

Medicinal Chemistry Strategies for Oral Squamous Cell Carcinoma: Target Identification, Drug Design, and Therapeutic Opportunities

Harsha Verma^{1*}, Sudhanshu Shandilya¹

¹Sona Devi University, Ghatsila, East Singhbhum, Jharkhand, 832303

*Corresponding Author E-mail: Vermaharsha45@gmail.com

Abstract:

Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies and remains associated with poor prognosis despite decades of therapeutic development, motivating sustained interest in applying modern medicinal chemistry methodology to this specific malignancy rather than relying solely on treatment strategies developed for other cancer types. This review examines the full medicinal chemistry pipeline as applied to OSCC, from molecular target identification through rational drug design to therapeutic translation. We first survey recent multi-omics and genomic approaches including TCGA/GEO-based expression analysis, Mendelian randomisation, and exome sequencing that have identified novel OSCC biomarkers and druggable gene targets, and examine the principal validated molecular target classes these approaches have converged on, including EGFR/kinase signalling, the PI3K/AKT/mTOR survival axis, cell-cycle regulators, and the PD-1/PD-L1 immune checkpoint. We then survey how established rational drug design strategies structure-based and fragment-based design, quantitative structure–activity relationship modelling, bioisosteric optimisation, and covalent inhibitor engineering have been or could be applied specifically to these OSCC-relevant targets, together with the emerging application of proteolysis-targeting chimeras (PROTACs) to oncogenic drivers in oral cancer. We further discuss therapeutic opportunities arising from computational drug repurposing, structure-guided combination therapy design, and artificial intelligence-guided property optimisation. Finally, we critically examine the gap between the rapidly expanding list of computationally and genomically nominated OSCC targets and the comparatively small number that have been pursued through to validated drug candidates, and outline priority directions including target validation rigor, OSCC-specific in vivo modelling, and closer integration of genomic target discovery with structure-based design needed to translate this expanding target landscape into genuine therapeutic advances for OSCC patients.

Keywords: oral squamous cell carcinoma; medicinal chemistry; target identification; drug design; structure–activity relationship; PROTAC; drug repurposing; PI3K/AKT/mTOR; EGFR; immune checkpoint

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1. Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies and continues to carry a poor prognosis, with a substantial proportion of cases diagnosed at advanced stage despite decades of therapeutic development across surgery, radiotherapy, and systemic pharmacotherapy¹². Global Cancer Observatory data recorded 377,713 new OSCC cases in 2020, part of a broader global cancer burden of 19.3 million new cancer cases and almost 10 million cancer deaths estimated across 36 cancer types that year, and research investment in oral cancer has historically lagged behind that directed at other common malignancies, contributing to a comparatively narrow set of OSCC-specific approved targeted therapies relative to cancers such as breast or lung carcinoma^{2,3,6}. This review addresses this gap by examining medicinal chemistry strategy as applied specifically to OSCC across the full discovery pipeline: target identification, rational drug design, and therapeutic translation.

The medicinal chemistry pipeline for any malignancy begins not with a candidate molecule but with a validated molecular target, and OSCC drug discovery has benefited substantially over the past several years from the application of multi-omics and systems genomics methodology to define this target landscape with increasing precision. Section 2 surveys these target identification approaches, including The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO)-based expression analysis, Mendelian randomisation, and exome sequencing studies, and the principal validated molecular target classes they have converged upon. Section 3 examines how established rational drug design methodologies—structure-based and fragment-based design, quantitative structure–activity relationship (QSAR) modelling, bioisosteric optimisation, and covalent inhibitor engineering—have been or could be applied to these OSCC-relevant targets. Section 4 surveys emerging therapeutic modalities, including proteolysis-targeting chimeras (PROTACs) directed at oncogenic drivers in oral cancer. Section 5 discusses therapeutic opportunities arising from drug repurposing and rational combination design, before Sections 6 and 7 critically examine the field's translational challenges and outline priority future directions.

2. Target Identification in Oral Squamous Cell Carcinoma

2.1 Multi-Omics and Genomic Approaches

Multi-omics data integration has become a central methodology for OSCC target identification over the past several years. A recent study combining gene expression data from TCGA and GEO databases with Mendelian randomisation and co-localisation analysis against expression quantitative trait loci (eQTL) and genome-wide association study (GWAS) databases analysed 315,025 oral cancer samples and identified 144 causal relationships between druggable genes and OSCC outcomes, further incorporating single-cell and immune cell infiltration analysis to characterise the tumour microenvironment and construct a drug sensitivity-informed prognostic nomogram³. This Mendelian randomisation approach offers a methodological advantage over simple expression-correlation analysis, since it exploits genetic variants as instrumental variables to infer causal rather than merely associative relationships between candidate genes and disease outcome, reducing the risk that a nominated target reflects reverse causation or confounding by tumour stage or treatment history.

A complementary multi-omics analysis integrating TCGA cohort data through consensus clustering identified distinct OSCC molecular subtypes and nominated carbonic anhydrase IX (CA9) as a therapeutic target within a prognostic signature subsequently validated experimentally, illustrating how unsupervised molecular subtyping can surface candidate targets not previously prioritised through single-gene, hypothesis-driven approaches⁴. Complementing these expression- and genotype-based approaches, exome sequencing of OSCC tumour cohorts has directly catalogued the landscape of altered, potentially druggable genes and pathways, finding that a substantial proportion of tumours harbour two or more co-occurring targetable alterations for example, combined TP53 and CCND1 alteration within the p53-cell cycle pathway was identified as potentially targetable in a substantial proportion of tongue-site tumours specifically indicating that anatomical site-specific and combination-targeted therapeutic strategies may be more broadly applicable in OSCC than single-target approaches alone⁵.

2.2 Biomarker Discovery and Clinical Validation

Beyond genomic target nomination, biomarker discovery spanning salivary, serum, and tissue-based analytes has continued to expand the diagnostic and prognostic toolkit available for OSCC, with candidate salivary metabolite biomarkers including sphinganine, S-carboxymethyl-L-cysteine, phytosphingosine, and L-phenylalanine reported for diagnostic purposes, and genomic markers including CD34 for recurrence detection and ITGB4/ITGA3 as drivers of distant metastasis and prognosis⁶. A comprehensive review of molecular biomarkers across the OSCC diagnosis, prognosis, and treatment-stratification continuum further catalogues predictive biomarkers specifically informative for chemotherapy and radiotherapy response, and for immunotherapy patient selection, underscoring that target identification and biomarker discovery are increasingly treated as a unified rather than separate discovery activity within contemporary OSCC research⁷.

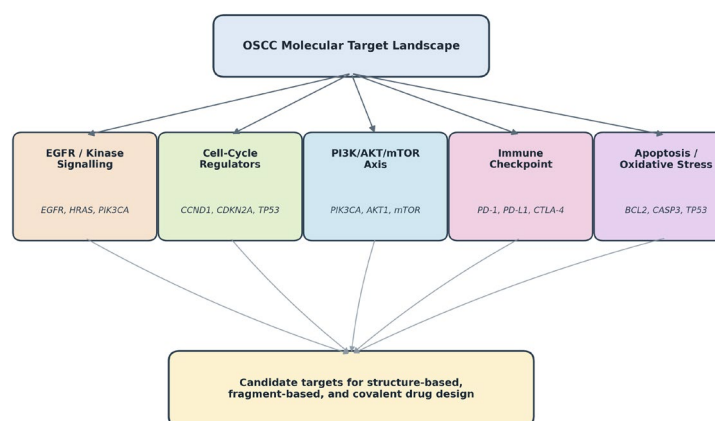


Figure 2. Schematic map of principal molecular target classes discussed for OSCC-directed drug design in this review.

Table 1. Principal OSCC molecular target classes identified through the genomic and biomarker discovery approaches discussed in Section 2

Target class	Representative genes/proteins	Identification approach	Ref.
EGFR/kinase signalling	EGFR, HRAS, PIK3CA	Exome sequencing; expression profiling	5
Cell-cycle regulators	CCND1, CDKN2A, TP53	Exome sequencing; co-occurrence pathway analysis	5
PI3K/AKT/mTOR axis	PIK3CA, AKT1, MTOR	Multi-omics/TCGA analysis; pathway review	3,11
Hypoxia/metabolic target	CA9 (carbonic anhydrase IX)	Multi-omics subtyping and experimental validation	4
Metastasis/prognosis markers	ITGB4, ITGA3, CD34	Genomic and recurrence-association analysis	6
Immune checkpoint	PD-1, PD-L1, CTLA-4	Immune infiltration analysis; clinical trial data	3,7

The economic and geographic distribution of this OSCC burden compounds the translational challenge discussed throughout this review: a global burden-of-disease analysis spanning 1990 to 2021 documents that OSCC incidence is highest in high-Sociodemographic-Index countries, while mortality and disability-adjusted life years remain disproportionately concentrated in low- and middle-Sociodemographic-Index regions, meaning that the populations bearing the greatest OSCC mortality burden are often those with the least access to the genomically informed, target-directed therapeutics surveyed in this review³⁵.

The rationale for pursuing combination and multi-target strategies throughout this review, rather than relying exclusively on single, maximally selective inhibitors, follows directly from the network pharmacology principle that complex diseases such as OSCC are frequently better understood as perturbations of interconnected molecular networks than as single-gene disorders, such that therapeutic strategies capable of engaging multiple network nodes simultaneously may achieve durability of response that single-target agents cannot³⁷.

3. Rational Drug Design Strategies Applied to OSCC Targets

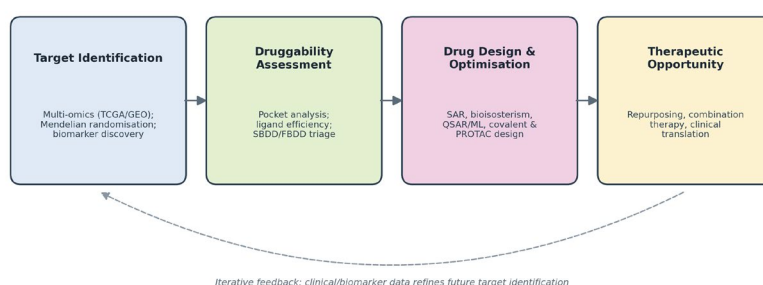


Figure 1. Medicinal chemistry pipeline from OSCC target identification to therapeutic opportunity, illustrating the iterative relationship between the stages discussed in Sections 2–5.

3.1 Structure-Based and Fragment-Based Design

Once a candidate target such as EGFR or a PI3K/AKT/mTOR pathway component has been nominated through the genomic approaches discussed in Section 2, structure-based drug design

(SBDD) uses the target's three-dimensional structure to guide compound design through molecular docking and structure-guided optimisation, an approach already extensively applied to EGFR given its long-established role as a validated oncology target across multiple cancer types¹². Fragment-based drug discovery (FBDD), which begins from low-molecular-weight chemical fragments rather than drug-sized compounds, offers a complementary strategy particularly valuable for OSCC targets that lack a well-defined, readily druggable binding pocket, following design principles and screening methodology established across oncology drug discovery more broadly and directly transferable to OSCC-specific target validation programmes¹³¹⁴¹⁵.

3.2 Ligand Efficiency, Drug-Likeness, and Structure–Activity Relationship Optimisation

Compound optimisation against validated OSCC targets should be guided by the same quantitative drug-likeness and ligand efficiency criteria established across medicinal chemistry more broadly: molecular weight, lipophilicity, and hydrogen-bonding criteria established to predict oral bioavailability, together with ligand efficiency metrics that evaluate potency relative to molecular size and complexity rather than in absolute terms, providing a systematic framework for prioritising candidate structures during OSCC-directed lead optimisation¹⁶¹⁷¹⁸. Bioisosteric replacement substituting a functional group with another of similar size, shape, or electronic character represents a further widely applicable tactic for addressing metabolic liabilities or improving selectivity while preserving the pharmacophoric features responsible for engagement of OSCC-relevant targets such as EGFR or PI3K²⁰.

3.3 Covalent Inhibitor Design

Covalent inhibitor design, in which a reactive electrophilic warhead forms an irreversible or slowly reversible bond with a nucleophilic target residue, has substantially expanded the druggable target space across oncology over the past two decades, with rational, structure-guided covalent inhibitor design enabled by improved understanding of warhead reactivity–selectivity relationships²¹. The clinical translation of covalent KRAS(G12C) inhibitors, developed against a GTPase target long considered undruggable using classical reversible approaches, provides a template directly relevant to several OSCC-relevant oncogenic drivers that similarly lack deep, well-defined small-molecule binding pockets amenable to conventional reversible inhibitor design²²²³, and a systematic taxonomy of covalent inhibition mechanisms provides the mechanistic framework for extending this design paradigm to additional nucleophilic-residue-bearing OSCC targets as they are identified through the genomic approaches discussed in Section 2²².

3.4 Computational and AI-Guided Design

Machine learning-based QSAR and absorption-distribution-metabolism-excretion-toxicity (ADMET) property prediction, discussed extensively in the broader medicinal chemistry literature, are increasingly applicable to OSCC-specific drug design as the volume of relevant bioactivity data expands. Systematic denoising of historical ADMET training data to correct for measurement variability and inconsistent experimental protocols across data sources has been shown to measurably improve downstream model prediction accuracy, a methodological

consideration directly relevant to building reliable OSCC-target-focused predictive models given the comparatively smaller and more heterogeneous OSCC-specific bioactivity datasets available relative to higher-incidence cancer types³⁸, while systematic analysis of the key methodological elements underlying molecular property prediction models more broadly provides further guidance directly relevant to this task²⁷. Artificial intelligence methods developed for natural product drug discovery, spanning genome mining, activity prediction, and generative molecular design, offer a further template directly transferable to the phytochemical and natural-product-derived OSCC candidates discussed elsewhere in the broader OSCC medicinal chemistry literature²⁶, while therapeutic-area-specific machine learning applications, exemplified by QSAR modelling for antidiabetic drug discovery, demonstrate the broader template for adapting general-purpose predictive methodology to a specific disease area such as OSCC²⁸. A fully automated AI/ML virtual screening cascade implemented at a drug discovery centre in Africa further illustrates how these computational tools are lowering the infrastructural barrier to conducting OSCC-focused, machine-learning-guided medicinal chemistry outside traditionally resource-concentrated research hubs²⁹. The AlphaFold 3 structure prediction system, capable of predicting protein–ligand and protein–protein complex structures with accuracy approaching experimental determination, is expected to be particularly valuable for expanding structure-based design (Section 3.1) to OSCC targets nominated through genomic analysis that currently lack an experimentally solved structure²⁴, and the demonstrated clinical translation of a generative-AI-discovered small molecule into a randomised phase 2a trial for an unrelated indication offers a proof-of-concept precedent directly relevant to generative design approaches now being explored across oncology drug discovery, including for OSCC-relevant targets²⁵.

3.5 Illustrative Compound-Level Examples of Target-Directed OSCC Design

The general design strategies discussed in Sections 3.1 through 3.4 are concretely illustrated by several recently reported OSCC-specific compounds that directly exemplify target-directed medicinal chemistry applied to the pathways discussed in Section 2. A synthetic oxadiazole-based small molecule was recently reported to selectively suppress STAT3 signalling in human OSCC cells, achieving sub-200-nanomolar antiproliferative potency against two independent OSCC cell lines, illustrating that OSCC-directed drug discovery continues to identify novel scaffold–target combinations beyond the EGFR- and PI3K/AKT/mTOR-focused targets emphasised in Section 2³². A series of quinazoline/1,2,4-triazole/chalcone hybrid EGFR inhibitors, evaluated by the National Cancer Institute's screening programme, demonstrated growth inhibition of up to 99.74% against several cancer cell lines while simultaneously acting as apoptotic inducers, directly exemplifying the multi-target hybrid design strategy discussed in Section 3.1 applied to the EGFR target class identified in Section 2³³. Acridine-core naphthoquinone compounds evaluated specifically against OSCC cell models produced pro-apoptotic antitumoural effects attributed to selective reactive oxygen species generation, illustrating the apoptosis-pathway targeting strategy discussed in Section 2.3 in direct compound-level form³⁴. A related penta-heterocyclic indole scaffold incorporating thiadiazole and triazole substructures has demonstrated nanomolar antiproliferative potency in other epithelial cancer models through EGFR and p53-MDM2 pathway modulation, offering a directly transferable structural template for OSCC-specific extension given the shared reliance of squamous carcinomas on these same signalling nodes⁴⁰. These examples, spanning STAT3,

EGFR, apoptosis-pathway, and dual EGFR/p53-MDM2 targeting respectively, together demonstrate that the target identification and drug design strategies surveyed throughout this review are already yielding concrete, OSCC-tested or directly transferable candidate molecules rather than remaining purely conceptual.

4. Emerging Modality: Targeted Protein Degradation in Oral Cancer

Proteolysis-targeting chimeras (PROTACs), heterobifunctional molecules that induce ubiquitination and proteasomal degradation of a target protein rather than sustained occupancy-dependent inhibition, represent an actively emerging therapeutic modality directly relevant to several OSCC oncogenic drivers. A dedicated review of PROTAC strategies in oral cancer surveys degrader molecules directed at oncogenic drivers relevant to head and neck squamous cell carcinoma, including BRD4, and discusses the specific pharmacokinetic and oral-bioavailability considerations relevant to developing orally administered PROTAC therapeutics for this indication⁸. This application builds on the broader validation of PROTAC technology across oncology more generally, comprehensively reviewed as having progressed from early proof-of-concept to a clinically validated modality with dozens of degrader molecules across multiple cancer types now in clinical development⁹.

Cell-cycle regulators identified as OSCC targets in Section 2 are particularly amenable to this degrader approach: cyclin-dependent kinase 4/6 (CDK4/6) PROTACs have been developed that selectively degrade CDK6 over CDK4 despite the near-identical ATP-binding-pocket sequence identity that limits selectivity achievable with classical reversible small-molecule inhibitors, directly addressing a target-class-specific selectivity limitation that reversible inhibitor chemistry has struggled to overcome¹⁰. This CDK4/6-degradation strategy is directly relevant to the cell-cycle-pathway alterations (CCND1, CDKN2A) identified as OSCC targets through the exome sequencing analysis discussed in Section 2.1, and a novel orally bioavailable degrader strategy successfully developed for a structurally analogous kinase target (FLT3) in acute myeloid leukaemia provides a directly transferable synthetic and pharmacokinetic optimisation template for analogous OSCC-relevant kinase degrader development⁹.

Table 2. Representative drug design strategies applied or directly transferable to OSCC molecular targets

Design strategy	Applicable OSCC target(s)	Key consideration	Ref.
Structure-based design (SBDD)	EGFR, PI3K/AKT/mTOR components	Requires reliable target structure; AI-predicted structures expand coverage	12,24
Fragment-based design (FBDD)	Targets lacking well-defined binding pockets	Weak initial affinity requires sensitive biophysical detection	13,14,15
Covalent inhibitor design	KRAS-family and other nucleophilic-residue-bearing drivers	Requires kinetic (kinact/KI) optimisation of warhead reactivity	21,22,23
PROTAC/targeted degradation	CDK4/6, BRD4, and related oncogenic drivers	Addresses selectivity limits of reversible inhibitors at near-identical binding pockets	8,9,10
AI/ML-guided design	Broad applicability across nominated targets	Requires OSCC-specific training data for reliable prediction	24,25,27,28,29

5. Therapeutic Opportunities: Repurposing and Rational Combination Design

5.1 Computational Drug Repurposing

Drug repurposing – identifying new therapeutic applications for existing approved or investigational compounds – offers a comparatively fast, lower-risk route to OSCC candidate identification given that repurposed agents typically carry an established human safety record. Structure-based computational repurposing screens, exemplified by a study docking over 12,000 approved and investigational drugs against CDK6 and aromatase to identify compounds capable of simultaneous dual-target inhibition, illustrate a methodology directly transferable to the OSCC-relevant CDK4/6 and PI3K/AKT/mTOR targets discussed in Sections 2 and 4¹⁹.

5.2 Rational Combination Therapy Design

The co-occurrence of multiple targetable genetic alterations within individual OSCC tumours, documented in Section 2.1, provides a direct molecular rationale for combination therapy strategies specifically informed by each patient's alteration profile rather than empirically assembled regimens. Clinical evaluation of CDK4/6 inhibition combined with EGFR-directed therapy in head and neck squamous cell carcinoma, including early-phase trials combining palbociclib with cetuximab, and phase II evaluation of palbociclib combined with platinum-based chemotherapy in recurrent or metastatic disease, represents direct clinical precedent for the combination strategies suggested by the co-occurring TP53/CCND1 and EGFR pathway alterations identified through the genomic approaches discussed in Section 2³⁰.

5.3 Nanomedicine-Enabled Delivery of OSCC-Directed Small Molecules

The anatomical characteristics of the oral cavity – continuous salivary clearance and mucosal permeability constraints – pose delivery challenges distinct from many other solid tumour sites, motivating nanoparticle-based delivery systems specifically engineered for OSCC-directed therapeutics, documented in a comprehensive review of organic, inorganic, and hybrid nanocarrier platforms designed to improve the bioavailability and tumour selectivity of both established chemotherapeutics and the newer targeted small molecules discussed throughout this review³¹, building on the broader validation of nanoparticle-based medicine delivery already achieved across multiple FDA-approved oncology applications³⁹.

6. Challenges and the Target-to-Candidate Translational Gap

Despite the substantial expansion of the genomically and computationally nominated OSCC target landscape documented in Section 2, a pronounced gap persists between the number of candidate targets identified and the number that have been pursued through to validated, OSCC-specific drug candidates.

This gap is partly structural, reflecting the sheer scale of target nomination achievable through modern multi-omics methodology relative to the comparatively slow, resource-intensive process of experimental target validation and compound optimisation: the Mendelian randomisation study discussed in Section 2.1 alone identified 144 causal gene–outcome relationships from a single analysis, a nomination rate that no medicinal chemistry programme

could plausibly pursue to completion in parallel. This mismatch between nomination throughput and validation capacity is not unique to OSCC but is characteristic of genomically driven target discovery across oncology more broadly, and underscores the importance of the prioritisation and triage methodology discussed in Section 3.2 ligand efficiency, druggability assessment, and structure-based feasibility screening for identifying which of the many nominated targets warrant the substantial downstream investment required for full medicinal chemistry programme development.

Table 3. Principal challenges constraining translation of OSCC target identification into validated drug candidates

Challenge	Description	Illustrative consequence
Target validation rigor	Genomic/computational target nomination (Section 2) does not by itself establish causal, druggable dependency	Risk of pursuing correlative rather than functionally essential targets
Limited OSCC-specific structural data	Many nominated targets lack OSCC-context-specific structural or functional characterisation	Design efforts often rely on structural data generated in other cancer contexts
Cross-cancer-type extrapolation	Much drug design methodology applicable to OSCC targets has been validated primarily in other cancers	Uncertain generalisability of reported activity to OSCC-specific molecular and microenvironmental context
Tumour molecular heterogeneity	Co-occurring alterations and anatomical site-specific differences (Section 2.1) complicate single-target strategies	May favour combination approaches over monotherapy, increasing regulatory and clinical trial complexity
PROTAC/degrader physicochemical properties	Heterobifunctional degraders exceed classical drug-likeness criteria	Constrains oral bioavailability; narrower accessible chemical space for first-generation OSCC degraders
Resource concentration	OSCC-specific drug discovery infrastructure remains less developed than for higher-incidence cancer types	Slower overall translational pace despite expanding target identification literature

7. Future Directions

Several directions are likely to shape continued progress in OSCC-directed medicinal chemistry. First, closer integration of the genomic target identification approaches discussed in Section 2 with the structure-based and computational design methodologies discussed in Section 3 for example, using AI-predicted structures to immediately assess the structural druggability of newly nominated targets would shorten the current gap between target nomination and design-stage engagement³²⁴. Second, expanded application of PROTAC and other induced-proximity design strategies to the co-occurring, combination-relevant targets identified through exome sequencing analysis represents a promising but still underexplored opportunity, building on the direct precedent established for CDK4/6 degraders in other cancer contexts^{5,10}.

Third, systematic, prospective computational drug repurposing screens focused specifically on the OSCC target landscape mapped in Section 2, rather than opportunistic single-target repurposing studies, could more efficiently identify near-term therapeutic candidates with established human safety profiles¹⁹. Finally, greater investment in OSCC-specific in vivo and

patient-derived xenograft validation, rather than continued reliance on cross-cancer-type extrapolation from structural and mechanistic data generated in other malignancies, will be essential for establishing which of the rapidly expanding list of genomically nominated OSCC targets represent genuinely tractable, clinically meaningful drug discovery opportunities³⁹⁻⁴⁰.

8. Conclusion

Medicinal chemistry strategy for OSCC has been substantially reshaped by the convergence of multi-omics target identification methodology with established rational drug design paradigms and emerging modalities such as targeted protein degradation. Multi-omics and exome sequencing approaches have expanded the validated OSCC target landscape considerably, converging on EGFR/kinase signalling, PI3K/AKT/mTOR survival signalling, cell-cycle regulators, and immune checkpoint pathways as principal therapeutic nodes, while structure-based, fragment-based, covalent, and AI-guided drug design methodologies developed across oncology more broadly offer directly transferable strategies for engaging these targets. PROTAC-based targeted protein degradation, computational drug repurposing, and rational combination therapy design further extend the therapeutic opportunity space beyond classical small-molecule occupancy. Nonetheless, a substantial gap persists between the rapidly expanding, genomically nominated OSCC target landscape and the comparatively small number of targets pursued through to validated, OSCC-specific drug candidates. Closing this gap will require rigorous target validation, OSCC-specific structural and in vivo characterisation, and closer integration of the target identification and drug design communities than has typically characterised this field to date, so that the considerable genomic and computational progress documented in this review can be translated into genuine therapeutic advances for OSCC patients.

The illustrative compound-level examples discussed in Section 3.5 spanning STAT3, EGFR, apoptosis-pathway, and dual EGFR/p53-MDM2-directed molecules demonstrate that this integrated target-identification-to-drug-design pipeline is not merely a conceptual framework but is already generating concrete, testable OSCC candidates. Extending this pipeline systematically, rather than relying on the largely opportunistic convergence of genomic and medicinal chemistry research that has characterised the field to date, represents the clearest path toward converting the rapidly expanding OSCC target landscape into a correspondingly expanding portfolio of validated therapeutic candidates for this persistently underserved malignancy.

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