Proteolysis-targeting chimeras in oral squamous cell carcinoma: Current evidence, translational challenges and future directions (Review)

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Received February 20, 2026; Accepted June 1, 2026

DOI: 10.3892/mmr.2026.13955

Abstract. Oral squamous cell carcinoma (OSCC) poses a significant clinical challenge due to its high recurrence rate, resistance to treatment and the functional morbidity associated with current therapies. Although proteolysis-targeting chimeras (PROTACs) have emerged as a promising oncological platform, their application in oral cancer remains in the early stages, largely supported by preclinical data. The present review reconsiders PROTAC development from an OSCC-specific perspective, rather than a generalized cross-cancer framework. Key findings directly relevant to OSCC/head and neck squamous cell carcinoma are highlighted, distinguishing them from hypotheses extrapolated from other solid tumors. Biologically validated candidate targets for protein degradation are summarized, and delivery strategies are evaluated for their translational relevance to the oral cavity. Local transmucosal delivery, stimuli-responsive activation and microneedle-assisted locoregional administration are particularly promising for OSCC, as these approaches may enhance local selectivity while minimizing systemic exposure. This review also assesses the current clinical validation of the degrader platform in other malignancies, noting that these results should be interpreted as platform-level evidence, not as oral cancer-specific conclusions. Finally, major barriers to translation in OSCC are outlined, including inadequate disease-specific target validation, delivery challenges, on-target/off-tumor toxicity and the lack of clinically relevant preclinical models. In conclusion, PROTACs offer a promising, though still nascent, therapeutic framework for OSCC, with future advancements reliant on biomarker-guided target prioritization, oral-cavity-specific delivery optimization and dedicated translational research.

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Key words: proteolysis targeting chimera, oral squamous cell carcinoma, head and neck squamous cell carcinoma, drug discovery, molecular targeted therapy

Contents

1. Introduction

Oral cancer, primarily represented by oral squamous cell carcinoma (OSCC), accounts for a significant proportion of head and neck squamous cell carcinoma (HNSCC) and presents a major global health challenge. Characterized by its aggressive nature, high recurrence rates and potential for metastasis, this malignancy leads to substantial morbidity and mortality, particularly in regions where risk factors such as tobacco and alcohol use, areca nut or betel quid chewing and human papillomavirus (HPV) infection are prevalent (1,2). Despite advances in diagnostic techniques and treatment options, the prognosis for patients with advanced oral cancer remains poor. Standard treatments, typically a combination of surgery, radiotherapy and chemotherapy, are often associated with significant systemic toxicity, limited efficacy against resistant tumors, and a lack of precision in targeting the molecular drivers of the disease (3-5). The inherent heterogeneity of oral tumors and the development of acquired drug resistance further complicate treatment, underscoring the need for more effective, targeted and less toxic therapeutic approaches (2,6).

In recent years, oncology has experienced a paradigm shift from traditional small-molecule inhibitors, which merely block protein activity, to novel strategies that promote the degradation and complete elimination of pathogenic proteins.

Among these emerging approaches, proteolysis targeting chimeras (PROTACs) have gained considerable attention as a transformative therapeutic platform. Their ability to target previously 'undruggable' proteins and circumvent resistance mechanisms has made them a promising candidate for cancer therapy (7-10). PROTACs are bifunctional molecules designed to harness the cell's ubiquitin-proteasome system, a sophisticated cellular machinery responsible for protein degradation, to selectively mark target proteins for destruction (11,12). This catalytic process enables a single PROTAC molecule to degrade multiple target proteins, offering distinct advantages over traditional inhibitors, including prolonged target suppression, reduced dosage requirements and the ability to target proteins lacking conventional binding sites (7,13).

Although the application of targeted protein degradation (TPD) in oral cancer is still in its early stages, recent clinical advancements in other malignancies, particularly breast and prostate cancer, underscore the broader therapeutic potential of PROTACs and provide essential proof of concept for their use in oncology. However, discussions around PROTACs in oral cancer often rely heavily on extrapolations from other tumor types, despite the unique biological and clinical challenges presented by OSCC. These challenges include locoregional behavior, continuous saliva exposure, mucosal barrier effects and the feasibility of local delivery.

The primary contribution of the present review is its re-framing of PROTAC development from an OSCC-specific perspective. Rather than treating all degradable targets and delivery strategies as universally applicable, this review differentiates findings directly supported by OSCC/HNSCC research from those extrapolated from other cancers. It prioritizes candidate targets based on oral cancer biology and assesses delivery methods for their translational relevance to the oral cavity. Additionally, this review summarizes current platform-level clinical evidence, identifies key translational barriers in OSCC, and outlines the research priorities most likely to advance PROTACs toward practical application in oral cancer.

This article is a narrative review informed by a structured literature search, rather than a formal systematic review. The databases searched were PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Scopus (https://www.scopus.com/) and ClinicalTrials.gov (https://clinicaltrials.gov/). Searches covered studies published up to March 2026 using combinations of terms including: 'PROTAC', 'targeted protein degradation', 'oral squamous cell carcinoma', 'oral cancer', 'head and neck squamous cell carcinoma', 'delivery', 'E3 ligase', 'EGFR', 'c-Myc', 'cyclin D1', 'CDK4/6', 'hexokinase 2', bromodomain-containing protein 4 ('BRD4'), CREB-binding protein ('CBP/p300') and 'epigenetic regulator'. Reference lists of relevant articles were also manually reviewed to identify additional studies. Included studies comprised original research, preclinical and clinical studies, as well as reviews directly related to PROTAC biology, degrader design, clinical development or OSCC/HNSCC-specific targets and delivery strategies. Reviews were considered high quality when they were recent, peer-reviewed, methodologically transparent, directly relevant to the topic and supported their conclusions with primary evidence. Conference abstracts were included if they provided clinically or translationally relevant data not yet available in full-length publications. Exclusions included duplicate records, non-English publications, studies unrelated to TPD, and those lacking sufficient methodological detail or direct relevance to oral cancer biology. The quality and relevance of included evidence were assessed qualitatively according to topical relevance, recency, source credibility, methodological clarity and consistency with primary data; no formal risk-of-bias or AMSTAR 2 assessment was applied because the present article is a narrative review rather than a systematic review. For clarity, evidence is categorized throughout the present review as OSCC-specific, HNSCC-supported or extrapolated from other solid tumors.

2. Paradigm shift: TPD and PROTACs

The advent of TPD has transformed drug discovery by shifting the pharmacological focus from transient target engagement to catalytic target elimination (7,8). Among TPD platforms, PROTACs are the most established degraders and have emerged as the leading framework for therapeutic protein degradation (7,11). Unlike conventional small-molecule inhibitors, which typically inhibit protein function by occupying a catalytic or allosteric site continuously, PROTACs recruit an E3 ubiquitin ligase to the target protein, promote its ubiquitination and facilitate its proteasomal degradation (8,11). This mechanism can be broken down into three key steps: The formation of a productive ternary complex, ubiquitination of the target protein and the catalytic recycling of the degrader after the target is degraded (11,14,15). This degradation-centric action helps explain why PROTACs can inhibit both enzymatic and non-enzymatic protein functions, and why they may retain efficacy in resistance settings where traditional inhibitors fail (7,16). Table I highlights the principal mechanistic and pharmacological differences between PROTACs and conventional inhibitors. For example, osimertinib exemplifies the conventional EGFR tyrosine kinase inhibitor paradigm, in which the target is functionally inhibited rather than eliminated (17).

However, PROTACs should not be regarded as universally superior to inhibitors (18,19). Their relatively large molecular size and complex physicochemical properties often limit passive permeability, formulation flexibility and systemic oral bioavailability (19,20). Furthermore, effective degradation depends not only on target binding but also on favorable ternary-complex geometry, adequate intracellular exposure and a suitable E3 ligase context (14,15). Additionally, degradation of biologically relevant proteins in normal tissues can result in on-target/off-tumor toxicity, meaning that increased mechanistic sophistication does not necessarily translate into a broader therapeutic window (16,18). Therefore, in OSCC, the therapeutic rationale for PROTACs is strongest when they are paired with biologically validated oral cancer targets and delivery strategies that enhance local selectivity and minimize systemic exposure (19,20).

3. PROTAC design principles most relevant to OSCC translation

A clinically viable PROTAC consists of three essential components: A ligand for the target protein, a ligand for the E3 ubiquitin

Table I. Comparison of PROTACs and small-molecule inhibitors.

Feature	PROTACs	Small-molecule inhibitors	(Refs.)
Core idea	Induce catalytic degradation and complete removal of target proteins via the ubiquitin-proteasome system.	Reversibly bind to and block the function of target proteins (for example, the active site).	(7,8,11)
Mechanism	Heterobifunctional molecules form a ternary complex between the target protein and an E3 ligase, leading to polyubiquitination and proteasomal degradation. This process is catalytic because one degrader molecule can promote degradation of multiple target molecules.	Small-molecule inhibitors directly bind to a specific site (for example, the active site) on the target protein and prevent its activity. This process is stoichiometric because sustained inhibition usually requires continued target occupancy.	(8,11,14,15)
Target scope	Can target 'undruggable' proteins that lack active sites (for example, transcription factors or scaffolding proteins). Requires only a binding surface.	Primarily targets proteins with well-defined active sites or deep binding pockets. Limited to 'druggable' targets.	(7,16,21)
Potency and duration	Catalytic activity allows for robust, sustained degradation at low (nM-pM) concentrations.	Requires continuous, high (μM) concentrations for sustained inhibition.	(7,11,13)
Resistance	Can overcome resistance mutations that affect inhibitor binding but not PROTAC-mediated degradation. Degrades the entire protein.	Susceptible to resistance mutations in the binding site or upregulation of compensatory pathways.	(7,16)
Functional impact	Eliminates the entire protein, abrogating all its functions (enzymatic and non-enzymatic).	Blocks a specific function (for example, enzymatic activity) at the binding site, leaving other protein functions intact.	(7,8,16)
Molecular weight	Generally larger (often >700 Da), posing challenges for cell permeability and oral bioavailability.	Generally smaller (<500 Da), often with greater cell permeability and oral bioavailability.	(19,20)
Example	Vepdegestrant (ER degrader)	Osimertinib (EGFR TKI)	(17,54)

PROTACs, proteolysis targeting chimeras; ER, estrogen receptor; TKI, tyrosine kinase inhibitor.

ligase and a linker that ensures proper spatial orientation between the two binding events (8,15). However, in the context of oral cancer, these design principles should be approached from a disease-specific perspective rather than solely from a medicinal chemistry standpoint (15,21). Specifically, target selection should be driven by OSCC/HNSCC biology, rather than by the mere existence of degraders in other cancer types. This means prioritizing proteins with documented relevance to oral carcinogenesis, invasion, metabolic reprogramming, treatment resistance or epigenetic dysregulation, while distinguishing these targets from those primarily extrapolated from breast, prostate or lung cancer (7,21).

Likewise, linker optimization and E3 ligase selection should be considered in terms of their translational impact, not merely their structural novelty (14,15). Given that current degrader designs predominantly rely on a limited set of ligases, particularly cereblon (CRBN) and von Hippel-Lindau (VHL), tissue selectivity remains a challenge (8,18). For OSCC, especially when local or transmucosal delivery is intended, the most important design factors will likely be compatibility with mucosal delivery, minimization of non-specific permeability and the feasibility of spatially restricted activation (19,20). Although unconventional formats, such as bridged, aptamer-guided or next-generation PROTAC architectures, may offer improvements in targetability or expand the design space, they should be viewed as enabling technologies rather than core considerations for OSCC delivery, safety and clinical feasibility (21-23).

4. Addressing delivery and specificity challenges in OSCC

Oral cancer requires a distinct delivery framework. Although the oral cavity is anatomically accessible, drug delivery in OSCC presents significant challenges. The oral environment is characterized by continuous saliva flow, epithelial turnover, tissue movement, and a mucosal barrier that can dilute, degrade or prematurely eliminate therapeutic agents before they achieve sufficient penetration (24,25). At the lesion level,

factors such as multilayered epithelium, intercellular lipids, microbiota-associated biochemical barriers, dense extracellular matrix, elevated interstitial pressure and hypoxia further restrict intratumoral distribution and reduce effective local exposure (24,26). Consequently, optimizing systemic pharmacokinetics alone is inadequate for OSCC; delivery strategies must also focus on prolonging local residence time, enabling directional release, and enhancing tissue penetration in a wet and mechanically dynamic mucosal environment (24,25,27).

A critical OSCC-specific consideration is that local therapy is not simply a formulation convenience; it is a clinical strategy intended to concentrate treatment at accessible mucosal lesions while limiting whole-body exposure and preserving oral functions such as speech, swallowing and mastication (24). Oral cavity tumors are often visible and accessible, allowing topical or transmucosal systems to be placed directly over the lesion, prolong contact with the mucosa and promote directional drug flux into tumor tissue; these mechanisms can increase intralesional drug concentrations while minimizing systemic exposure (24,28). However, this accessibility also introduces design constraints, as formulations must remain adherent despite constant saliva flow, speaking, swallowing and mastication (24,25). For PROTACs, which are often limited by permeability issues and poor systemic bioavailability after oral administration, achieving a balance between accessibility and overcoming local barriers is particularly important (19,20).

Priority delivery strategies for OSCC. The priority delivery and activation strategies for OSCC-oriented PROTAC development are summarized in Table II. Local mucoadhesive and transmucosal platforms should be prioritized. For OSCC, local mucoadhesive and transmucosal platforms should be considered the most immediately relevant delivery strategies. Compared with fully systemic administration, mucoadhesive patches, bilayer transmucosal devices and intelligent hydrogels can extend residence time at the lesion, counteract salivary clearance and maintain high local drug concentrations while limiting systemic exposure (24,25). This approach is particularly promising for superficial or anatomically accessible lesions on the tongue, floor of mouth, buccal mucosa and gingiva (24). Additionally, directional or backing-layer designs are particularly valuable in the oral cavity, as they can reduce washout and promote drug flux toward the lesion rather than into the saliva (25,28).

The strongest clinical proof-of-principle for localized delivery in oral cancer is not yet demonstrated by a PROTAC, but by the PRV111 transmucosal cisplatin patch (28). In a phase 1/2 study, PRV111 achieved significant local tumor reduction within ~7 days, with high response rates and negligible systemic cisplatin exposure (28). The patch architecture was specifically designed to enhance transmucosal penetration and reduce washout in the oral cavity. Although this does not validate PROTAC efficacy in OSCC, it strongly supports the translational potential of localized transmucosal delivery for oral cancer (24,28). Therefore, PROTACs adapted to similar local-retention platforms may be more clinically relevant to OSCC than strategies focusing solely on systemic administration (19,24,28).

Stimuli-responsive local activation integrated with radiotherapy or light is the second most promising strategy. The second most promising strategy for OSCC is stimuli-responsive local activation (24,29). This approach holds particular promise in oral cancer due to the direct accessibility of numerous lesions to light and the ongoing role of radiotherapy in locoregional treatment (24,29). In the broader PROTAC field, radiotherapy-triggered PROTAC prodrugs have demonstrated X-ray-controlled activation, allowing spatiotemporal restriction of target degradation (30). Similarly, near-infrared-activatable PROTAC nanocages and related smart nano-PROTAC platforms have shown that external local triggers can enhance selectivity and minimize premature systemic activity (29,31).

For oral cancer, this strategy offers a conceptual advantage over constitutively active degraders, as it could restrict protein degradation to the irradiated or illuminated tumor region, thereby limiting systemic and off-tissue degradation (24,29). Moreover, oral lesions are more amenable to controlled local illumination than deeply seated visceral tumors, making photoactivatable or PDT-coupled degrader systems more feasible in this context than in other solid tumors (24,29). However, these systems remain technically complex and should be regarded as high-potential but early-stage approaches, rather than near-clinical solutions (29,31).

Microneedle-assisted locoregional delivery is a highly relevant enabling technology. Microneedle-assisted delivery warrants special consideration in an OSCC-focused review due to its potential to address a key limitation of PROTACs: Inadequate penetration across epithelial and mucosal surfaces (26,32,33). A proof-of-concept study has demonstrated that microneedle patches can deliver PROTACs directly into tumors, validating the feasibility of localized physical delivery for degraders (32). Concurrently, oral mucosal delivery research indicates that microneedles can cross the oral epithelium with minimal pain, while environment-adaptive and mucoadhesive designs are being developed to overcome challenges such as wet adhesion failure, salivary clearance and limited penetration in oral lesions (26,33). However, this strategy must be critically assessed. Microneedle systems still face practical limitations related to drug loading, reproducibility, sterility testing, retention under oral motion and integration into clinical workflows (26,33). Therefore, microneedles should be viewed as an enabling method for localized PROTAC delivery, rather than as a fully mature clinical solution.

Broad systemic nanocarriers and conjugate platforms should be presented as complementary, not primary, strategies. Conventional nanocarriers, exosomes, antibody-based conjugates and other biomolecule-assisted platforms remain scientifically valuable, particularly for metastatic, deeply infiltrative or non-accessible disease (20,27). However, in the context of an OSCC-focused review, these platforms should not dominate the delivery discussion (24,27). A key reason is that passive tumor accumulation via the enhanced permeability and retention (EPR) effect is heterogeneous across human solid tumors and becomes less reliable as tumor architecture and perfusion complexity increase (27). Therefore, claims that nanoparticles will preferentially accumulate in OSCC solely due to EPR should be reconsidered. These platforms become more compelling when combined with oral-cancer-specific ligands, local administration strategies or multi-stimulus activation, rather than being presented as universally superior solutions (20,27).

Table II. Priority-ranked delivery and activation strategies for OSCC-oriented PROTAC development.

Strategy	Why it fits OSCC	Key translational advantage	Main limitation	Representative examples	(Refs.)
Local mucoadhesive/ transmucosal platforms (high priority)	OSCC lesions are often accessible, but local therapy is limited by salivary washout and short mucosal residence time.	Prolongs local residence, achieves high intralesional concentration and reduces systemic exposure.	Less suitable for deeply infiltrative, nodal or metastatic disease; retention may vary by lesion site.	PRV111 transmucosal cisplatin patch; mucoadhesive patches/films; intelligent hydrogels.	(24,25,28)
Stimuli-responsive local activation integrated with radiotherapy or light (high priority)	A number of oral lesions are directly accessible to light, and radiotherapy is central to locoregional OSCC treatment.	Provides spatiotemporal control of activation and may reduce off-tissue degradation.	Requires external triggers or specialized equipment; light penetration and formulation complexity remain limitations.	Radiotherapy-triggered PROTAC prodrugs; NIR-activatable PROTAC nanocages; photoactivatable PROTAC systems.	(24,29-31)
Microneedle-assisted locoregional delivery (moderate-to-high priority)	Can bypass the oral mucosal barrier and improve deposition into accessible lesions or premalignant fields.	Improves penetration and local retention for poorly permeable degrader cargos.	Drug loading, reproducibility, sterility, retention under oral motion and workflow integration remain challenging.	Microneedle patch delivery of PROTACs; oral environment-adaptive microneedle systems.	(26,32,33)
Systemic nanocarriers/ nano-PROTACs (moderate/complementary)	May be useful for deeper, less accessible, or disseminated disease and can support combination delivery.	Improves solubility and stability; may enable active targeting in selected settings.	Human enhanced permeability and retention is heterogeneous; dense ECM, immune clearance, and manufacturing complexity limit translation.	Polymeric micelles; lipid nanoparticles; membrane-camouflaged nanoparticles; self-assembled nano-PROTACs.	(20,27,29,31,57)
Conjugate-based targeting platforms (moderate/ complementary)	May suit biomarker-selected OSCC/HNSCC if robust surface markers or aptamer-recognized targets are identified.	Can improve targeting specificity and may reduce systemic toxicity.	Complex synthesis and release kinetics; possible immunogenicity; depends on reliable targetable antigens.	Degrader-antibody conjugates; aptamer-based PROTACs; affibody-PROTAC conjugates.	(20,21,41)

PROTACs, proteolysis targeting chimeras; OSCC, oral squamous cell carcinoma; NIR, near-infrared; ECM, extracellular matrix.

Resistance, safety and rational combination strategies. For OSCC, combination strategies should be examined within a locoregional clinical framework, rather than simply as generic multi-drug approaches (24,29). Rational combinations may involve PROTACs paired with radiotherapy-triggered activation, PDT-enabled activation for superficial lesions or postoperative local delivery to high-risk mucosal areas (28,30). However, these opportunities should be discussed alongside their limitations, such as overlapping mucosal toxicity, uncertain effects on wound healing, incomplete penetration into deeply infiltrative tumor regions, and limited effectiveness for nodal or distant disease. This is particularly critical in oral cancer, where local control, function preservation and quality of life are intricately linked.

5. Critical target proteins and clinical applications for oral cancer

The efficacy of PROTACs in cancer treatment fundamentally relies on the identification and successful degradation of key oncogenic proteins involved in tumor initiation, progression and metastasis. While the direct application of PROTACs to oral cancer is still in its early stages, extensive research in other cancer types provides a strong foundation for identifying relevant targets and formulating potential therapeutic strategies for OSCC. Similar to other malignancies, oral cancer is characterized by the dysregulation of multiple signaling pathways, epigenetic alterations and the presence of 'undruggable' oncogenes, making it a promising candidate for PROTAC-based intervention.

Validated and candidate degradable targets in OSCC/HNSCC. To improve the alignment of target protein ligand selection with the pathogenesis of OSCC, degradable targets should be prioritized based on the strength of oral cancer-specific evidence rather than the mere availability of PROTAC chemistry. It is useful to categorize the evidence into three levels: i) Proteins where degrader activity has been demonstrated in OSCC/HNSCC models; ii) proteins with strong biological validation in OSCC but lacking oral cancer-specific degrader data; and iii) targets primarily supported by extrapolation from other solid tumors. This classification is crucial in oral cancer, where a number of promising degrader targets remain biologically plausible but lack disease-specific validation; for example, c-Myc or CDK/cyclin-axis degraders may be relevant to OSCC biology but still require direct OSCC/HNSCC degrader testing before they can be considered validated oral cancer targets.

Direct PROTAC evidence in oral cancer is currently limited and remains preclinical; however, several relevant HNSCC models provide useful insights. For example, the small-molecule STAT3 degrader (TSM-1) demonstrated selective STAT3 degradation and robust antitumor activity in STAT3-dependent HNSCC models, including patient-derived systems (34). Similarly, Fos-related antigen 1 (FOSL1)-targeting PROTAC probes effectively degraded FOSL1 and suppressed cancer stem cell phenotypes in HNSCC, with enhanced potency compared with the parent ligand (35). Additionally, radiotherapy-activated PROTAC prodrug-integrated nanosensitizers have shown tumor regression in HNSCC models, illustrating that targeted degradation can be integrated into clinically relevant treatment settings in head and neck cancer (36). BET-family degrader activity, particularly targeting BRD4, has also been explored in cisplatin-resistant HNSCC, supporting the concept that targeted degradation can address therapy resistance rather than simply baseline tumor growth (37).

Among biologically supported candidate targets in OSCC, EGFR remains highly relevant due to its frequent overexpression and association with poor prognosis in oral and oropharyngeal squamous cell carcinoma (38,39). While oral cancer-specific EGFR degraders have not been clinically validated, the development of orally active EGFR-PROTAC candidates in other epithelial tumors supports further translational investigation. c-Myc is also biologically relevant in OSCC, but current degrader evidence mainly comes from non-oral tumor models, making it more appropriate to consider c-Myc a plausible rather than validated oral cancer degrader target at this stage (40,41).

The cell-cycle axis is more directly supported in OSCC than is apparent from generalized PROTAC discussions. Cyclin D1 overexpression is consistently linked to aggressive clinicopathological features and a poor prognosis in OSCC, including lymph node metastasis and inferior survival outcomes (42-44). Consequently, the discussion of cyclin-directed or CDK/cyclin-axis degraders is biologically justified in OSCC, even though current degrader data predominantly come from non-OSCC models. The same rationale applies to metabolic vulnerabilities. Hexokinase 2 (HK2) has been associated with glycolytic reprogramming, invasion and metastasis in OSCC and tongue squamous cell carcinoma, indicating that HK2-targeted degradation may address a biologically substantiated dependency rather than a generic cancer pathway (45-47).

Epigenetic regulators are among the most compelling candidates for targeted degradation in oral cancer, supported by both oral cancer biology and the tractability of degrader approaches. BRD4 is upregulated in primary HNSCC and has been implicated in OSCC invasion and metastasis, while p300 (encoded by EP300)-related signaling is also associated with OSCC progression (48-51). Consequently, BET/BRD4 and CBP/p300 degraders represent more convincing candidates for OSCC than several targets currently discussed through cross-cancer analogy. Notably, a recent multi-omics analysis suggests that OSCC is not a molecularly uniform disease and that precision stratification based on biomarkers, such as EGFR-associated or immune-related states, may provide more informative guidance than a one-size-fits-all development strategy (52). The strongest priorities for oral cancer, therefore, are targets that meet two criteria: Biological relevance in OSCC/HNSCC and practical tractability for TPD. By contrast, targets without clear enrichment or validation in oral carcinogenesis should be framed explicitly as speculative extensions rather than core priorities for OSCC.

Current clinical evidence and translational challenges for oral cancer. Clinical progress in TPD has established proof of principle in oncology, but OSCC/HNSCC-specific clinical validation of PROTACs has not yet been established. Available clinical evidence has not yet demonstrated OSCC/HNSCC-specific outcomes such as objective response, progression-free survival or survival benefit;

therefore, current evidence in this disease context should be interpreted as HNSCC-supported preclinical evidence or platform-level clinical extrapolation rather than oral cancer-specific proof (7,16,34,36,37). Among current clinical-stage degrader programs, breast cancer provides one of the clearest examples of clinical validation, where vepdegestrant demonstrated phase 3 efficacy in the VERITAC-2 program. A more pronounced benefit was observed in patients with estrogen receptor 1 (ESR1)-mutated, estrogen receptor (ER)-positive, HER2-negative advanced breast cancer (53,54). In this ESR1-mutated population, vepdegestrant improved median progression-free survival time compared with fulvestrant (5.0 vs. 2.1 months; hazard ratio, 0.58), whereas the benefit in the overall population was more modest, suggesting biomarker-defined rather than universal efficacy (54). In prostate cancer, bavdegalutamide and HP518 have shown promising early clinical activity in phase 1/2 and phase 1 studies, respectively (55,56). Bavdegalutamide achieved a median radiographic progression-free survival time of 8.2 months in tumors with androgen receptor (AR) ligand-binding-domain mutations excluding L702H and 11.1 months in the AR 878/875 subgroup without co-occurring L702H; HP518 phase 1 data included two partial responses and three prostate-specific antigen reduction of ≥50% (PSA50) responses (55,56). However, these programs highlight an important lesson for the field: Clinical benefit may be biomarker-defined and pharmacologically constrained, rather than uniformly observed across all patients (54,55). Collectively, these findings validate the PROTAC platform in humans, but they do not establish efficacy in OSCC/HNSCC (16,54,56).

In OSCC/HNSCC, available direct evidence remains mainly preclinical. STAT3 degradation by TSM-1 has shown antitumor activity in STAT3-dependent HNSCC models, including patient-derived systems (34). Radiotherapy-activated PROTAC prodrug-integrated nanosensitizers and BET degraders have also shown activity in HNSCC models or cisplatin-resistant HNSCC cells (36,37). These studies support the biological plausibility of targeted degradation in head and neck cancer, but they do not yet provide patient-level clinical endpoints. Thus, OSCC/HNSCC-related evidence should be viewed as a translational rationale for further development rather than as clinical validation.

For oral cancer, the primary translational gap is no longer whether PROTACs can work clinically in principle, but whether the correct target, route of delivery and exposure profile can be achieved in a disease characterized by distinct locoregional behavior and mucosal biology (7,16). In this context, it is more defensible to prioritize proteins already supported by OSCC/HNSCC biology or direct head and neck degrader studies, while explicitly labeling other applications as hypothesis-generating rather than validated.

Several practical barriers remain particularly relevant for translating PROTACs to oral cancer. First, their relatively high molecular weight and complex physicochemical properties complicate membrane permeability, formulation and systemic oral exposure (19,20,57). Second, selectivity is limited by the small number of commonly recruited E3 ligases, primarily CRBN and VHL, which may restrict tissue specificity (7,18). Third, on-target/off-tumor toxicity and adaptive resistance remain significant concerns, especially when degraded proteins play key physiological roles in normal tissues or when tumors can rewire compensatory signaling and proteostasis pathways (16,18). Fourth, while a number of advanced delivery systems are conceptually elegant, they also introduce manufacturing, scalability and regulatory challenges. From an oral cancer perspective, local or locoregional delivery is appealing, though this strategy still requires dedicated validation in oral tumor models and clinically realistic settings (20,57).

In summary, current clinical evidence should be viewed as platform-level validation rather than oral cancer-specific proof (16,54,56). For OSCC, the next step is not merely adopting successful degraders from other tumor types, but developing biomarker-guided, disease-contextualized PROTAC strategies that reflect the unique molecular dependencies and therapeutic constraints of oral cancer itself (7,20,57).

Future directions for oral cancer treatment. The future development of PROTAC-based strategies for OSCC should shift from generalized enthusiasm for TPD to a more focused, biomarker-guided, disease-contextualized approach. The first priority is target nomination based on oral cancer-specific molecular stratification, rather than indiscriminately borrowing degrader targets from other malignancies (52,58). Recent multi-omics studies in OSCC have revealed that distinct biomarker-defined subgroups, including EGFR-associated and immune-inflamed states, exhibit varying recurrence risks and therapeutic vulnerabilities. This highlights the necessity for degrader development programs that align with the biological context of oral cancer, rather than relying solely on generic pathway prevalence (52,58). These findings support a strategy that incorporates both tumor-intrinsic oncogenic drivers and microenvironment-linked dependencies (52,58).

The second priority is the intentional development of local and locoregional PROTAC delivery strategies tailored to the oral cavity (24-26). In OSCC, the translational question is not simply whether a degrader can be systemically administered, but whether it can be retained, activated and distributed effectively within a wet, mobile and barrier-rich mucosal environment. For this reason, local transmucosal platforms, stimuli-responsive systems integrated with radiotherapy or light, and microneedle-assisted delivery should be prioritized as primary approaches, rather than supplementary strategies for oral cancer translation (26,28). Additionally, future medicinal chemistry efforts should more explicitly consider compatibility with local delivery, focusing on parameters such as directional release, wet adhesion and spatially restricted activation, instead of solely optimizing conventional systemic drug-likeness (19,20).

A third priority is the use of clinically relevant preclinical platforms that can support biomarker selection, drug screening and resistance analysis (59-61). OSCC and HNSCC organoid systems provide a more accurate framework for modeling epithelial-stromal interactions, treatment responses and intra-tumoral heterogeneity than conventional 2D cell lines alone (59,61). In HNSCC, patient-derived tumor organoid workflows have demonstrated practical feasibility for treatment decision-making in a notable proportion of patients, although procedural and logistical challenges remain (60). Reviews of OSCC preclinical platforms emphasize that patient-derived cell lines, xenografts and organoids should be integrated, as each model captures different aspects of tumor biology and therapeutic vulnerability (62,63).

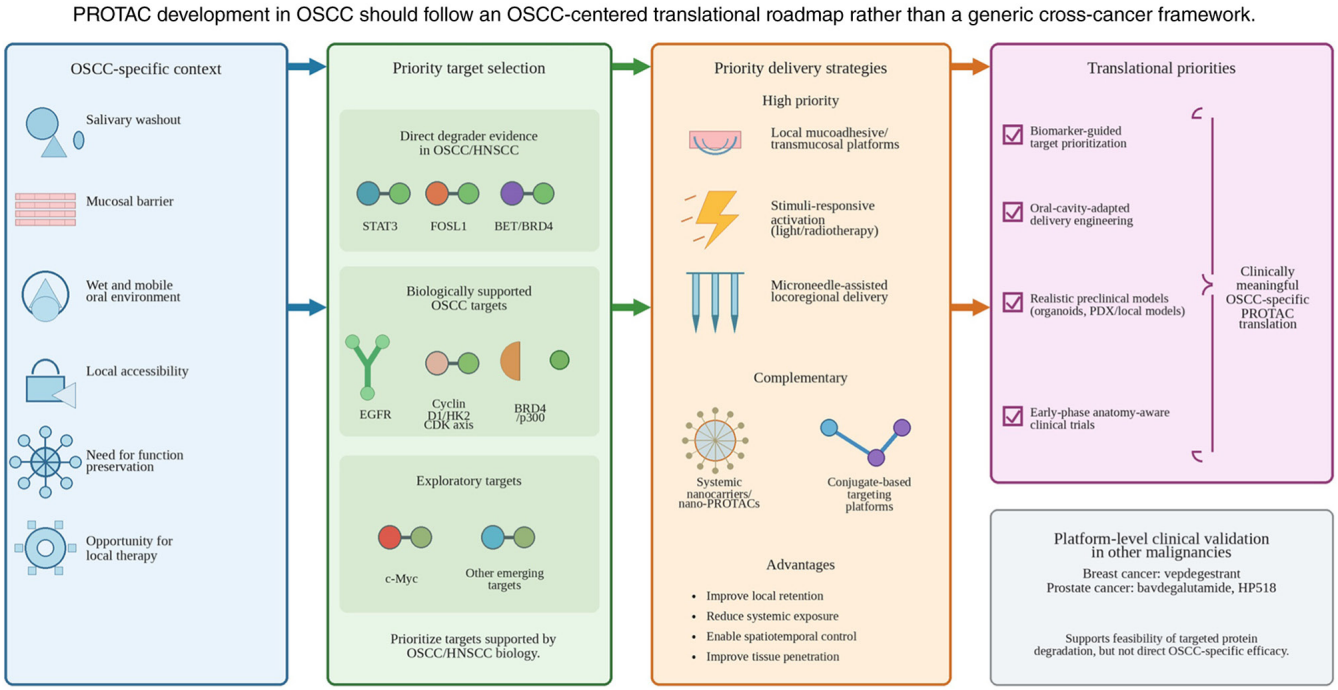

Figure 1. Discovery-to-clinic priorities for PROTAC development in OSCC. This figure summarizes the OSCC-specific clinical context, prioritizes degradable targets, outlines preferred delivery strategies and identifies the major translational steps necessary to advance targeted protein degradation toward clinically meaningful application in oral cancer. OSCC, oral squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; FOSL1, Fos-related antigen 1; BET, bromodomain and extraterminal; BRD4, bromodomain-containing protein 4; HK2, hexokinase 2; PDX, patient-derived xenograft; PROTACs, proteolysis targeting chimeras.

Finally, the clinical translation of PROTACs in OSCC will likely require small, biomarker-enriched, anatomy-aware early-phase studies, rather than broad efficacy trials (52,58,60). Initial trials may be best designed around accessible lesions, clearly defined target-expression profiles and delivery platforms that allow pharmacodynamic sampling of degraded proteins within local tissue (28,60). This approach would facilitate PROTAC development in oral cancer with stronger mechanistic validation and more precise patient selection than is currently possible by broadly extrapolating from other solid tumors. In this context, the next step for PROTACs in OSCC is not simply further chemistry, but enhanced biological prioritization, refined local delivery engineering and improved translational models (19,20). Fig. 1 summarizes this proposed discovery-to-clinic pathway by linking OSCC biological stratification, target prioritization, local or locoregional delivery selection, pharmacodynamic sampling and early-phase clinical validation.

Limitations of the present review. The present review has several limitations. First, while TPD has gained increasing clinical validation as a therapeutic platform, direct evidence supporting PROTAC application in OSCC remains limited and predominantly preclinical. Consequently, some of the discussion relies on data from HNSCC or extrapolation from other solid tumors, such as breast and prostate cancer, which may not fully capture the unique molecular dependencies, tumor microenvironment and treatment context of OSCC. Second, the present study is a narrative review informed by a structured literature search rather than a formal systematic review or meta-analysis. As a result, study selection bias and heterogeneity in the quality of included evidence cannot be entirely excluded. Third, the degrader literature is highly heterogeneous in terms of target selection, chemical scaffolds, E3 ligase usage, model systems, delivery platforms and pharmacodynamic endpoints, limiting direct cross-study comparison. Fourth, some clinically relevant information in this field is still emerging from conference abstracts, early-phase reports or rapidly evolving trial updates, which may affect the stability of evidence interpretation. Finally, OSCC itself is biologically heterogeneous, with variations in anatomical subsite, stromal architecture, local microbial and salivary environment, and treatment setting. These disease-specific factors remain insufficiently addressed in most current degrader studies. These limitations highlight that the present review should be regarded as an OSCC-centered translational framework rather than definitive clinical guidance.

6. Conclusion

PROTAC technology offers a promising therapeutic framework for OSCC by enabling the elimination of oncogenic proteins rather than merely inhibiting them, an approach that is difficult to achieve with conventional small-molecule therapies. Clinical progress in other malignancies supports the broader feasibility of TPD as a therapeutic modality, but oral cancer-specific validation remains limited and largely preclinical. Currently, the most viable translational path for OSCC is to prioritize biologically validated OSCC/HNSCC targets, clearly distinguish direct evidence from cross-cancer extrapolation, and integrate degrader design with delivery strategies optimized for the oral cavity, particularly local transmucosal and stimuli-responsive approaches. By addressing these disease-specific challenges through biomarker-guided target selection, enhanced local delivery and dedicated oral

cancer studies, PROTACs have the potential to become a valuable addition to precision therapy for OSCC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

YB conceived the study framework, conducted comprehensive literature retrieval and synthesis, analyzed and interpreted information from published studies related to PROTAC mechanisms, design principles and oral cancer-related targets, and drafted the initial manuscript. DM collated and analyzed published evidence on advanced PROTAC delivery systems and clinical applications, contributed to the interpretation of pharmacokinetic limitations and revised the manuscript critically for intellectual content. XY researched oncogenic targets specific to oral squamous cell carcinoma and PROTAC resistance mechanisms, revised the review structure, and cross-checked the extracted literature and reference information. MW supervised the overall research direction, provided critical insights into the integration of PROTAC technology with oral cancer therapy, revised the manuscript comprehensively and finalized the submitted version. Data authentication is not applicable. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work, ensuring that any questions relating to research integrity or scientific accuracy are appropriately addressed.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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