

Personalized Targeted Therapeutic Strategies against Oral Squamous Cell Carcinoma. An Evidence-Based Review of Literature

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Abstract: Oral squamous cell carcinoma (OSCC) is the most common type of malignant tumor in the head and neck, with a poor prognosis mainly due to recurrence and metastasis. Classical treatment modalities for OSCC like surgery and radiotherapy have difficulties in dealing with metastatic tumors, and together with chemotherapy, they have major problems related to non-specific cell death. Molecular targeted therapies offer solutions to these problems through not only potentially maximizing the anticancer efficacy but also minimizing the treatment-related toxicity. Among them, the receptor-mediated targeted delivery of anticancer therapeutics remains the most promising one. As OSCC exhibits a heterogeneous nature, selecting the appropriate receptors for targeting is the prerequisite. Hence, we reviewed the OSCC-associated receptors previously used in targeted therapy, focused on their biochemical characteristics and expression patterns, and discussed the application potential in personalized targeted therapy of OSCC. We hope that a better comprehension of this subject will help to provide the fundamental information for OSCC personalized therapeutic planning.

Keywords: oral squamous cell carcinoma, receptors, targeted therapy, active targeting, drug delivery

Introduction

Oral squamous cell carcinoma (OSCC), originating from the mucosa of the tongue, buccal, palate, floor of the mouth, alveolar ridge, and other parts of the oral cavity, is the most common malignant tumor in the head and neck. The newest global cancer statistics reported that OSCC accounted for over 370,000 new cancers and 170,000 cases of death.¹ Despite lots of efforts having been put on treatment of OSCC, its five-year survival rate is still no more than 50%. The leading causes for poor prognosis might be correlated to recurrence and metastasis, which could be due to incomplete resection of tumor and neglected metastases.^{2,3} Developing more efficient therapeutics is essential for improving prognosis of OSCC.

The principal strategies for OSCC treatment are surgery, chemotherapy, radiotherapy, or a combination of these modalities based on the severity of disease.^{4,5} Surgery remains the most efficient treatment for OSCC, while it inevitably damages the functions and aesthetics of the orofacial region.⁶ Moreover, together with radiotherapy, they have difficulties in dealing with metastatic tumors.⁷ Chemotherapy could inhibit rapidly growing cells including those in metastatic sites via inhibiting cell growth and division.^{8,9} However, its selective toxicity is relatively low, and normal cells with enhanced proliferation rates such as the hair follicles, bone marrow and gastrointestinal tract could also be harmed.¹⁰ To alleviate toxicities to normal cells, chemotherapeutics is often used at suboptimal doses, which might lead to the final failure of

treatment, and even drug resistance and metastatic disease. Therefore, there has been a great pursuit for development of targeted anticancer drugs to increase the selective toxicity in cancer therapy.

At present, two targeted approaches are being explored for improving the selective toxicity. One is developing newer drugs that alter specific signaling pathways of cancer cells.^{11,12} For example, bevacizumab, a monoclonal antibody that directly targets vascular endothelial growth factor receptor (VEGFR), suppresses functions of all VEGF-A isoforms and blocks correlated downstream signaling, leading to cell-cycle arrest, apoptosis and anti-angiogenesis.¹³ However, researches for these molecular targeted therapies will not be pressed ahead further, as these may cause a series of adverse effects in normal cells that usually distinct from classical cytotoxic chemotherapy.¹⁴ The other emerging one is targeted delivery of anticancer drugs to cancer region, increasing the drug dosages that reach the malignant tissue and avoiding the undesirable side effects to the normal tissue through specific receptors targeting.^{15,16} A paradigmatic example is trastuzumab emtansine, an antibody-drug conjugate targeting HER2-positive breast cancer cells and functioning via transporting cytotoxic compound emtansine, which was approved by the US Food and Drug Administration (FDA) in 2013.¹⁷ Thus, in the first place, it is essential to select the appropriate receptors for targeting, especially in OSCC which remains a heterogeneous nature.

Where Do We Stand in Oral Squamous Cell Carcinoma Treatment?

Targeted anticancer therapy generates the concept of personalized cancer therapy, which can be explained as conducting the specific targeted therapy on patients according to their specific molecular characterization of cancer cells and cancer microenvironment, thus promoting clinical outcome. In brief, that is performing the right therapeutics on the right patient at the right time, and has become an irresistible trend in the field of anticancer research.^{18,19} A simplified example is that patients with non-small-cell lung cancer (NSCLC) usually respond to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors erlotinib and gefitinib well when they have specific EGFR mutations.²⁰ During the personalized cancer therapy, the urgent need is to identify biomarkers uniquely expressed or overexpressed in cancer compared to normal tissues, and use them for early detection, prognosis prediction, clinical outcome evaluation, or personalized diagnostic and therapeutic planning.^{21–23}

Till now, two kinds of molecular targeted treatment have been approved by FDA for OSCC therapeutics. The first one is EGFR targeted therapy. EGFR is the member of ErbB family of receptor tyrosine kinase. Activated by either its ligands EGF or transforming growth factor- α (TGF- α), EGFR becomes phosphorylated and subsequently activates signal transduction pathways, such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase (PI3K)/ Akt pathway, and Src pathway. These processes play crucial roles in a variety of cellular behaviors especially growth and migration, in both normal and neoplastic cells.²⁴ Studies have reported that EGFR activity is increased in a large majority of cancers, such as NSCLC, breast, colorectal, pancreatic and head and neck cancer,²⁵ and almost all premalignant and malignant lesions of oral cavity are witnessed with EGFR overexpression.^{26,27} In 2006, a chimeric monoclonal antibody cetuximab which competitively inhibits binding of EGFR to its ligands was approved by FDA for the treatment of OSCC under certain conditions.^{28,29} However, the clinical outcome has not been remarkably improved as the median survival time of those administered with cetuximab plus chemotherapy increased marginally from 7.4 to 10.1 months compared to those with chemotherapy alone.³⁰

Another recently approved targeted therapeutics for OSCC is the immune checkpoint blockade-based anti-PD1 therapy. In cancer immune microenvironment, the immune checkpoint programmed cell death 1 (PD1) expressed on the surface of CD8⁺ T cells and its ligand programmed cell death ligand 1 (PDL1) expressed on the surface of cancer cells and associated stromal cells, act as accomplices to blunt the anticancer effects of CD8⁺ T cells. Anti-PD1 therapy blocks the interaction of PD1/PDL1, thus abolishing the inhibition of CD8⁺ T cells and promoting the immune normalization.^{31–33} In OSCC, anti-PD1 therapy using pembrolizumab and nivolumab was approved by FDA in 2016.^{34,35} Although there was a statistically significant improvement in overall survival in patients with metastatic and recurrent head and neck squamous cell carcinoma (HNSCC) when administered with pembrolizumab plus chemotherapy, compared to those administered with cetuximab plus chemotherapy as reported by a recent clinical trial, only a fraction of patients responded to anti-PD1 therapy and toxicities existed in organs like lung, which also express PDL1.³⁶ Hence, existing targeted therapies remain limited for OSCC patients, and other targeting strategies need to be explored.

How Strategic is Targeting Specific Oral Squamous Cell Carcinoma Cell Receptors?

As introduced before, receptors- or antigens-mediated targeted delivery of anticancer drugs to cancer cells or cancer-associated regions will be a rapidly growing field of research and a source of newer anticancer products for clinical use. Herein, searching for appropriate targeting receptors is regarded as the key factor to this targeted anticancer therapy, except for selecting cytotoxic drugs, drug carriers, etc.³⁷ OSCC, as well as other types of cancer, exhibits various surface receptors. These receptors might have unique expressions indicating that they are only expressed or functional in tumor regions, or have evidently higher expressions in tumor regions compared to those in normal sites, thus exhibiting the possibility of being utilized for mediating drug delivery. Next, we will review the OSCC cell receptors that have been previously targeted in published researches concerning targeted delivery of anticancer therapeutics to OSCC region, focusing on their biochemical characteristics, expression patterns, and targeting strategies (Figure 1, Table 1).

Targeting Receptors with Cancer Specific Expression Urokinase-Type Plasminogen Activator Receptor (uPAR)

uPAR is a cell membrane protein important for cancer invasion, angiogenesis and metastasis of various cancers, including OSCC.^{38–40} The main mechanism underlying these functions is uPAR's binding to its ligand urokinase-type plasminogen activator (uPA) in cell membrane of migrating cells, thus mediating the extracellular matrix remodeling.⁴¹ Additionally, uPAR activates many intracellular pathways through interaction with transmembrane receptors, and thus induces malignant behaviors of cancer cells.⁴² uPAR expression is usually cancer specific, and in most cases, its high expression correlates with increased aggressiveness, thus conferring it the ability of being as a promising diagnostic, therapeutic and prognostic biomarker.^{43,44} For example, in breast cancer, bladder cancer, and prostate cancer, a uPAR-targeting peptide was used for tumor imaging in a Phase I clinical trial.⁴⁵

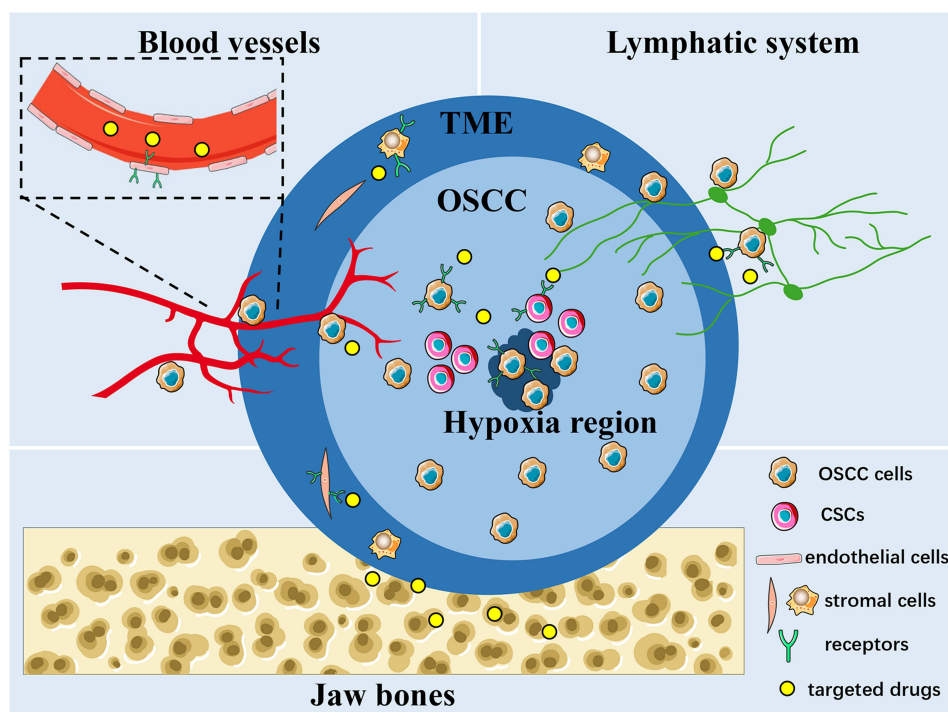


Figure 1 Schematic illustration of target receptors in OSCC and OSCC-associated regions for anticancer drugs delivery.

Notes: Except for targeting receptors expressed on OSCC cells, biomarkers of OSCC-associated regions can also be targeted for anticancer drugs delivery, such as CSCs, cancer cells in hypoxia regions, stromal cells, blood endothelial cells, metastatic lymph nodes, and jaw bones adjacent to oral malignancies.

Abbreviations: CSCs, cancer stem cells; OSCC, oral squamous cell carcinoma; TME, tumor microenvironment.

Table 1 OSCC-Associated Receptors That Have Been Used in Targeted Therapy

Classification	Receptors	Representative Ligands in OSCC Therapy	Representative Targets	Ref
Cancer specific expression	uPAR	AE105	Cancer cells and cancer-associated stroma cells	[50, 51]
	$\alpha v\beta 6$	RGD, anti- $\alpha v\beta 6$ mAb	Epithelial cancer cells	[57, 58]
	Folate receptors	Folic acid	Cancer cells	[62–65]
Cancer overexpression	EGFR	Cetuximab	Cancer cells and cells from dysplasia, normal epithelium and normal salivary gland	[66–70]
	PDL1	Anti-PDL1 Ab	Cancer cells	[72]
	c-Met	cMBP	Solid cancer cells especially OSCC cells	[78, 79]
	GRPR	Bombesin, TMI	Cancer cells	[85, 86]
	PDPN	Anti-PDPN Ab	Cancer cells and lymphatic endothelial cells	[92]
	Sigma receptors	Anisamide	Cancer cells	[97, 98]
	TfR1	Ferritin heavy chain	Cancer cells and activating lymphocytes and osteoclasts	[101, 102]
	$\alpha v\beta 3$	RGD	Cancer cells, osteoclasts and vascular endothelial cells	[109–111]
	SPARC	HSA	Cancer cells and CAFs in some cancers including OSCC	[114]
	LDLR	Anti-LDLR Ab	OSCC cells in hypoxia regions	[116]
	CD44	Anti-CD44 Ab, hyaluronic acid	Cancer stem cells	[118, 119]
	P-selectin	Fucoidan	Vascular endothelial cells of various cancers	[121]
	CXCR4	SDF-1	Metastatic lymph nodes	[122]

Abbreviations: CAFs, cancer-associated fibroblasts; c-Met, mesenchymal-epithelial transition factor; cMBP, cMet-binding peptide; CXCR4, CXC chemokine receptor 4; EGFR, epidermal growth factor receptor; GRPR, gastrin-releasing peptide receptor; HSA, human serum albumin; LDLR, low-density lipoprotein receptor; mAb, monoclonal antibody; OSCC, oral squamous cell carcinoma; PDPN, podoplanin; PDL1, programmed cell death ligand 1; RGD, Arg-Gly-Asp tripeptide; SDF-1, stromal cell-derived factor-1; SPARC, Secreted Protein Acidic and Rich in Cysteine; TfR1, transferrin receptor 1; uPAR, urokinase-type plasminogen activator receptor.

In OSCC, it has been reported that enhanced uPAR expression was associated with cancer invasion, lymph node metastasis, high recurrence rate and significant reduction in overall survival of OSCC patients. Also, uPAR is highly cancer specific in OSCC, where it is expressed on OSCC cells and stromal cells like fibroblasts and inflammatory cells in the cancer microenvironment, and almost absent in normal cells (Figure 2A). Moreover, uPAR has been found to have strong expressions at the invasive front of OSCC.^{46,47} The early investigation for clinical potential of uPAR in OSCC is tumor imaging and intraoperative guidance.^{45,48,49} For example, Christensen et al have developed a uPAR-targeting fluorescent agent and a PET agent using conjugates of AE105 (a ligand for uPAR) and fluorophore ICG or radioactive isotope ⁶⁴Cu, for fluorescence-guided tumor resection or preoperative tumor imaging of OSCC and the metastatic lymph nodes (Figure 2B).⁵⁰ In addition, Zuo et al constructed therapeutic drugs-encapsulated dendritic mesoporous silica nanoparticles (NPs) decorated with AE105 targeting uPAR, and applied them for photonic hyperthermal and sonodynamic targeted therapy of OSCC.⁵¹

Integrin $\alpha v\beta 6$

The integrin $\alpha v\beta 6$ is composed of an αv subunit and a $\beta 6$ subunit, both of which contain three domains: the cytoplasmic domain, the extracellular domain, and the transmembrane domain. The extracellular domains recognize and adhere to specific ligand which contains the Arg-Gly-Asp (RGD) motif, while the cytoplasmic domain of $\beta 6$ subunit transmits

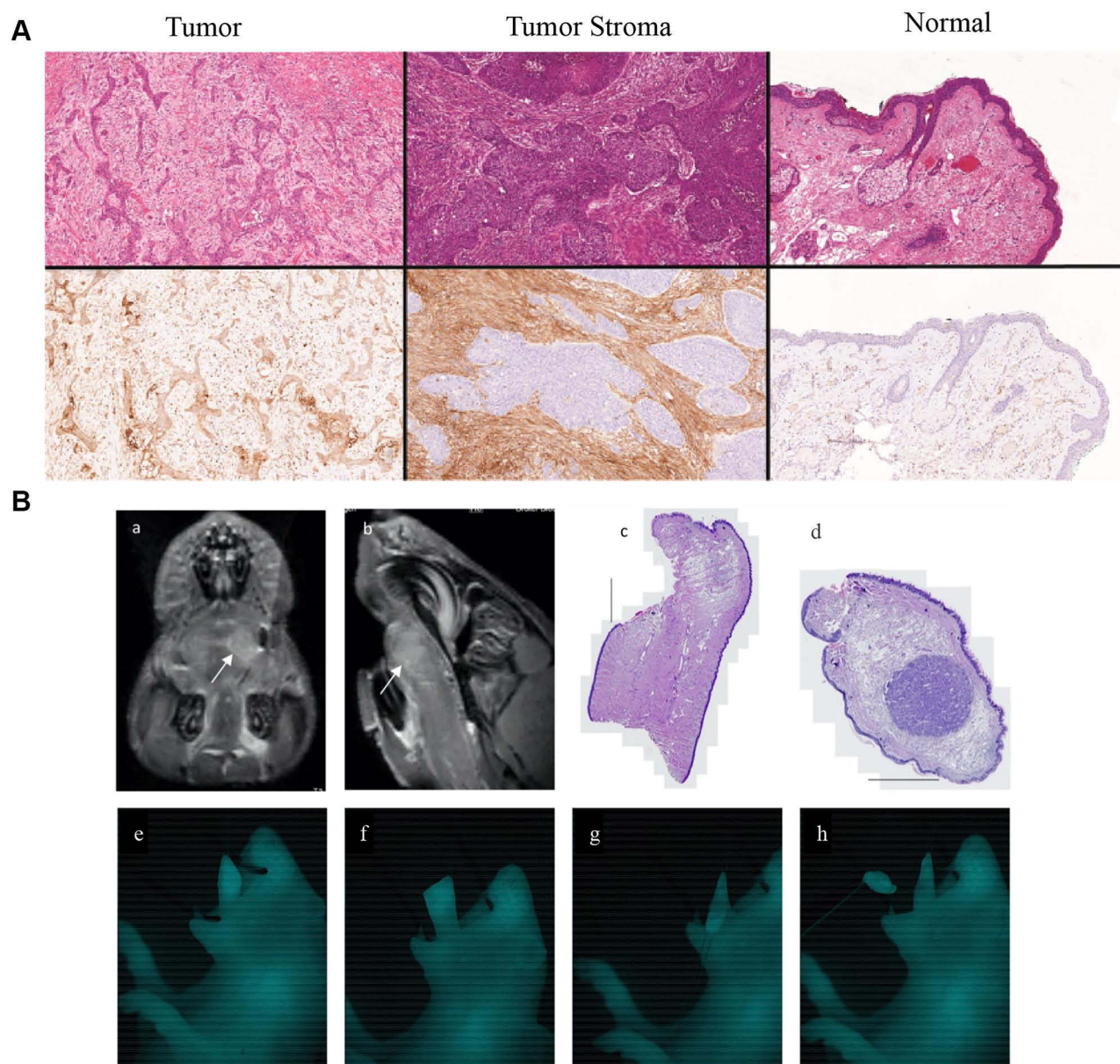


Figure 2 The expression pattern and targeting efficiency of uPAR in OSCC.

Notes: (A) Images of H&E and uPAR immunohistochemical staining showing the results of uPAR expression in tumor (left), tumor stroma (middle) and normal squamous epithelium. Reproduced from Baart VM, van Duijn C, van Egmond SL et al. EGFR and $\alpha v\beta 6$ as promising targets for molecular imaging of cutaneous and mucosal squamous cell carcinoma of the head and neck region. *Cancers*. 2020;12(6):1474. [Creative Commons Attribution License](#).⁴⁶ (B) Fluorescence-guided tumor resection using fluorescence agent ICG-Glu-Glu-AEI05 targeting uPAR. Mice with a tumor in the left anterior tongue as shown on preoperative MRI (a, b, white arrow indicates tumor). A time sequence fluorescence imaging showing that the tongue was fixed with a suture in the tip of the tongue, and tumor resection was performed guided by real-time optical imaging (e-h). H&E staining showing the tongue specimen had a clear resection margin (c), and the resection specimen showed a localized tumor, indicating radicality of tumor resection (d). Reproduced from Christensen A, Juhl K, Persson M et al uPAR-targeted optical near-infrared (NIR) fluorescence imaging and PET for image-guided surgery in head and neck cancer: proof-of-concept in orthotopic xenograft model. *Oncotarget*. 2017;8(9):15,407–15,419. [Creative Commons Attribution License](#).⁵⁰

various extracellular stimulus to cytoskeleton and vast intracellular signaling pathways.^{52,53} As the $\beta 6$ subunit only binds to αv , it is the $\beta 6$ subunit that contributes to its epithelial specific expression, and many unique functions of $\alpha v\beta 6$ especially in cancer invasion and metastasis.⁵⁴ $\alpha v\beta 6$ is almost undetectable in normal epithelial cells, while highly expressed in malignant epithelial cancers including OSCC,⁵⁵ in which its high expression correlates with invasion and poor prognosis,⁵⁶ providing the possibility of using $\alpha v\beta 6$ as a promising biomarker for OSCC therapeutics. For example, a study conjugated peptides containing RGD to the surface of NPs and exerted the OSCC-targeting effects by

$\alpha\text{v}\beta 6$ -mediated endocytosis.⁵⁷ In addition, Legge and teamworkers constructed an anti- $\alpha\text{v}\beta 6$ monoclonal antibody-conjugated functional NPs for OSCC targeting, and for further therapy.⁵⁸

Folate Receptor

Folate receptors (FRs) including FR α , FR β and FR γ , are cell surface glycoproteins that bind folic acid with high affinity. Usually expressed at low levels in most tissues, FRs, especially FR α , have high expressions in numerous cancers including OSCC, in order to meet the dramatically increasing need of rapidly growing cancer cells for folic acid.^{59,60} Interestingly, although FR α expression in cancer cells is not cancer specific, we categorize it into this kind of receptors as it localizes at the luminal surface of polarized epithelial cells and is separated from the circulation in nonmalignant situation. However, in malignant situation, FR α is expressed on the cell surface with high densities, becoming easily targeted for cancer therapy.⁶¹ In OSCC, various folic acid-linked NPs have been designed to improve the OSCC targeting efficiency and for gene therapy, drug delivery or photothermal therapy (PTT).^{62–65}

Targeting Receptors with Cancer Overexpression

EGFR and PDL1

As the applications of anti-EGFR therapy and PD1/PDL1 blocking therapy have been described previously, the concept using EGFR or PDL1 as the targeting receptor for OSCC therapeutics has also been put forward. EGFR has been found to be highly expressed in a majority of cancers, and up to 90% of HNSCC exhibits overexpressed EGFR. However, EGFR lacks a cancer specific expression. Specimens containing dysplasia, normal epithelium and normal salivary gland tissues also exhibit regular EGFR expressions.^{46,47} Studies have already shown the use of EGFR monoclonal antibody such as cetuximab for targeting EGFR on the surface of OSCC cells, and conjugating with contrast agents for the purpose of imaging-guided therapy.^{66–68} However, as reported by a phase I clinical trial, normal epithelium and salivary gland tissues outside the OSCC compartment also showed signals with the use of an EGFR targeting imaging agent.⁶⁹ Hence, EGFR targeting needs to be improved further. Recently, Wang et al constructed a kind of NPs which exposed the peptide targeting EGFR of OSCC cells in the acidic cancer environment, while sequestered it in the physiological condition, thus improving the problem of cancer non-specific expression of EGFR.⁷⁰

Also, targeting PDL1 has been utilized for receptor-mediated drug delivery in OSCC therapeutics, as PDL1 was reported to be highly expressed in human OSCC tissues when compared with healthy tissues, and its overexpression in OSCC correlated with disease progression and increased tumor infiltrating CD8⁺ T cells.⁷¹ In this case, a recent study modified a kind of drug-encapsulated NPs with an anti-PDL1 antibody in OSCC targeted therapy, to improve both drug specificity and immune function.⁷²

Mesenchymal-Epithelial Transition Factor (c-Met)

c-Met, a member of the tyrosine protein kinase receptor family, is also called the hepatocyte growth factor (HGF) receptor, as it is the only receptor that binds to HGF. As a key transmembrane protein encoded by the proto-oncogene c-MET, it can promote the growth of hepatocytes, and is overexpressed in a broad range of solid cancers to stimulate proliferation, survival, migration, invasion and angiogenesis.^{73,74} When compared with other cancers and normal tissues, OSCC cells exhibit highly expressed c-Met.⁷⁵ According to an investigation, 90% of HNSCC cell lines and 84% of patient tissues had upregulated c-Met expression, indicating its potential for targeted therapeutics.^{76,77} Recently, the main application of targeting c-Met in OSCC is the field of imaging for early diagnosis, intraoperative navigation and prognosis prediction.^{78,79}

Gastrin-Releasing Peptide Receptor (GRPR)

GRPR, which binds to GRP with high affinity, has regulatory roles in various parts of the body, such as the brain, the vascular system, intestinal mucosa and the endocrine system. In physiologically normal organs, GRP/GRPR has low concentrations, while in human cancer, it is highly overexpressed and can stimulate cancer growth.⁸⁰ Initially, GRPR was found to be overexpressed in prostate cancer and used as a diagnostic tool. Nowadays, more cancers have been

recognized with increased GRPR, and emerging studies have investigated the possibility of targeted diagnosis and therapy using GRPR, such as in breast cancer, gastrointestinal cancer, colorectal cancer, and so on.^{81–83} In OSCC, Lango et al have reported that GRPR expression was six times higher than that in normal tissues, and four times higher than that in adjacent normal epithelial tissues.⁸⁴ Furthermore, studies focusing on near-infrared fluorescent imaging of OSCC utilized GRPR targeting, and results showed that it's available in intraoperative surgical margin decision and metastatic lymph node detection.^{85,86}

Podoplanin (PDPN)

PDPN is a small mucin-type transmembrane protein, which has a majority of physiological and pathological effects including regulation of organ development, cell motility, tumorigenesis and metastasis.⁸⁷ PDPN is expressed in a variety of normal cells, but overexpressed in cancer and cancer-associated cells of several cancer types, including squamous cell carcinoma of the lung, head and neck, malignant mesothelioma, and brain tumors. In addition, PDPN is a specific marker of lymphatic vessels, and increased PDPN correlates with cancer lymphangiogenesis and migration of cancer cells into the lymphatic system.^{88,89} Thus, it is clear that PDPN overexpression plays a critical role in cancer progression and metastasis. In OSCC, studies have reported that PDPN was upregulated and associated with malignant phenotype.^{90,91} Liu et al established a multifunctional gold nanoplatfrom conjugated with anti-PDPN antibody and anticancer drug Dox, to actively target OSCC for chemo/photothermal therapy.⁹²

Sigma Receptors

Sigma receptors, including sigma-1 and sigma-2, are a unique class of membrane proteins ubiquitously expressed and highly conserved throughout the mammalian body, indicating their important roles in cellular function.⁹³ Encoded from different genes, sigma-1 receptor has been detected in plasma membrane and membranes of endoplasmic reticulum and mitochondria of various organs, and has evidently high expressions in embryonic stem cells during all stages of embryogenesis.⁹⁴ Sigma-2 receptor is expressed in the central nervous system, gastrointestinal tract, kidney, liver and heart, with lower expression levels than sigma-1.⁹⁵ Overexpression of sigma receptors is observed in various cancers, including NSCLC, breast cancer, melanoma, and so on, with a similar subcellular localization, suggesting their critical roles in both caspase-dependent and caspase-independent cell death pathways.⁹⁶ As reported by recent studies, sigma receptors were highly expressed in OSCC tissues. Modifying anisamide on the outer-leaflet of certain NPs has been developed for actively targeting sigma receptors and then transporting agents like siRNA to the OSCC cells.^{97,98}

Transferrin Receptor I (TfR1)

TfR1, a homodimer expressed in the cell membrane, binds to transferrin (Tf)-bound iron and transports it as the complex through the clathrin-mediated endocytosis. TfR1 expression depends on the cellular iron status. It increases in iron-deficient cellular context, while decreases in the presence of excess iron.⁹⁹ Rapidly proliferating cells and energy-requiring cells, such as cancer cells, activating lymphocytes and osteoclasts, exhibit high expressions of TfR1, due to the fast-growing need for iron. Emerging studies have reported that TfR1 showed specific overexpression in a wide number of cancers, and up to 100 times higher than that in normal tissues.¹⁰⁰ Hence, targeting TfR1 for cancer diagnosis and treatment has attracted extensive attention. Damiani et al have successfully developed a human ferritin heavy chain-based carriers which can actively target TfR1 on the surface of OSCC cells, and be freely internalized as a complex for further therapy.^{101,102}

Integrin $\alpha\beta3$

The integrin $\alpha\beta3$, composed of an αv subunit and a $\beta3$ subunit, is an integrin essential for angiogenesis and tumor cell biology. The same as $\alpha\beta6$, $\alpha\beta3$ is one of the eight integrins that can recognize peptides containing the RGD sequence and facilitate extracellular matrix proteins-integrins interaction.¹⁰³ Rapidly dividing cells including cancer cells and certain nonmalignant cells especially osteoclasts and endothelial cells of blood vessels, express large amounts of $\alpha\beta3$, whereas quiescent cells usually have little or no expressions.¹⁰⁴ Moreover, it has been reported that smooth muscle cells, skeleton muscle myoblasts, platelets and activated macrophages contain functional $\alpha\beta3$ expressions, and the

normal colon, brain, salivary gland and thyroid gland express quite low, but detectable levels of $\alpha v\beta 3$.^{104,105} Thus, $\alpha v\beta 3$ is important for not only malignant behaviors of cancer cells, but also some physiological functions maintaining. In OSCC, $\alpha v\beta 3$ was reported to be expressed solely on the neovasculature of tumors using RGD-based tracers specific for $\alpha v\beta 3$.^{106,107} However, Lobeek et al identified that OSCC with highly keratinizing phenotype also showed $\alpha v\beta 3$ expression on cancer cells using⁶⁸ Ga-RGD PET/CT imaging, while $\alpha v\beta 3$ expressed at low levels in metastatic lesions as compared with primary OSCC tissues.¹⁰⁸ Researchers usually modified multi-functional nanoplateforms with RGD containing peptides to actively target $\alpha v\beta 3$ for OSCC therapeutics,^{109–111} indicating its potential role in targeted therapy.

Secreted Protein Acidic and Rich in Cysteine (SPARC)

SPARC, also termed as osteonectin, is an extracellular matrix glycoprotein first isolated as the main non-collagenous component of bone, and induces calcium deposition after binding to collagen. Furthermore, SPARC has been investigated to be expressed by a variety of tissues undergoing repair or remodeling due to wound healing, disease, or natural process.¹¹² In cancer microenvironment, SPARC exhibits diverse functions depending on the specific cancer type. Some types of cancer have high levels of SPARC expression and this high expression correlates with disease progression and poor prognosis, while in some other types of cancer, SPARC acts as a tumor suppressor.¹¹³ In OSCC, SPARC reveals higher expressions in tumor tissues especially in cancer cells and cancer-associated fibroblasts (CAFs) than that in normal tissues.^{114,115} A study used human serum albumin (HSA) as a nanocarrier to actively target SPARC expressed on OSCC cells and CAFs, to exert PTT/photodynamic therapy (PDT)/chemotherapy after SPARC-mediated transcytosis of NPs and further release of functional agents.¹¹⁴

How Strategic is Targeting Oral Squamous Cell Carcinoma-Associated Microenvironment Biomarkers?

Except for targeting receptors mainly expressed on cancer cells, biomarkers of OSCC-associated regions can also be targeted for personalized therapeutics, in order to increase sensitivity to classical therapeutic strategies, prevent cancer recurrence and metastasis, and enhance overall treatment efficacy. For example, modifying the surface of multifunctional NPs with antibodies against low-density lipoprotein receptor (LDLR), which was reported to be a specific OSCC biomarker in hypoxia regions, has been proved to successfully target OSCC and exert tumoricidal effects using PDT/PTT and chemotherapeutic agents.¹¹⁶ As the hypoxia region, which means the core area of tumors, has a close relationship with chemoresistance, actively targeting this region might be helpful for preventing chemoresistance-induced treatment failure.¹¹⁷ Moreover, cancer stem cells (CSCs), a group of cancer cells capable of self-renewal and both initiating tumorigenesis and promoting metastasis, are also one of the leading causes of resistance to chemotherapy and radiotherapy. Su's research used the anti-CD44 antibody-modified superparamagnetic iron oxide NPs to target CD44-overexpressed CSCs in OSCC, and kill them under an alternating magnetic field-induced hyperthermia.¹¹⁸ Similar study exists using hyaluronic acid, which is one of the ligands of CD44, for CSCs targeted therapy in OSCC.¹¹⁹

Tumor vasculature and metastatic lymph nodes of OSCC are also the essential targets for therapy, as OSCC is a stroma-rich tumor and metastasize mainly through the lymphatic system.¹²⁰ P-selectin, a cell adhesion molecule overexpressed in the vasculature of several cancers including OSCC, was targeted by fucoidan-based NPs for further delivery of anticancer agents.¹²¹ Another study prepared a stromal cell-derived factor-1 (SDF-1)-modified nanosystem to co-deliver chemotherapeutic drug DOX and PTT photosensitizer ICG, and actively targeted CXCR4 chemokine receptor 4 (CXCR4)-expressed metastatic lymph nodes using SDF-1's binding to CXCR4, for synergistic PTT/chemotherapy in metastatic OSCC and cutting off the metastasis pathway.¹²²

Furthermore, preventing bone invasion is a special aspect in OSCC targeted therapeutics, as jaw bones' close anatomical relationship with oral malignancies.¹²³ In such case, researchers have designed a delicate biomimetic nanoparticle using the HNSCC and red blood cell membrane hybrid exterior shell with PTT agents containing inside, and then modified with the octapeptide (Asp8) which has high binding affinities to hydroxyapatite, for exerting tumor and bone dual targeting effects.¹²⁴

What are Other Active Targeting Strategies in Oral Squamous Cell Carcinoma?

In addition to the already known receptors or biomarkers-mediated drug delivery, other active targeting strategies also exist. For example, researchers isolated a novel peptide HN-1 from an M13 single-stranded phage-based random peptide-display library when using human HNSCC cells to allow endocytosis to occur. HN-1, a 12-amino acid peptide, can specifically bind to and be efficiently internalized into HNSCC cells, but not normal cells or other types of cancer cells, indicating that HN-1 uptake does not occur ubiquitously.¹²⁵ Since then, various studies have used HN-1 to conjugate with anticancer drugs or tumor imaging agents for HNSCC-targeted therapeutics in vitro and in vivo.^{126,127} In our previous study, HN-1 also showed a significantly enhanced ability to mediate cellular uptakes of nanoparticles.¹²⁸ However, although scientists considered that HN-1 may exert this targeting effect through specific interaction with a cellular receptor, the exact receptor is currently not known and requires further analysis. Additionally, studies also utilized cancer cell membrane-camouflaged biomimetic NPs to enhance the specific targeting capacities to cancer cells.¹²⁹ Moreover, as OSCC exhibits upregulated macropinocytosis, an endocytotic, nutrient-scavenging pathway that promotes albumin internalization into cells, therapeutic agents bound to albumin could also selectively target OSCC cells, except for via the SPARC receptor.¹³⁰

The Future Perspectives

Exploring the molecular biology of cancer cells for more effective targeted therapeutics is an unavoidable trend in the winding way of tackling cancer, and selecting the tumor-specific biomarkers remains the prerequisite. In this review, receptors or biomarkers that were utilized for targeted treatments of OSCC were summarized. These receptors are either uniquely expressed or overexpressed in OSCC or OSCC-associated regions. However, several problems exist concerning the current literatures of OSCC targeted therapy. Firstly, most studies utilized generally the same cell lines to investigate the efficiency of receptor-mediated drug delivery to OSCC regions. Although the results were promising turned out, they still do not fit the reality very well as OSCC exhibits a heterogeneous nature and the specific chosen receptors shall be different and dependent on patients with distinct risk habits and anatomical sites where OSCC arises. Additionally, with the development of nanotechnology, receptors-mediated active targeting strategy modified in nanosystem has attracted great interests in the field of oncological research.^{131,132} On one hand, the nanoparticle itself exhibits the passive targeting effect, namely the enhanced permeability and retention (EPR) effect due to its small size.¹³³ On the other hand, receptors or other factors-mediated active targeting strategies reviewed above could increase specificity and uptake efficiency, and overcome the multiple-drug resistance after initial accumulation, since EPR effect is not taken place in some hypovascular cancers, and permeability of new blood vessels could vary in a single cancer.^{134–136} However, limitations are that no nanoparticles with active targeting strategies have gained the FDA approval to date, and only a few anticancer drugs conjugated with active targeting agents have been developed for clinical use in cancer therapeutics except for OSCC.¹³⁷

On the positive side, summarizing the target receptors in OSCC personalized therapy and studying their biochemical characteristics and expression patterns could undoubtedly provide basic and valuable information for further clinical research and application. Currently, emerging studies have put their efforts to improve the targeting and tumor killing effects by optimizing therapeutic strategy. For example, Chen et al developed a drug delivery nanosystem with bone and OSCC cells dual targeting function, to maximize the treatment efficiency for OSCC with bone invasion.¹²⁴ In addition, cancer targeting has been improved by not only targeting molecules highly expressed on cancer cell membranes, but also self-reinforcing of the targeting molecule which has upregulated expression in response to cellular attack via cancer treatments.¹³⁸ Furthermore, cancer targeted therapy has been combined with other treatments like phototherapy, sonodynamic therapy, immune therapy, etc. to completely destroy cancer and compensate for the poor efficiency of single receptor targeting.^{139,140} Therefore, investigating the target receptors provides huge potential in further researches and oncological clinical applications including the field of early detection, prognosis prediction, clinical outcome evaluation, and personalized diagnosis and therapies,¹⁴¹ while great challenges need to be solved with well-designed therapeutic strategy and further proper randomized clinical trials for personalized OSCC therapy.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Chow LQM. Head and Neck Cancer. *N Engl J Med*. 2020;382(1):60–72. doi:10.1056/NEJMra1715715
3. Allen CT, Law JH, Dunn GP, Uppaluri R. Emerging insights into head and neck cancer metastasis. *Head Neck*. 2013;35(11):1669–1678. doi:10.1002/hed.23202
4. Colevas AD, Yom SS, Pfister DG, et al. NCCN Guidelines Insights: head and Neck Cancers, Version 1.2018. *J Natl Compr Canc Netw*. 2018;16(5):479–490. doi:10.6004/jnccn.2018.0026
5. Chai AWY, Lim KP, Cheong SC. Translational genomics and recent advances in oral squamous cell carcinoma. *Semin Cancer Biol*. 2020;61:71–83. doi:10.1016/j.semcancer.2019.09.011
6. Hinni ML, Ferlito A, Brandwein-Gensler MS, et al. Surgical margins in head and neck cancer: a contemporary review. *Head Neck*. 2013;35(9):1362–1370. doi:10.1002/hed.23110
7. Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. Local Cancer Recurrence: the Realities, Challenges, and Opportunities for New Therapies. *CA Cancer J Clin*. 2018;68(6):488–505. doi:10.3322/caac.21498
8. Chabner BA, Roberts TG Jr. Timeline: chemotherapy and the war on cancer. *Nat Rev Cancer*. 2005;5(1):65–72. doi:10.1038/nrc1529
9. DeVita VT Jr, Chu E. A history of cancer chemotherapy. *Cancer Res*. 2008;68(21):8643–8653. doi:10.1158/0008-5472.CAN-07-6611
10. Cheung-Ong K, Giaever G, Nislow C. DNA-damaging agents in cancer chemotherapy: serendipity and chemical biology. *Chem Biol*. 2013;20(5):648–659. doi:10.1016/j.chembiol.2013.04.007
11. Liu X, Liu S, Lyu H, Riker AI, Zhang Y, Liu B. Development of Effective Therapeutics Targeting HER3 for Cancer Treatment. *Biol Proced Online*. 2019;21:5. doi:10.1186/s12575-019-0093-1
12. Scott SD. Rituximab: a new therapeutic monoclonal antibody for non-Hodgkin's lymphoma. *Cancer Pract*. 1998;6(3):195–197. doi:10.1046/j.1523-5394.1998.006003195.x
13. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335–2342. doi:10.1056/NEJMoa032691
14. Keefe DM, Bateman EH. Tumor control versus adverse events with targeted anticancer therapies. *Nat Rev Clin Oncol*. 2011;9(2):98–109. doi:10.1038/nrclinonc.2011.192
15. Chari RV, Miller ML, Widdison WC. Antibody-drug conjugates: an emerging concept in cancer therapy. *Angew Chem Int Ed Engl*. 2014;53(15):3796–3827. doi:10.1002/anie.201307628
16. Panowski S, Bhakta S, Raab H, Polakis P, Junutula JR. Site-specific antibody drug conjugates for cancer therapy. *MAbs*. 2014;6(1):34–45. doi:10.4161/mabs.27022
17. Boyraz B, Sendur MA, Aksoy S, et al. Trastuzumab emtansine (T-DM1) for HER2-positive breast cancer. *Curr Med Res Opin*. 2013;29(4):405–414. doi:10.1185/03007995.2013.775113
18. Gonzalez de Castro D, Clarke PA, Al-Lazikani B, Workman P. Personalized cancer medicine: molecular diagnostics, predictive biomarkers, and drug resistance. *Clin Pharmacol Ther*. 2013;93(3):252–259. doi:10.1038/clpt.2012.237
19. Meric-Bernstam F, Mills GB. Overcoming implementation challenges of personalized cancer therapy. *Nat Rev Clin Oncol*. 2012;9(9):542–548. doi:10.1038/nrclinonc.2012.127
20. Brugger W, Triller N, Blasinska-Morawiec M, et al. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. *J Clin Oncol*. 2011;29(31):4113–4120. doi:10.1200/JCO.2010.31.8162
21. Kalia M. Biomarkers for personalized oncology: recent advances and future challenges. *Metabolism*. 2015;64(3 Suppl 1):S16–21. doi:10.1016/j.metabol.2014.10.027
22. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. *J Clin Oncol*. 2013;31(8):1039–1049. doi:10.1200/JCO.2012.45.3753
23. Hiss D. Optimizing molecular-targeted therapies in ovarian cancer: the renewed surge of interest in ovarian cancer biomarkers and cell signaling pathways. *J Oncol*. 2012;2012:737981. doi:10.1155/2012/737981
24. Lippman SM, Sudbø J, Hong WK. Oral cancer prevention and the evolution of molecular-targeted drug development. *J Clin Oncol*. 2005;23(2):346–356. doi:10.1200/JCO.2005.09.128
25. Rajaram P, Chandra P, Ticku S, Pallavi BK, Rudresh KB, Mansabdar P. Epidermal growth factor receptor: role in human cancer. *Indian J Dent Res*. 2017;28(6):687–694. doi:10.4103/ijdr.IJDR_534_16
26. Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. *Cancer Res*. 1993;53(15):3579–3584.
27. Shin DM, Ro JY, Hong WK, Hittelman WN. Dysregulation of epidermal growth factor receptor expression in premalignant lesions during head and neck tumorigenesis. *Cancer Res*. 1994;54(12):3153–3159.

28. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a Phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* **2010**;11(1):21–28. doi:10.1016/S1470-2045(09)70311-0
29. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* **2006**;354(6):567–578. doi:10.1056/NEJMoa053422
30. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* **2008**;359(11):1116–1127. doi:10.1056/NEJMoa0802656
31. Lei Q, Wang D, Sun K, Wang L, Zhang Y. Resistance Mechanisms of Anti-PD1/PDL1 Therapy in Solid Tumors. *Front Cell Dev Biol.* **2020**;8:672. doi:10.3389/fcell.2020.00672
32. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity.* **2013**;39(1):1–10. doi:10.1016/j.immuni.2013.07.012
33. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science.* **2011**;331(6024):1565–1570. doi:10.1126/science.1203486
34. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: results From a Single-Arm, Phase II Study. *J Clin Oncol.* **2017**;35(14):1542–1549. doi:10.1200/JCO.2016.70.1524
35. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med.* **2016**;375(19):1856–1867. doi:10.1056/NEJMoa1602252
36. Burtneß B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet.* **2019**;394(10212):1915–1928. doi:10.1016/S0140-6736(19)32591-7
37. Allen TM. Ligand-targeted therapeutics in anticancer therapy. *Nat Rev Cancer.* **2002**;2(10):750–763. doi:10.1038/nrc903
38. Boonstra MC, Verspaget HW, Ganesh S, et al. Clinical applications of the urokinase receptor (uPAR) for cancer patients. *Curr Pharm Des.* **2011**;17(19):1890–1910. doi:10.2174/138161211796718233
39. Noh H, Hong S, Huang S. Role of urokinase receptor in tumor progression and development. *Theranostics.* **2013**;3(7):487–495. doi:10.7150/thno.4218
40. Pavón MA, Arroyo-Solera I, Céspedes MV, Casanova I, León X, Mangués R. uPA/uPAR and SERPINE1 in head and neck cancer: role in tumor resistance, metastasis, prognosis and therapy. *Oncotarget.* **2016**;7(35):57351–57366. doi:10.18632/oncotarget.10344
41. Blasi F, Sidenius N. The urokinase receptor: focused cell surface proteolysis, cell adhesion and signaling. *FEBS Lett.* **2010**;584(9):1923–1930. doi:10.1016/j.febslet.2009.12.039
42. Danø K, Behrendt N, Hoyer-Hansen G, et al. Plasminogen activation and cancer. *Thromb Haemost.* **2005**;93(4):676–681. doi:10.1160/TH05-01-0054
43. Dohn LH, Pappot H, Iversen BR, et al. uPAR Expression Pattern in Patients with Urothelial Carcinoma of the Bladder—Possible Clinical Implications. *PLoS One.* **2015**;10(8):e0135824. doi:10.1371/journal.pone.0135824
44. Grøndahl-Hansen J, Peters HA, van Putten WL, et al. Prognostic significance of the receptor for urokinase plasminogen activator in breast cancer. *Clin Cancer Res.* **1995**;1(10):1079–1087.
45. Skovgaard D, Persson M, Brandt-Larsen M, et al. Safety, Dosimetry, and Tumor Detection Ability of (68) Ga-NOTA-AE105: First-in-Human Study of a Novel Radioligand for uPAR PET Imaging. *J Nucl Med.* **2017**;58(3):379–386. doi:10.2967/jnumed.116.178970
46. Baart VM, van Duijn C, van Egmond SL, et al. EGFR and $\alpha v \beta 6$ as Promising Targets for Molecular Imaging of Cutaneous and Mucosal Squamous Cell Carcinoma of the Head and Neck Region. *Cancers.* **2020**;12:6. doi:10.3390/cancers12061474
47. Christensen A, Kiss K, Lelkaitis G, et al. Urokinase-type plasminogen activator receptor (uPAR), tissue factor (TF) and epidermal growth factor receptor (EGFR): tumor expression patterns and prognostic value in oral cancer. *BMC Cancer.* **2017**;17(1):572. doi:10.1186/s12885-017-3563-3
48. Baart VM, van Manen L, Bhairasingh SS, et al. Side-by-Side Comparison of uPAR-Targeting Optical Imaging Antibodies and Antibody Fragments for Fluorescence-Guided Surgery of Solid Tumors. *Mol Imaging Biol.* **2021**. doi:10.1007/s11307-021-01657-2
49. Boonstra MC, Van Driel P, Keereweer S, et al. Preclinical uPAR-targeted multimodal imaging of locoregional oral cancer. *Oral Oncol.* **2017**;66:1–8. doi:10.1016/j.oraloncology.2016.12.026
50. Christensen A, Juhl K, Persson M, et al. uPAR-targeted optical near-infrared (NIR) fluorescence imaging and PET for image-guided surgery in head and neck cancer: proof-of-concept in orthotopic xenograft model. *Oncotarget.* **2017**;8(9):15407–15419. doi:10.18632/oncotarget.14282
51. Zuo J, Huo M, Wang L, Li J, Chen Y, Xiong P. Photonic hyperthermal and sonodynamic nanotherapy targeting oral squamous cell carcinoma. *J Mater Chem B.* **2020**;8(39):9084–9093. doi:10.1039/D0TB01089H
52. Horton ER, Humphries JD, James J, Jones MC, Askari JA, Humphries MJ. The integrin adhesome network at a glance. *J Cell Sci.* **2016**;129(22):4159–4163. doi:10.1242/jcs.192054
53. Campbell ID, Humphries MJ. Integrin structure, activation, and interactions. *Cold Spring Harb Perspect Biol.* **2011**;3:3. doi:10.1101/cshperspect.a004994
54. Koivisto L, Bi J, Häkkinen L, Larjava H. Integrin $\alpha v \beta 6$: structure, function and role in health and disease. *Int J Biochem Cell Biol.* **2018**;99:186–196. doi:10.1016/j.biocel.2018.04.013
55. Niu J, Li Z. The roles of integrin $\alpha v \beta 6$ in cancer. *Cancer Lett.* **2017**;403:128–137. doi:10.1016/j.canlet.2017.06.012
56. Li HX, Zheng JH, Fan HX, Li HP, Gao ZX, Chen D. Expression of $\alpha v \beta 6$ integrin and collagen fibre in oral squamous cell carcinoma: association with clinical outcomes and prognostic implications. *J Oral Pathol Med.* **2013**;42(7):547–556. doi:10.1111/jop.12044
57. Austin LA, Kang B, Yen CW, El-Sayed MA. Plasmonic imaging of human oral cancer cell communities during programmed cell death by nuclear-targeting silver nanoparticles. *J Am Chem Soc.* **2011**;133(44):17594–17597. doi:10.1021/ja207807t
58. Legge CJ, Colley HE, Lawson MA, Rawlings AE. Targeted magnetic nanoparticle hyperthermia for the treatment of oral cancer. *J Oral Pathol Med.* **2019**;48(9):803–809. doi:10.1111/jop.12921
59. Assaraf YG, Leamon CP, Reddy JA. The folate receptor as a rational therapeutic target for personalized cancer treatment. *Drug Resist Updat.* **2014**;17(4–6):89–95. doi:10.1016/j.drug.2014.10.002
60. Chen C, Ke J, Zhou XE, et al. Structural basis for molecular recognition of folic acid by folate receptors. *Nature.* **2013**;500(7463):486–489. doi:10.1038/nature12327

61. Ledermann JA, Canevari S, Thigpen T. Targeting the folate receptor: diagnostic and therapeutic approaches to personalize cancer treatments. *Ann Oncol*. 2015;26(10):2034–2043. doi:10.1093/annonc/mdv250
62. Fan L, Wang J, Xia C, et al. Glutathione-sensitive and folate-targeted nanoparticles loaded with paclitaxel to enhance oral squamous cell carcinoma therapy. *J Mater Chem B*. 2020;8(15):3113–3122. doi:10.1039/C9TB02818H
63. Xu L, Kittrell S, Yeudall WA, Yang H. Folic acid-decorated polyamidoamine dendrimer mediates selective uptake and high expression of genes in head and neck cancer cells. *Nanomedicine*. 2016;11(22):2959–2973. doi:10.2217/nmm-2016-0244
64. Chen CW, Lee PH, Chan YC, et al. Plasmon-induced hyperthermia: hybrid upconversion NaYF(4): yb/Er and gold nanomaterials for oral cancer photothermal therapy. *J Mater Chem B*. 2015;3(42):8293–8302. doi:10.1039/C5TB01393C
65. Hattori Y, Maitani Y. Enhanced in vitro DNA transfection efficiency by novel folate-linked nanoparticles in human prostate cancer and oral cancer. *J Control Release*. 2004;97(1):173–183. doi:10.1016/j.jconrel.2004.03.007
66. Zhu CN, Chen G, Tian ZQ, et al. Near-Infrared Fluorescent Ag(2) Se-Cetuximab Nanoprobes for Targeted Imaging and Therapy of Cancer. *Small*. 2017;13(3). doi:10.1002/sml.201602309.
67. Yang K, Zhang FJ, Tang H, et al. In-vivo imaging of oral squamous cell carcinoma by EGFR monoclonal antibody conjugated near-infrared quantum dots in mice. *Int J Nanomedicine*. 2011;6:1739–1745. doi:10.2147/IJN.S23348
68. Melancon MP, Lu W, Zhong M, et al. Targeted multifunctional gold-based nanoshells for magnetic resonance-guided laser ablation of head and neck cancer. *Biomaterials*. 2011;32(30):7600–7608. doi:10.1016/j.biomaterials.2011.06.039
69. de Boer E, Warram JM, Tucker MD, et al. In Vivo Fluorescence Immunohistochemistry: localization of Fluorescently Labeled Cetuximab in Squamous Cell Carcinomas. *Sci Rep*. 2015;5:10169. doi:10.1038/srep10169
70. Wang CS, Chang CH, Tzeng TY, Lin AM, Lo YL. Gene-editing by CRISPR-Cas9 in combination with anthracycline therapy via tumor microenvironment-switchable, EGFR-targeted, and nucleus-directed nanoparticles for head and neck cancer suppression. *Nanoscale Horiz*. 2021;6(9):729–743. doi:10.1039/D1NH00254F
71. Chen XJ, Tan YQ, Zhang N, He MJ, Zhou G. Expression of programmed cell death-ligand 1 in oral squamous cell carcinoma and oral leukoplakia is associated with disease progress and CD8+ tumor-infiltrating lymphocytes. *Pathol Res Pract*. 2019;215(6):152418. doi:10.1016/j.prp.2019.04.010
72. Chen XJ, Zhang XQ, Tang MX, Liu Q, Zhou G. Anti-PD-L1-modified and ATRA-loaded nanoparticles for immuno-treatment of oral dysplasia and oral squamous cell carcinoma. *Nanomedicine*. 2020;15(10):951–968. doi:10.2217/nmm-2019-0397
73. Bouattour M, Raymond E, Qin S, et al. Recent developments of c-Met as a therapeutic target in hepatocellular carcinoma. *Hepatology*. 2018;67(3):1132–1149. doi:10.1002/hep.29496
74. Christensen JG, Burrows J, Salgia R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. *Cancer Lett*. 2005;225(1):1–26. doi:10.1016/j.canlet.2004.09.044
75. Sun Z, Liu Q, Ye D, Ye K, Yang Z, Li D. Role of c-Met in the progression of human oral squamous cell carcinoma and its potential as a therapeutic target. *Oncol Rep*. 2018;39(1):209–216. doi:10.3892/or.2017.6073
76. Seiwert TY, Jagadeeswaran R, Faoro L, et al. The MET receptor tyrosine kinase is a potential novel therapeutic target for head and neck squamous cell carcinoma. *Cancer Res*. 2009;69(7):3021–3031. doi:10.1158/0008-5472.CAN-08-2881
77. De Herdt MJ. HGF and c-MET as Potential Orchestrators of Invasive Growth in Head and Neck Squamous Cell Carcinoma. *Front Biosci*. 2008;13:2516–2526. doi:10.2741/2863
78. Wu J, Liu J, Lin B, Lv R, Yuan Y. Met-Targeted Dual-Modal TX. MRI/NIR II Imaging for Specific Recognition of Head and Neck Squamous Cell Carcinoma. *ACS Biomater Sci Eng*. 2021;7(4):1640–1650. doi:10.1021/acsbmaterials.0c01807
79. Lin B, Wu J, Wang Y, et al. Peptide functionalized upconversion/NIR II luminescent nanoparticles for targeted imaging and therapy of oral squamous cell carcinoma. *Biomater Sci*. 2021;9(3):1000–1007. doi:10.1039/D0BM01737J
80. Mansi R, Fleischmann A, Mäcke HR, Reubi JC. Targeting GRPR in urological cancers—from basic research to clinical application. *Nat Rev Urol*. 2013;10(4):235–244. doi:10.1038/nrurol.2013.42
81. Montemagno C, Raes F, Ahmadi M, et al. In Vivo Biodistribution and Efficacy Evaluation of NeoB, a Radiotracer Targeted to GRPR, in Mice Bearing Gastrointestinal Stromal Tumor. *Cancers*. 2021;13(5):1051. doi:10.3390/cancers13051051
82. Liu P, Tu Y, Tao J, et al. GRPR-targeted SPECT imaging using a novel bombesin-based peptide for colorectal cancer detection. *Biomater Sci*. 2020;8(23):6764–6772. doi:10.1039/D0BM01432J
83. Chao C, Ives K, Hellmich HL, Townsend CM Jr, Hellmich MR. Gastrin-releasing peptide receptor in breast cancer mediates cellular migration and interleukin-8 expression. *J Surg Res*. 2009;156(1):26–31. doi:10.1016/j.jss.2009.03.072
84. Lango MN, Dyer KF, Lui VW, et al. Gastrin-releasing peptide receptor-mediated autocrine growth in squamous cell carcinoma of the head and neck. *J Natl Cancer Inst*. 2002;94(5):375–383. doi:10.1093/jnci/94.5.375
85. Li R, Gao R, Wang Y, et al. Gastrin releasing peptide receptor targeted nano-graphene oxide for near-infrared fluorescence imaging of oral squamous cell carcinoma. *Sci Rep*. 2020;10(1):11434. doi:10.1038/s41598-020-68203-y
86. Suganya SA, Kochurani KJ, Nair MG, et al. TM1-IR680 peptide for assessment of surgical margin and lymph node metastasis in murine orthotopic model of oral cancer. *Sci Rep*. 2016;6:36726. doi:10.1038/srep36726
87. Astarita JL, Acton SE, Turley SJ. Podoplanin: emerging functions in development, the immune system, and cancer. *Front Immunol*. 2012;3:283. doi:10.3389/fimmu.2012.00283
88. Suzuki-Inoue K. Platelets and cancer-associated thrombosis: focusing on the platelet activation receptor CLEC-2 and podoplanin. *Blood*. 2019;134(22):1912–1918. doi:10.1182/blood.2019001388
89. Bieniasz-Krzywiec P, Martín-Pérez R, Ehling M, et al. Podoplanin-Expressing Macrophages Promote Lymphangiogenesis and Lymphoinvasion in Breast Cancer. *Cell Metab*. 2019;30(5):917–36.e10. doi:10.1016/j.cmet.2019.07.015
90. Mei Y, Zhang P, Zuo H, et al. Ebp1 activates podoplanin expression and contributes to oral tumorigenesis. *Oncogene*. 2014;33(29):3839–3850. doi:10.1038/onc.2013.354
91. Sun Q, Zhang J, Cao W, et al. Dysregulated miR-363 affects head and neck cancer invasion and metastasis by targeting podoplanin. *Int J Biochem Cell Biol*. 2013;45(3):513–520. doi:10.1016/j.biocel.2012.12.004
92. Liu Z, Shi J, Zhu B, Xu Q. Development of a multifunctional gold nanoplatform for combined chemo-photothermal therapy against oral cancer. *Nanomedicine*. 2020;15(7):661–676. doi:10.2217/nmm-2019-0415

93. Schmidt HR, Kruse AC. The Molecular Function of σ Receptors: past, Present, and Future. *Trends Pharmacol Sci.* **2019**;40(9):636–654. doi:10.1016/j.tips.2019.07.006
94. Crottès D, Guizouarn H, Martin P, Borgese F, Soriani O. The sigma-1 receptor: a regulator of cancer cell electrical plasticity? *Front Physiol.* **2013**;4:175. doi:10.3389/fphys.2013.00175
95. Huang YS, Lu HL, Zhang LJ, Wu Z. Sigma-2 receptor ligands and their perspectives in cancer diagnosis and therapy. *Med Res Rev.* **2014**;34(3):532–566. doi:10.1002/med.21297
96. Megalizzi V, Le Mercier M, Decaestecker C. Sigma receptors and their ligands in cancer biology: overview and new perspectives for cancer therapy. *Med Res Rev.* **2012**;32(2):410–427. doi:10.1002/med.20218
97. Lecaros RL, Huang L, Lee TC, Hsu YC, VEGF-A ND. siRNA Enhances Photodynamic Therapy for Head and Neck Cancer Treatment. *Mol Ther.* **2016**;24(1):106–116. doi:10.1038/mt.2015.169
98. Chen WH, Lecaros RL, Tseng YC, Huang L, Hsu YC. Nanoparticle delivery of HIF1 α siRNA combined with photodynamic therapy as a potential treatment strategy for head-and-neck cancer. *Cancer Lett.* **2015**;359(1):65–74. doi:10.1016/j.canlet.2014.12.052
99. Kawabata H. Transferrin and transferrin receptors update. *Free Radic Biol Med.* **2019**;133:46–54. doi:10.1016/j.freeradbiomed.2018.06.037
100. Shen Y, Li X, Dong D, Zhang B, Xue Y, Shang P. Transferrin receptor 1 in cancer: a new sight for cancer therapy. *Am J Cancer Res.* **2018**;8(6):916–931.
101. Damiani V, Falvo E, Fracasso G, et al. Therapeutic Efficacy of the Novel Stimuli-Sensitive Nano-Ferritins Containing Doxorubicin in a Head and Neck Cancer Model. *Int J Mol Sci.* **2017**;18(7):7. doi:10.3390/ijms18071555
102. Li L, Fang CJ, Ryan JC, et al. Binding and uptake of H-ferritin are mediated by human transferrin receptor-1. *Proc Natl Acad Sci U S A.* **2010**;107(8):3505–3510. doi:10.1073/pnas.0913192107
103. Plow EF, Haas TA, Zhang L, Loftus J, Smith JW. Ligand binding to integrins. *J Biol Chem.* **2000**;275(29):21785–21788. doi:10.1074/jbc.R000003200
104. Davis PJ, Mousa SA, Cody V, Tang HY, Lin HY. Small molecule hormone or hormone-like ligands of integrin $\alpha V\beta 3$: implications for cancer cell behavior. *Horm Cancer.* **2013**;4(6):335–342. doi:10.1007/s12672-013-0156-8
105. Mittra ES, Goris ML, Iagaru AH, et al. Pilot pharmacokinetic and dosimetric studies of (18) F-FPPRGD2: a PET radiopharmaceutical agent for imaging $\alpha(v)\beta(3)$ integrin levels. *Radiology.* **2011**;260(1):182–191. doi:10.1148/radiol.11101139
106. Terry SY, Abiraj K, Frielink C, et al. Imaging integrin $\alpha v\beta 3$ on blood vessels with 111In-RGD2 in head and neck tumor xenografts. *J Nucl Med.* **2014**;55(2):281–286. doi:10.2967/jnumed.113.129668
107. Beer AJ, Grosu AL, Carlsen J, et al. [18F]galacto-RGD positron emission tomography for imaging of $\alpha v\beta 3$ expression on the neovasculature in patients with squamous cell carcinoma of the head and neck. *Clin Cancer Res.* **2007**;13(22 Pt 1):6610–6616. doi:10.1158/1078-0432.CCR-07-0528
108. Lobeek D, Rijpkema M, Terry SYA, et al. Imaging angiogenesis in patients with head and neck squamous cell carcinomas by [(68)Ga] Ga-DOTA-E-[c(RGDfK)](2) PET/CT. *Eur J Nucl Med Mol Imaging.* **2020**;47(11):2647–2655. doi:10.1007/s00259-020-04766-2
109. Gong Z, Liu X, Zhou B, et al. Tumor acidic microenvironment-induced drug release of RGD peptide nanoparticles for cellular uptake and cancer therapy. *Colloids Surf B Biointerfaces.* **2021**;202:111673. doi:10.1016/j.colsurfb.2021.111673
110. Shi S, Zhang L, Zhu M, et al. Reactive Oxygen Species-Responsive Nanoparticles Based on PEGlated Prodrug for Targeted Treatment of Oral Tongue Squamous Cell Carcinoma by Combining Photodynamic Therapy and Chemotherapy. *ACS Appl Mater Interfaces.* **2018**;10(35):29260–29272. doi:10.1021/acsami.8b08269
111. Li Q, Wen Y, You X, et al. Development of a reactive oxygen species (ROS)-responsive nanoplatform for targeted oral cancer therapy. *J Mater Chem B.* **2016**;4(27):4675–4682. doi:10.1039/C6TB01016D
112. Brekken RA, Sage EH. SPARC, a matricellular protein: at the crossroads of cell-matrix communication. *Matrix Biol.* **2001**;19(8):816–827. doi:10.1016/S0945-053X(00)00133-5
113. Chlenski A, Cohn SL. Modulation of matrix remodeling by SPARC in neoplastic progression. *Semin Cell Dev Biol.* **2010**;21(1):55–65. doi:10.1016/j.semedb.2009.11.018
114. Wang Y, Xie D, Pan J, et al. A near infrared light-triggered human serum albumin drug delivery system with coordination bonding of indocyanine green and cisplatin for targeting photochemistry therapy against oral squamous cell cancer. *Biomater Sci.* **2019**;7(12):5270–5282. doi:10.1039/C9BM01192G
115. Jing Y, Jin Y, Wang Y, et al. SPARC promotes the proliferation and metastasis of oral squamous cell carcinoma by PI3K/AKT/PDGFB/PDGFR β axis. *J Cell Physiol.* **2019**;234(9):15581–15593. doi:10.1002/jcp.28205
116. Song C, Tang C, Xu W, et al. Hypoxia-Targeting Multifunctional Nanoparticles for Sensitized Chemotherapy and Phototherapy in Head and Neck Squamous Cell Carcinoma. *Int J Nanomedicine.* **2020**;15:347–361. doi:10.2147/IJN.S233294
117. Singh SR, Rameshwar P, Siegel P. Targeting tumor microenvironment in cancer therapy. *Cancer Lett.* **2016**;380(1):203–204. doi:10.1016/j.canlet.2016.04.009
118. Su Z, Liu D, Chen L, et al. CD44-Targeted Magnetic Nanoparticles Kill Head And Neck Squamous Cell Carcinoma Stem Cells In An Alternating Magnetic Field. *Int J Nanomedicine.* **2019**;14:7549–7560. doi:10.2147/IJN.S215087
119. Wang Y, Zhang W, Sun P, et al. A Novel Multimodal NIR-II Nanoprobe for the Detection of Metastatic Lymph Nodes and Targeting Chemo-Photothermal Therapy in Oral Squamous Cell Carcinoma. *Theranostics.* **2019**;9(2):391–404. doi:10.7150/thno.30268
120. Hwang-Bo J, Bae MG, Park JH, Chung IS. 3-O-Acetyloleonic acid inhibits VEGF-A-induced lymphangiogenesis and lymph node metastasis in an oral cancer sentinel lymph node animal model. *BMC Cancer.* **2018**;18(1):714. doi:10.1186/s12885-018-4630-0
121. Mizrahi A, Shamay Y, Shah J, et al. Tumour-specific PI3K inhibition via nanoparticle-targeted delivery in head and neck squamous cell carcinoma. *Nat Commun.* **2017**;8:14292. doi:10.1038/ncomms14292
122. Xiong J, Feng J, Qiu L, et al. SDF-1-loaded PLGA nanoparticles for the targeted photoacoustic imaging and photothermal therapy of metastatic lymph nodes in tongue squamous cell carcinoma. *Int J Pharm.* **2019**;554:93–104. doi:10.1016/j.ijpharm.2018.10.064
123. Qallandar OB, Ebrahimi F, Islam F, et al. Bone Invasive Properties of Oral Squamous Cell Carcinoma and its Interactions with Alveolar Bone Cells: an In Vitro Study. *Curr Cancer Drug Targets.* **2019**;19(8):631–640. doi:10.2174/1568009618666181102144317
124. Chen H, Deng J, Yao X, et al. Bone-targeted erythrocyte-cancer hybrid membrane-camouflaged nanoparticles for enhancing photothermal and hypoxia-activated chemotherapy of bone invasion by OSCC. *J Nanobiotechnology.* **2021**;19(1):342. doi:10.1186/s12951-021-01088-9

125. Hong FD, Clayman GL. Isolation of a peptide for targeted drug delivery into human head and neck solid tumors. *Cancer Res.* 2000;60(23):6551–6556.
126. Li R, Wang Y, Du J, et al. Graphene oxide loaded with tumor-targeted peptide and anti-cancer drugs for cancer target therapy. *Sci Rep.* 2021;11(1):1725. doi:10.1038/s41598-021-81218-3
127. Un F, Zhou B, Yen Y. The utility of tumor-specifically internalizing peptides for targeted siRNA delivery into human solid tumors. *Anticancer Res.* 2012;32(11):4685–4690.
128. Wang Y, Wan G, Li Z, et al. PEGylated doxorubicin nanoparticles mediated by HN-1 peptide for targeted treatment of oral squamous cell carcinoma. *Int J Pharm.* 2017;525(1):21–31. doi:10.1016/j.ijpharm.2017.04.027
129. Cai D, Liu L, Han C, et al. Cancer cell membrane-coated mesoporous silica loaded with superparamagnetic ferroferric oxide and Paclitaxel for the combination of Chemo/Magnetocaloric therapy on MDA-MB-231 cells. *Sci Rep.* 2019;9(1):14475. doi:10.1038/s41598-019-51029-8
130. Adkins D, Ley J, Atiq O, et al. Nanoparticle albumin-bound paclitaxel with cetuximab and carboplatin as first-line therapy for recurrent or metastatic head and neck cancer: a single-arm, multicenter, Phase 2 trial. *Oral Oncol.* 2021;115:105173. doi:10.1016/j.oraloncology.2020.105173
131. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol.* 2007;2(12):751–760. doi:10.1038/nnano.2007.387
132. Talelli M, Oliveira S, Rijcken CJ, et al. Intrinsically active nanobody-modified polymeric micelles for tumor-targeted combination therapy. *Biomaterials.* 2013;34(4):1255–1260. doi:10.1016/j.biomaterials.2012.09.064
133. Fang J, Nakamura H, The MH. EPR effect: unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. *Adv Drug Deliv Rev.* 2011;63(3):136–151. doi:10.1016/j.addr.2010.04.009
134. Tan DS, Gerlinger M, Teh BT, Swanton C. Anti-cancer drug resistance: understanding the mechanisms through the use of integrative genomics and functional RNA interference. *Eur J Cancer.* 2010;46(12):2166–2177. doi:10.1016/j.ejca.2010.03.019
135. Mamot C, Ritschard R, Wicki A, et al. Tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded anti-EGFR immunoliposomes in advanced solid tumours: a Phase 1 dose-escalation study. *Lancet Oncol.* 2012;13(12):1234–1241. doi:10.1016/S1470-2045(12)70476-X
136. Maeda H, Sawa T, Konno T. Mechanism of tumor-targeted delivery of macromolecular drugs, including the EPR effect in solid tumor and clinical overview of the prototype polymeric drug SMANCS. *J Control Release.* 2001;74(1–3):47–61. doi:10.1016/S0168-3659(01)00309-1
137. Lammers T, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. *J Control Release.* 2012;161(2):175–187. doi:10.1016/j.jconrel.2011.09.063
138. Ye JJ, Yu W, Xie BR, et al. Self-Reinforced Cancer Targeting (SRCT) Depending on Reciprocally Enhancing Feedback between Targeting and Therapy. *ACS Nano.* 2022;16(4):5851–5866. doi:10.1021/acsnano.1c10999
139. Zou MZ, Li ZH, Bai XF, Liu CJ, Zhang XZ. Hybrid Vesicles Based on Autologous Tumor Cell Membrane and Bacterial Outer Membrane To Enhance Innate Immune Response and Personalized Tumor Immunotherapy. *Nano Lett.* 2021;21(20):8609–8618. doi:10.1021/acs.nanolett.1c02482
140. Chen B, Liu X, Li Y, et al. iRGD Tumor-Penetrating Peptide-Modified Nano-Delivery System Based on a Marine Sulfated Polysaccharide for Enhanced Anti-Tumor Efficiency Against Breast Cancer. *Int J Nanomedicine.* 2022;17:617–633. doi:10.2147/IJN.S343902
141. Irimie AI, Sonea L, Jurj A, et al. Future trends and emerging issues for nanodelivery systems in oral and oropharyngeal cancer. *Int J Nanomedicine.* 2017;12:4593–4606. doi:10.2147/IJN.S133219