIR light irradiation, ICG converted light into acoustic signals, allowing real-time monitoring of tumor progression. In vitro tissue studies confirmed the NPs'ability to suppress lymph node metastasis of oral cancer (Xiong et al. 2019). In a study by Geoffrey P Luke et al., they synthesized a molecularly activated plasma nanoprobe-based sensor (MAPS) that can be used for ultrasound-guided spectral PAI (sPA) of micrometastases in lymph nodes. In a mouse model of oral cancer metastasis, MAPS targeting EGFRs of oral cancer cells exhibited specific interactions with metastatic cells in lymph nodes, allowing the transfer of their optical absorption spectra to the red-NIR region for noninvasive detection using sPA. Experimental results indicated that MAPS could detect lymph node metastases as small as 50 μm at depths of centimeters, demonstrating high sensitivity and specificity (Luke et al. 2014).

Due to the heterogeneous absorption of laser light by biological tissues, PAI signals generated by nanomaterials can be distorted by surrounding non-target tissues, reducing image contrast and diagnostic accuracy for oral cancer. Additionally, several factors—such as hemodynamics, targeting efficiency, and the physicochemical stability of the nanomaterials—can influence their in vivo distribution during PAI. These variables may result in signal inconsistencies and hinder the reliability of oral cancer imaging.

Clinical applications of nanodiagnostic materials and their impact on imaging sensitivity and specificity

Since the launch of the U.S. Cancer Nanotechnology Plan two decades ago, nearly 40 NP formulations have received clinical approval, with several others undergoing clinical translation (Anselmo et al. 2021, Namiot et al. 2023; Pallares et al. 2022). The first clinically used NPs were 99 mTc colloids for planar scintigraphy and later single-photon emission computed tomography (SPECT) imaging. These radiolabeled sulfur colloids have been in use since the mid-1960 s (Thakor et al. 2016). SPIONs have also been employed for macrophage imaging in patients with high-grade gliomas (Iv et al. 2019). Overall, the integration of nanomaterials into medical imaging technologies has significantly enhanced the sensitivity and specificity of MRI, SERS, SPRS, and PAI. In MRI, magnetic nanomaterials such as superparamagnetic iron oxide NPs serve as contrast agents by altering local magnetic fields, thereby significantly enhancing signal intensity and improving the detection sensitivity of pathological tissues such as tumors. Furthermore, surface modification with targeting molecules enables specific imaging. In SERS and SPRS, noble metal nanomaterials like gold and silver NPs amplify Raman or optical signals through LSPR, enabling single-molecule detection and highly specific recognition of biological markers. In PAI, nanomaterials such as AuNRs or carbon-based materials function as light absorbers, converting optical energy into acoustic waves for high-resolution deep tissue imaging. The sensitivity and specificity of these methods can be further optimized by adjusting the size, shape, and surface chemistry of the nanomaterials. Despite these advancements, challenges remain regarding the biocompatibility, long-term stability, and potential toxicity of nanomaterials. Extensive research is needed to ensure their clinical safety and efficacy. In summary, nanomaterials, by enhancing signal intensity and targeting ability, open new possibilities for the advancement of medical imaging technologies. A Nanobionic Delivery System for Tumor Hypoxia Modulation and Imaging-Guided Cancer Therapy. A biomimetic nanodelivery system has been designed to improve tumor hypoxia, respond to the TME, and effectively load ICG. This system offers a cost-effective and convenient strategy for synergistic phototherapy and CDT in cancer treatment (Wang et al. 2024).

Nanomaterials for integrated diagnosis and therapy of oral cancer

The integration of diagnostics and therapeutics on a nanoscale platform presents an innovative approach for early disease detection and immediate intervention, combining the precision of nanotechnology with the comprehensive needs of modern medicine. By incorporating drugs, imaging agents, and therapeutic components into a single nanocarrier, this platform enables simultaneous imaging and treatment of pathological lesions. Its primary advantage lies in its high targeting specificity, which minimizes systemic side effects, enhances therapeutic efficacy, and allows real-time monitoring of treatment responses—thereby advancing personalized medical care.

Unimodal imaging-guided single/multi-modality therapy

MRI-or CT-guided therapy for oral cancer

MRI, with its high resolution and superior soft tissue contrast, enables precise visualization and differentiation between tumors and normal tissues, thereby facilitating targeted therapy. For example, Marites P. Melancon et al. synthesized multifunctional superparamagnetic iron oxide-gold shell NPs (SPIO@Au NS) with optical and magnetic properties and decorated them with C225 monoclonal antibodies to achieve targeted therapy, imaging, and treatment of oral cancer through EGFR targeting (Melancon et al. 2011). Moreover, MRI-guided multimodal therapy has shown promising results. Rui Ge et al. designed a theranostic nano-platform based on Cu^{2+}-loaded polydopamine NPs (CuPDA NPs), enabling

MRI-guided photothermal combined chemotherapy. Cu^{2+} is released in the acidic TME while simultaneously increasing the electron–proton dipole–dipole interaction-related time τC, shortening the T1 of the PDA NPs to enhance the longitudinal relaxivity (r1), thus serving as a T1-weighted contrast agent in MRI. In vivo and in vitro results showed that CuPDA NPs exhibited prolonged circulation time, leading to their maximum accumulation at the tumor site and enhanced therapeutic efficacy against oral cancer (Ge et al. 2017). In a similar manner, as drug-resistant tumor cells often result in increased sialic acid and higher cell membrane potential, Shuwei Liu et al. prepared PEG-encapsulated Cu(II) and vincristine-chondroitin sulfate A co-doped polyaniline nano-shells (VCR-PEG-CuPani-NSs). These positively charged nanospheres target tumor cells and accumulate at the tumor site, enabling real-time MRI monitoring of photothermal combination therapy (Liu et al. 2019).

CT offers high-resolution, three-dimensional imaging, enabling accurate localization and assessment of oral cancer for effective treatment planning. Sisini Sasidharan et al. synthesized branched gold NPs (BGNs) via a straightforward reduction method (Figure S10). These BGNs demonstrated strong CT contrast capabilities and exhibited photothermal properties under 800 nm laser irradiation, effectively inducing cytotoxicity in various tumor cell types, including oral cancer cells. As such, BGNs hold significant potential for combined CT imaging and PTT applications in oral cancer diagnosis and treatment (Sasidharan et al. 2016).

FL or PAI-guided oral cancer treatment

Fluorescence imaging-guided therapy for oral cancer is a diagnostic and therapeutic strategy that employs fluorescent probes to label cancer cells and enables real-time monitoring through fluorescence detection techniques. This approach offers high-contrast, real-time visualization, effectively delineating tumor margins from adjacent healthy tissues. Its high-resolution imaging capability facilitates the detection of subtle pathological changes, thereby enhancing treatment precision and minimizing damage to surrounding normal tissues.

In a single treatment approach guided by FL, Rahul K Das et al. (Das et al. 2023) employed Tween-X as a structure-directing agent to synthesize size-uniform nitrogen-rich mesoporous carbon NPs for FL-guided PTT. Furthermore, combined treatment approaches guided by FL have also received attention. Guorong Zhang et al. developed novel NPs based on a new semiconductor molecule (ITTC) with strong photostability, high photothermal conversion efficiency, and good singlet oxygen (1O2) generation capability. The results demonstrated that the combination of ITTC NPs and TPZ presented excellent synergistic effects in oral cancer tumor ablation through PTT, PDT, and hypoxia-activated chemotherapy (Zhang et al. 2021).

The advantages of NIR FL imaging lie in the stronger tissue penetration and lower autofluorescence background of NIR light. The more red-shifted the wavelength, the more notable the effect. In 2019, Yufeng Wang et al. (Wang et al. 2019a, b, c, d) loaded a novel NIR-II probe, TQTPA, and the chemotherapeutic drug cisplatin (CDDP) onto hyaluronic acid carriers to prepare HT@CDDP NPs. These NPs clearly outlined the contours of in situ tongue tumors and metastatic lymph nodes, enabling a combination of chemotherapy and PTT. Subsequently, in 2021, Mengqin Gu et al. (Gu et al. 2021) designed yttrium-doped hydroxyapatite (HATb) loaded with the NIR photothermal agent PDA and the anti-cancer drug DOX using the same strategy for FL imaging-guided chemotherapy-PTT combination therapy in oral cancer. Additionally, to target oral cancer angiogenesis, Huihui Zou et al. prepared an organic semiconductor molecule, T8IC, and incorporated the anti-angiogenic drug sorafenib into it to form TS NPs through nanoprecipitation. Under NIR-II light irradiation, FL imaging guided the sorafenib-induced disruption of tumor blood vessels, combined with PTT/PDT for oral cancer eradication (Zou et al. 2021). Leitao Zhang et al. designed AIE tunable NPs NMB@NPs (Figure S11A). Upon accumulation in the tumor, when exposed to 808 nm laser irradiation, the NMB in NMB@NPs generated photothermal effects, causing the nanomaterial to break down and release carbon radicals. Meanwhile, the FL of NMB guided the corresponding thermodynamic therapy (TDT) and PTT synergy, inhibiting oral cancer growth (Zhang et al. 2023a, b).

This section highlights the application of PAI, which integrates the high contrast of optical imaging with the deep tissue penetration of ultrasound, to guide oral cancer therapy. For instance, in 2021, Sujuan Zeng and colleagues designed and synthesized

multifunctional NPs composed of hyaluronic acid-modified AuNRs and mesoporous silica, loaded with DOX (Figure S11B). These NPs enabled PAI-guided synergistic chemotherapy and PTT, demonstrating effective therapeutic outcomes without significant toxicity to normal tissues (Zeng et al. 2021).

Dual-modality imaging-guided mono/multi-therapy

Dual-modality imaging, which integrates two complementary imaging techniques, enables precise localization of oral cancer and provides enhanced diagnostic accuracy and therapeutic monitoring. In 2018, Xiangdong Xue et al. developed dual-size and charge-switchable "Trojan horse" NPs (pPhD NPs) (Figure S12). These NPs undergo transformation in the TME, reducing in size and increasing surface charge to enhance tumor penetration and cellular uptake in oral cancer cells. The pPhD NPs offer dual-modality imaging capabilities: NIR FL imaging enables real-time visualization of biodistribution, while MRI monitors NP accumulation and therapeutic response at the tumor site. This approach effectively guided PTT, PDT, and chemotherapy in both subcutaneous and orthotopic oral cancer models, achieving complete tumor eradication (Xue et al. 2018).

Dual-modality imaging combined with photostimulation offers an effective approach for both diagnosis and treatment. For instance, in 2022, M. Ling et al. synthesized the NIR-II fluorescence dye SQ890, which was assembled into NPs for NIR-II fluorescence/PAI dual-modality imaging-guided PTT of oral cancer (Ling et al. 2022).

Another example involves the integration of MRI with chemiluminescence (CL) signals. In 2023, Yining Tao et al. employed lanthanide coordination chemistry and flash nanoprecipitation (FNP) technology to construct a multifunctional nanomaterial, Pa–Mn&CH-A@P, which combines a photosensitizer, MRI contrast agents, and CL probes. The MRI component enabled high-resolution tracking of in vivo biodistribution, while the CL signal provided real-time feedback on the PDT response at the tumor site (Tao et al. 2023).

Multimodal imaging-guided single/multiple therapies

Multimodal imaging, integrating two or more imaging modalities, holds great potential for precise treatment of oral cancer. In 2023, Zhe Yang et al. developed multifunctional Au/Mn NDs capable of simultaneous CT, MRI, and NIR FI imaging, serving as a guide for treatment and converting NIR light into heat for PTT of oral cancer. The use of Au/Mn NDs for CT/MRI imaging allows for accurate positioning prior to treatment, while NIR FL can be used to determine tumor boundaries during PTT (Yang et al. 2023). A biomimetic nanodelivery system has been developed to improve hypoxia, respond to the TME, and effectively load ICG. This system offers a cost-effective and convenient strategy for synergistic phototherapy and CDT in cancer treatment (Wang et al. 2024). In the same year, Mengqin Gu et al. utilized the same imaging techniques to prepare upconversion hydroxyapatite (FYH) NPs doped with rare earth ions, followed by modification with PDA and DOX to create FYH-PDA-DOX. FYH-PDA-DOX exhibited high photothermal conversion efficiency and, under low pH and NIR irradiation, selectively released DOX with FL/CT/MRI used to monitor the metabolic distribution of FYH-PDA-DOX in vivo, providing real-time feedback on treatment efficacy (Figure S13). The research findings demonstrated that, upon exposure to an 808 nm laser, the responsive release of DOX significantly enhanced PTT/chemotherapy effectiveness while also triggering ICD and an anti-tumor immune response. Therefore, FYH-PDA-DOX possesses prospects as an intelligent nano platform for multimodal imaging-guided multi-modal therapy of oral cancer (Gu et al. 2023). Early diagnosis of oral cancer is crucial for improving treatment outcomes. Multimodal imaging systems, which integrate multiple imaging techniques such as CT, MRI, and optical imaging, provide comprehensive and precise tumor information, significantly enhancing diagnostic sensitivity and specificity. For instance, CT effectively visualizes the three-dimensional structure of tumors, while MRI offers high-resolution imaging of soft tissues. When combined with optical imaging techniques such as fluorescence imaging, real-time intraoperative navigation becomes possible. The integration of nanomaterials has led to revolutionary breakthroughs in multimodal imaging. By designing multifunctional nanoprobes, multiple imaging modalities can be incorporated into a single nanoplatform. For example, selenium-based and manganese carbonate-based theranostic agents enable MRI imaging while also providing high-resolution tumor boundary information

through PAI. Additionally, the high surface area and modifiability of nanomaterials allow for the attachment of targeting ligands such as antibodies or peptides, facilitating the specific recognition of tumor biomarkers and enhancing imaging precision. In summary, nanomaterials enhance the sensitivity, specificity, and functionality of multimodal imaging systems, offering new possibilities for the early diagnosis and precise treatment of oral cancer. With the continued advancement of nanotechnology, multimodal imaging systems are expected to become standardized tools in oral cancer diagnosis.

Real-time monitoring capabilities of nanomaterial-based theranostic platforms

Nanomaterial-based theranostic platforms, often referred to as "integrated diagnosis and treatment" platforms, provide real-time monitoring capabilities, a core advantage in precision medicine (Ma et al. 2016; Li et al. 2024). By integrating diagnostic and therapeutic functionalities within a single nanosystem, these platforms enable dynamic tracking of disease progression and treatment efficacy, facilitating personalized therapeutic adjustments. The real-time monitoring capabilities of nanomaterials stem from their high surface area and multifunctionality, allowing them to simultaneously carry imaging agents, therapeutic drugs, and targeting ligands. Furthermore, nanomaterials with responsive properties—such as pH-sensitive, redox-sensitive, or enzyme-sensitive designs—can activate imaging functions or release drugs in response to specific biological conditions, providing real-time feedback on TME changes. For instance, pH-responsive nanomaterials can selectively release drugs in the acidic TME while enabling fluorescence or PAI to monitor drug release and therapeutic effects in real time. Similarly, photothermal nanomaterials such as AuNRs or carbon-based materials generate localized heat upon NIR irradiation, enabling tumor ablation while allowing for real-time temperature monitoring via PAI to minimize damage to normal tissues. A study by Liu et al. (Chen et al. 2014) demonstrated the synthesis of self-assembled HSA-IR825 complexes, where IR825 binding to HSA resulted in a new absorbance band at 600–630 nm, leading to high fluorescence quantum yield (42%) and efficient photothermal conversion under 820 nm irradiation. This theranostic system achieved both NIR imaging and PTT, enabling effective tumor ablation at low doses. Similarly, Chen et al. (Huang et al. 2014) reported a novel"chameleon"theranostic platform composed of NIR dye IR820 loaded into ferritin nanocages (DFRT). The tight packing of IR820 molecules within DFRT resulted in fluorescence quenching at 550 nm excitation while preserving fluorescence at 770 nm, effectively integrating fluorescence imaging with PTT. The multimodal imaging capabilities of nanomaterials further enhance the precision of real-time monitoring. By combining MRI, fluorescence imaging, and PAI into a single nanoplatform, complementary biological information can be obtained. MRI provides high-resolution structural data of deep tissues, while fluorescence and PAI enable molecular-level monitoring with high sensitivity. Despite their immense potential, the clinical application of nanomaterial-integrated theranostic platforms faces challenges such as long-term biocompatibility, degradation pathways, and potential immunogenicity. Additionally, the processing and analysis of real-time monitoring data require advanced computational algorithms to enable rapid and accurate decision-making. As nanotechnology advances and interdisciplinary collaborations deepen, nanomaterial-integrated theranostic platforms are expected to play a pivotal role in the management of cancer, cardiovascular diseases, and neurodegenerative disorders, providing strong technological support for precision medicine. The Role of Machine Learning and Bioinformatics in Oral Cancer Staging and Treatment Planning Machine learning and bioinformatics play an increasingly critical role in the staging and treatment planning of oral cancer. By integrating multi-omics data (e.g., genomics, transcriptomics, and proteomics) with clinical information, these technologies provide more precise staging and personalized treatment strategies (Su et al. 2022). Machine learning algorithms such as support vector machines, random forests, and deep learning models can analyze vast amounts of patient data, including imaging, pathology, molecular markers, and medical history, to more accurately predict tumor stage, invasiveness, and metastatic potential. For example, by analyzing tumor gene expression profiles or mutational characteristics, machine learning models can identify key molecular biomarkers associated with tumor progression, helping differentiate early-stage and late-stage cases and even predicting responses to specific treatments.

Bioinformatics tools enable the integration of oral cancer data from public databases such as The Cancer Genome Atlas (TCGA), revealing potential biological pathways and drug targets, thus providing a scientific basis for treatment decisions. Additionally, AI-driven imaging analysis can automatically detect tumor features in CT, MRI, or pathology slides, improving the objectivity and accuracy of staging. By combining clinical data with machine learning predictive models, clinicians can devise more precise treatment plans, such as determining surgical margins, radiation doses, or targeted therapy options, ultimately optimizing therapeutic outcomes while minimizing side effects. In conclusion, machine learning and bioinformatics provide data-driven decision support for the staging and treatment of oral cancer, promoting the development of precision medicine and significantly improving patient prognosis and quality of life.

Cost-effectiveness of nanotechnology-based diagnostic and therapeutic solutions and translational research for clinical implementation

Nanotechnology-based diagnostic and therapeutic solutions not only enhance medical outcomes but also offer significant cost-effectiveness advantages. First, the multifunctionality and high sensitivity of nanomaterials enable the integration of diagnosis and treatment into a single platform, reducing the need for multiple examinations and procedures, thereby lowering medical expenses. For instance, nanotheranostic platforms can simultaneously achieve tumor localization, drug release, and therapeutic effect monitoring in a single procedure, eliminating the high costs associated with multiple imaging scans and surgeries required by conventional methods. Second, the high targeting precision of nanomaterials significantly improves treatment efficiency, reducing drug dosage and adverse effects, which further lowers treatment costs. For example, nanocarrier-based chemotherapeutics can deliver drugs directly to tumor sites, minimizing damage to normal tissues while enhancing bioavailability, thus reducing drug wastage. Additionally, the application of nanotechnology in early disease diagnosis, such as nanomaterial-based biosensors, enables early detection and intervention, preventing the progression to advanced disease stages that require expensive treatment. However, the initial research and development, as well as manufacturing costs of nanotechnology, remain high, and its implementation requires rigorous regulatory and safety assessments, which may limit widespread adoption in the short term. Overall, as technology matures and large-scale production is achieved, nanotechnology-based diagnostic and therapeutic solutions are expected to significantly improve the cost-effectiveness of healthcare systems in the long run, benefiting both patients and healthcare providers.

The successful translation of nanotechnology innovations into routine clinical practice requires systematic research to overcome the challenges associated with transitioning from laboratory research to clinical applications. First, fundamental research must explore the physicochemical properties, biocompatibility, and mechanisms of action of nanomaterials to ensure their safety and efficacy in vivo. This includes in vitro studies and animal models to validate the targeting ability, drug release kinetics, and toxicity of nanomaterials. Second, translational research must address the technical challenges of large-scale production, including nanomaterial synthesis processes, quality control, and large-scale stability assessments to ensure clinical applicability. Furthermore, clinical trials play a crucial role in verifying the feasibility and safety of nanotechnology. Multicenter, randomized controlled trials are needed to evaluate therapeutic efficacy, side effects, and long-term impacts. Regulatory approval and the establishment of standardized guidelines are also critical for facilitating the clinical adoption of nanotechnology. Given the complexity of nanomaterials, regulatory agencies need to develop new evaluation frameworks to assess their safety, pharmacokinetics, and efficacy. Lastly, interdisciplinary collaboration across materials science, biology, medicine, and engineering, along with industry-academia partnerships, can accelerate the translational process of nanotechnology. In conclusion, systematic translational research is essential for bringing nanotechnology innovations from the laboratory to clinical practice, providing more precise and effective solutions for disease diagnosis and treatment.

The integration of nanomaterials into existing approved therapies presents several regulatory challenges. First, the unique physicochemical properties of nanomaterials (e.g., size, shape, surface charge) may result in biological behaviors that differ significantly from traditional drugs, necessitating a

reassessment of their safety, efficacy, and toxicological characteristics by regulatory agencies. For example, nanomaterials may cross the blood–brain barrier or placental barrier, potentially leading to neurotoxicity or reproductive toxicity, which must be thoroughly evaluated in clinical trials. Second, the complexity of nanomaterial characterization and standardization increases regulatory hurdles. Since the performance of nanomaterials is highly dependent on their physicochemical parameters (e.g., particle size distribution, surface modifications), regulatory agencies need to establish new characterization methods and standards to ensure consistency and reproducibility. Additionally, the long-term biocompatibility of nanomaterials and the impact of their degradation products on human health and the environment remain unclear, requiring comprehensive risk assessments before regulatory approval. Finally, due to the multidisciplinary nature of nanomaterials, regulatory agencies must collaborate closely with experts in materials science, toxicology, and clinical medicine to develop scientifically sound regulatory frameworks. In summary, while nanomaterials hold great potential for therapeutic applications, addressing regulatory challenges requires technological innovation, standardization, and multidisciplinary collaboration to ensure their safety and efficacy.

Nanomaterials for the treatment of localized oral cancer and future prospects

The application of nanotechnology in oral cancer treatment represents a major advancement in modern medicine. Initially, nanomaterials were incorporated into anticancer DDSs due to their excellent biocompatibility and efficient drug-carrying capabilities. These systems exploit the unique physicochemical properties of NPs to improve the targeted delivery of chemotherapeutic agents to malignant tissues, thereby minimizing systemic distribution and reducing toxicity to healthy cells. Beyond drug delivery, nanomaterials have also emerged as effective imaging contrast agents for the early diagnosis and monitoring of oral cancer. Owing to their distinctive optical and electronic properties, nanoscale contrast agents significantly enhance imaging resolution and sensitivity, particularly in multimodal imaging techniques such as MRI, SPRS, and SERS, thus facilitating better detection and tracking of disease progression. As research advances, the role of nanomaterials has expanded beyond drug carriers or imaging agents to include direct therapeutic applications, leveraging intrinsic properties such as photothermal and photodynamic effects to ablate cancer cells. A particularly promising development is the emergence of theranostic nanoplatforms that integrate diagnostic and therapeutic functions within a single system. These multifunctional systems enable real-time disease monitoring, adaptive treatment modulation, and immediate feedback on therapeutic efficacy, thereby advancing the prospect of personalized oral cancer therapy. We have summarized the applications of nanomaterials in oral cancer diagnosis and treatment in Table 2 and provided a comparative illustration of the different materials discussed in this study and their respective applications in oral cancer (Figure S14) (Umapathy et al. 2023). Looking forward, continued progress in nanomaterial design and synthesis, coupled with deeper insights into oral cancer pathophysiology, is expected to yield more efficient, safer, and highly precise nanoscale DDSs. These innovations hold great promise for optimizing treatment strategies, improving patient survival rates, and enhancing quality of life. Nevertheless, several critical challenges remain, as outlined in the following section.

How can nanomaterials avoid clearance from the body while ensuring they do not accumulate for extended periods?

The in vivo behavior of nanomaterials is inherently complex. Ideally, nanomedicines should remain in circulation long enough to reach the target site and exert their therapeutic effects. However, prolonged retention may result in undesirable accumulation and potential toxicity. Current strategies to modulate circulation time often involve surface modifications, such as PEGylation, which improves blood stability and enhances tumor-targeting efficiency. Nevertheless, excessive PEGylation can introduce unintended consequences, including increased protein adsorption, which may alter the biodistribution and pharmacokinetics of the nanomaterials.

Table 2 Applications of nanomaterials in the diagnosis and treatment of oral cancer

Application Field	Strategy	Advantages	Disadvantages
Diagnosis	Nanoparticle Detection	High sensitivity enables early detection of oral cancer biomarkers	High cost
		Rapid and accurate, e.g., gold nanoparticles and quantum dots for cancer cell detection	Requires complex equipment and technical support
Diagnosis	Nanosensors	High specificity for detecting biomolecules in the oral environment	Stability needs further validation
		Suitable for early diagnosis	Clinical applications remain immature
Diagnosis	Imaging Technology	Enhances imaging resolution and contrast	Potential biological toxicity
		Example: superparamagnetic iron oxide nanoparticles for MRI	Targeting needs optimization
Treatment	Nanodrug Carriers	Targeted drug delivery reduces side effects	Drug release control needs optimization
		Increases drug concentration at tumor sites	Long-term safety remains to be validated
Treatment	Photothermal Therapy	Uses nanoparticle-mediated photothermal effects for precise tumor ablation	Limited effectiveness for deep-seated tumors
		Minimally invasive with low side effects	Requires specific wavelength light sources
Treatment	Immune Activation	Nanomaterials activate the immune system to enhance anti-cancer effects	Potential risk of excessive immune response
		Example: bismuth-based nanomaterials generating hydrogen peroxide for immune activation	Long-term effects require further research
Treatment	Radiotherapy Enhancement	Nanomaterials improve radiotherapy efficacy while reducing radiation dosage	Possible damage to normal tissues
		Example: gold nanoparticles enhance radiotherapy sensitivity	Optimization of targeting is required
Treatment	Tissue Regeneration	Nanomaterials promote oral tissue regeneration	Slow repair process
		Example: nano-hydroxyapatite for repairing damaged tissue	Long-term effects require further validation

Based on the aforementioned issues and integrating findings from previous studies, we propose several possible solutions:

1. Designing biodegradable nanomaterials that can degrade under specific internal and external conditions ensures the material can decompose itself and be safely eliminated from the body after exerting therapeutic effects.
2. Developing novel responsive PEG chains that can detach from the surface of NPs upon reaching the target site, reducing the accumulation of nanomaterials within the body. Specific conditions in the TME can trigger the detachment of PEG chains, such as pH-sensitive bonds or enzyme-sensitive linkers.
3. Managing protein corona formation by adjusting the surface charge or hydrophobicity of NPs or using specific anti-protein adsorption coatings, reducing the formation of protein coronas. The development of materials with a"protein corona repulsion"function can decrease plasma protein adsorption and improve biodistribution.
4. Designing NPs with surfaces that possess multiple functional groups to avoid recognition by the

immune system before reaching the tumor target and enhance their specificity and therapeutic efficiency under specific conditions.
5. Optimizing the biodistribution and pharmacokinetics of NPs by accurately controlling the degree of PEGylation and PEG chain length, avoiding excessive PEGylation.
6. Investigating the use of autologous materials, such as autologous RBC membranes or platelet membranes, to wrap NPs, improving their biocompatibility and avoiding clearance by the immune system.
7. Developing NPs that can release therapeutic agents precisely in time and space, minimizing damage to surrounding normal oral tissues and reducing toxicity.
8. For oral cancer, since the treatment site is relatively well-defined and expansive, the design of locally applied biodegradable nanomaterials may also be an effective approach.

How can nanomaterials achieve specificity for oral cancer over other types of cancer?

Effective targeted therapy for oral cancer necessitates the identification and exploitation of tumor-specific biomarkers. To enhance specificity, nanomaterials can be functionalized with ligands—such as antibodies, small molecules, or peptides—that selectively bind to receptors overexpressed on oral cancer cells. For instance, the C225 monoclonal antibody has been used to target EGFR, a protein commonly overexpressed in oral cancer cells (Ge et al. 2017). However, this strategy also presents challenges, as many target receptors are not exclusive to oral cancer and may be expressed in healthy tissues or other tumor types, potentially resulting in off-target drug accumulation and associated toxicity.

Based on previous studies, the anticipated solutions are as follows:

1. Multi-targeting: Designing NPs that simultaneously target several specific biomarkers overexpressed in oral cancer, using this multi-targeting strategy to enhance selectivity and reduce accumulation in non-cancerous cells.
2. TME exploitation: Developing NPs that can respond to unique oral cancer microenvironment conditions, activating or altering their surface properties and releasing therapeutic agents only in the TME to enhance specificity targeting and reduce drug exposure to normal tissues.
3. Cell membrane camouflage strategy: Using the membrane of oral cancer cells to cloak NPs, reducing immune system clearance through this"disguising"technique and increasing their affinity for oral cancer cells.
4. Precise control of targeting ligand density and arrangement: Adjusting the density and spatial arrangement of surface-targeting ligands on NPs to enhance their affinity and specificity for overexpressed receptors.
5. Dynamic surface modifications: Developing NPs capable of dynamically changing their surface properties in response to the in vivo environment, effectively adapting to different biological barriers and enhancing their specificity.

Patient-specific applications of nanomaterials and challenges in achieving personalized treatment

Nanomaterials have demonstrated immense potential in the medical field, particularly in patient-specific applications. However, achieving personalized treatment using nanotechnology presents several challenges. Current clinical studies and trials remain in early stages of development. From a therapeutic perspective, nanomaterials can be designed to deliver drugs precisely based on individual patient disease characteristics. For instance, for patients with specific genetic mutations associated with cancer, nanocarriers can be modified to recognize abnormal surface proteins on cancer cells, facilitating highly efficient targeted therapy. This approach significantly enhances treatment efficacy while minimizing damage to normal tissues. However, realizing patient-specific applications is challenging. One major issue is the substantial variability in physiological conditions and metabolic rates among individuals. Different patients'immune systems may respond differently to nanomaterials—some may exhibit heightened immune activation, recognizing nanomaterials as

foreign substances and triggering strong immune rejection, leading to treatment failure or severe adverse reactions. Conversely, some patients may have weak immune responses, rendering nanomaterials ineffective. Another significant challenge lies in obtaining precise and detailed physiological data from patients. Current diagnostic techniques are not yet capable of accurately tracking nanomaterial distribution, metabolic pathways, and interactions with biomolecules within the body, making it difficult to tailor nanomaterial-based treatments to individual patients. In the field of oral cancer treatment, nanomaterials offer unique advantages that hold promise for patient-specific applications. By designing nanomaterials to target specific molecular markers in oral cancer tissues, researchers can create highly precise therapeutic approaches. For instance, in oral cancer patients with specific genetic mutations or overexpressed proteins, NPs can be surface-modified with corresponding ligands to selectively bind to cancer cells. These NPs can efficiently deliver chemotherapeutic drugs or enable PTT, thereby improving treatment efficacy while reducing damage to healthy oral tissues. However, several barriers hinder the personalization of nanomaterial-based treatments for oral cancer. First, the heterogeneity of oral cancer tumors among patients is highly pronounced. Genetic expression, proteomic characteristics, and TMEs vary significantly among individuals, making it difficult to develop a single nanomaterial-based treatment applicable to all patients. Additionally, patients' physiological conditions and lifestyle habits may impact nanomaterial efficacy. For example, oral cancer patients with long-term smoking or alcohol consumption histories may exhibit altered mucosal physiology and metabolism, potentially affecting nanomaterial absorption, distribution, metabolism, and excretion, thereby influencing treatment outcomes. Furthermore, current diagnostic technologies remain insufficiently precise and comprehensive in capturing key data on nanomaterial dynamics within oral cancer tissues, their interactions with cancer cells, and the patient's immune response to nanomaterials. This lack of data presents a significant obstacle to designing truly personalized nanomaterial-based treatments. Moreover, from an economic and time–cost perspective, tailoring nanomaterial treatments for each oral cancer patient is expensive and involves lengthy development cycles, posing a major challenge for large-scale clinical application.

Challenges in the clinical application of nanomaterials for oral cancer

Currently, several liposomal formulations have been used for the treatment of ovarian cancer, HIV-associated Kaposi's sarcoma, and various solid tumors, including Doxil®/Caelyx® liposomes (Li et al. 2022b, a) and Myocet® liposomes for breast cancer treatment (Mrózek et al. 2005). However, according to the World Health Organization's clinical database, nanomaterials for oral cancer treatment—such as PLGA-PEG NPs loaded with QCT—remain in the clinical trial phase and have not yet achieved widespread clinical adoption. The clinical translation of nanomaterials faces several challenges. Key issues include standardization of manufacturing processes, ensuring biocompatibility, achieving long-term stability, and scaling up production. While preclinical studies demonstrate promising therapeutic potential, clinical outcomes may be influenced by factors such as patient variability, the TME, and tumor heterogeneity. Furthermore, the pharmacokinetics, biodistribution, and potential toxicity of nanomedicines require comprehensive investigation, as these variables may result in unanticipated outcomes or adverse effects during clinical trials.

Therefore, to address these issues, the following measures should be taken:

1. Develop highly reproducible and scalable manufacturing processes to ensure consistency in the quality of nanomedicines per batch.
2. Assess the biocompatibility and potential long-term toxicity of nanomaterials through rigorous preliminary research and long-term follow-up.
3. Advance personalized treatment by utilizing individual genomics and tumor-specific biomarkers to tailor nanotherapy, thereby enhancing efficacy and reducing side effects.
4. Develop smart nanocarriers and precision DDSs to optimize the pharmacokinetic properties of nanomedicines through chemical modifications or the use of biomolecules, aiming to enhance their biodistribution and reduce systemic toxicity.

Future research directions for nanotechnology in oral cancer treatment

The integration of AI with nanotechnology is expected to revolutionize oral cancer treatment strategies. AI, with its powerful data analysis and pattern recognition capabilities, can significantly optimize treatment approaches. By analyzing large-scale clinical data, including patient demographics, tumor characteristics, and treatment outcomes, AI algorithms can predict the most effective treatment strategies for individual patients. For instance, AI can determine whether a patient would benefit more from traditional chemotherapy and radiotherapy or from novel combination therapies. Nanomaterials can be engineered with unique functionalities such as targeted drug delivery, enhanced imaging capabilities, and improved therapeutic efficacy. When combined with AI, the design of personalized nanomaterials for oral cancer treatment can be further refined. AI can simulate interactions between nanomaterials and biological systems at the molecular level, predicting how different nanomaterial structures, surface modifications, and drug-loading strategies will behave in the complex oral cancer microenvironment. This enables researchers to develop nanomaterials precisely tailored to the genetic and molecular characteristics of individual patients' oral cancer. For example, AI-driven modeling can help design nanocarriers that specifically target overexpressed receptors on certain oral cancer cells. These nanocarriers can be engineered to deliver drugs or therapeutic agents in a controlled manner once they reach the tumor site, thereby improving treatment efficacy while minimizing systemic side effects. Looking ahead, the future research directions of nanomaterials in oral cancer treatment should focus on further deepening this integration. Development of Advanced AI Models: More sophisticated AI models should be developed to account for the complex factors influencing oral cancer progression, such as the impact of the oral microbiome on tumor growth. Large-Scale Synthesis and Manufacturing of AI-Optimized Personalized Nanomaterials: Research should focus on developing new manufacturing technologies to ensure the reproducibility and quality control of these custom-designed nanomaterials. Long-Term Safety and Biocompatibility Studies: A deeper understanding of the long-term safety and biological fate of AI-designed nanomaterials is required. This includes evaluating their potential to trigger immune responses, the fate of their degradation products, and their effects on normal oral tissues over time. In summary, the integration of AI and nanotechnology is establishing a new paradigm in oral cancer treatment. By leveraging AI's capabilities to optimize treatment strategies and enhance the design of personalized nanomaterials, more effective and patient-specific treatment methods are on the horizon.

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Declarations

Ethical approval Ethics is not applicable because this study is based exclusively on published literature.

Consent for publication Not applicable.

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