International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Current Application of Nanoparticle Drug Delivery Systems to the Treatment of Anaplastic Thyroid Carcinomas

Chonggao Wang[1,2], Yewei Zhang[3]

[1]Department of Thyroid Surgery, Nanjing Hospital of Chinese Medicine, Nanjing, 210001, People's Republic of China; [2]School of Medicine, Southeast University, Nanjing, 210001, People's Republic of China; [3]Hepatopancreatobiliary Center, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, 210009, People's Republic of China

Correspondence: Yewei Zhang, Email zhangyewei@njmu.edu.cn

Abstract: Anaplastic thyroid carcinomas (ATCs) are a rare subtype of thyroid cancers with a low incidence but extremely high invasiveness and fatality. The treatment of ATCs is very challenging, and currently, a comprehensive individualized therapeutic strategy involving surgery, radiotherapy (RT), chemotherapy, BRAF/MEK inhibitors (BRAFi/MEKi) and immunotherapy is preferred. For ATC patients in stage IVA/IVB, a surgery-based comprehensive strategy may provide survival benefits. Unfortunately, ATC patients in IVC stage barely get benefits from the current treatment. Recently, nanoparticle delivery of siRNAs, targeted drugs, cytotoxic drugs, photosensitizers and other agents is considered as a promising anti-cancer treatment. Nanoparticle drug delivery systems have been mainly explored in the treatment of differentiated thyroid cancer (DTC). With the rapid development of drug delivery techniques and nanomaterials, using hybrid nanoparticles as the drug carrier to deliver siRNAs, targeted drugs, immune drugs, chemotherapy drugs and phototherapy drugs to ATC patients have become a hot research field. This review aims to describe latest findings of nanoparticle drug delivery systems in the treatment of ATCs, thus providing references for the further analyses.

Keywords: anaplastic thyroid carcinomas, anti-cancer treatment, nanomaterials, nanoparticle, nanomedicine

Introduction

Anaplastic thyroid carcinomas (ATCs) are a type of rare malignancy with an annual incidence of 0.12/100,000 and 0.1–0.3/100,000 in the United States[1] and Europe,[2,3] respectively. It is characterized by rapid onset and poor prognosis. The median survival of ATC patients is less than 5 months, with the 2-year and 5-year survival of less than 15% and 7%, respectively.[4] Local infiltration of the trachea, esophagus, blood vessels, and muscles, and distant metastases of the lung, pleura, bone, and brain are detectable in most of ATC patients at the initial time of diagnosis, which are all surgical contraindications[5] (Figures 1 and 2). Notably, about 5–20% of DTC patients can experience dedifferentiation and aggravate into ATCs.[6]

Generally speaking, surgery-based comprehensive treatment provides survival benefits to ATC patients in stage IVA with the tumor lesions restricted within the thyroid. However, the application of surgery to ATC patients in stage IVB/IVC with extra thyroid metastases is controversial. Xu et al[7] reported that the scope of surgery and the integrity of tumor resection do not influence the survival of ATC. The majority of ATC patients can only be treated with local RT, systemic chemotherapy, targeted therapy and immunotherapy[8,9] (Figure 3).

External beam radiation therapy (EBRT) is still preferred to ATC patients in R0/R1 resection. A retrospective study illustrated that EBRT is highly heterogenic in dose management, division, technique and combination treatment.[10] The clinical benefit of EBRT on the prognosis relies on the combination with surgery and chemotherapy. Chemotherapy is a widely recognized treatment to prolong the survival.[11] The latest American Thyroid Association guidelines recommended the systemic treatment of ATC using genotoxic drugs like paclitaxel plus carboplatin, cisplatin plus doxorubicin, docetaxel plus doxorubicin, paclitaxel alone or doxorubicin alone.[12,13] Primary chemotherapy resistance is a common

Received: 12 July 2023
Accepted: 18 October 2023
Published: 25 October 2023

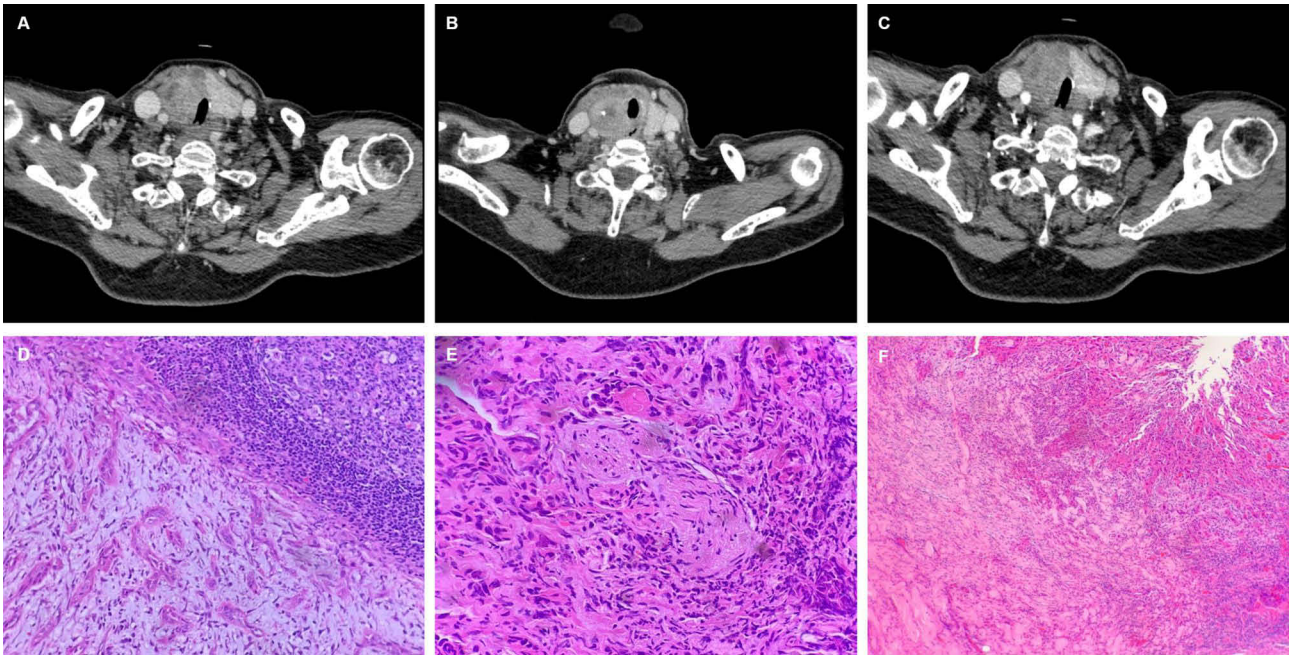

Figure 1 Representative pathological images of a case of ATC. (**A**) CT scan of the involvement of the trachea by ATC. (**B**) Intratumoral calcification and the involvement of the trachea by ATC. (**C**) CT scan of lymph node metastases in the carotid sheath. (**D**) Pathological image of cervical lymph node metastases (magnification=200×). (**E**) Pathological image of perineural invasion by ATC (magnification=400×). (**F**) Pathological image of skeletal muscle invasion by ATC (magnification=100×).

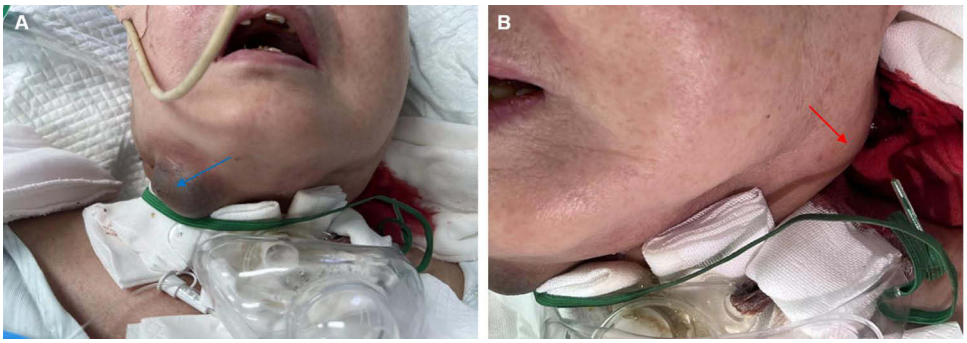

Figure 2 A 76-year-old female patient with ATC after 1-year of surgery. The patient was managed by palliative resection of ATC one year ago, and developed massive metastases in the cervical region. She was further managed by supportive treatment in our center and suffered rupture and hemorrhage of the cervical metastatic tumor. (**A**) A 5×4×4 cm metastatic tumor (blue arrow) in the right mandibular region invaded soft tissues and muscles in the cervical region. (**B**) A 3×3×2 cm metastatic tumor in the left cervical region, with rupture and hemorrhage (red arrow).

cause of treatment failure in ATC patients, leading to the mean progression-free survival (PFS) of less than 3 months. The poor prognosis of ATC may be attributed to the infiltration of tumor-associated macrophages (TAMs), which account for 50% of the tumor volume. Meanwhile, the paracrine signaling transmitted by the CSF1/CSF-1R axis also accelerates chemotherapy resistance and tumor progression.[14]

Targeted therapy is another option to ATC patients. Donafenib combined with trametinib is recommended to ATC patients carrying BRAF V600E mutations, although this specific population only accounts of 20–50% of the total ATC patients.[15] ATC patients barely benefit from PI3K/AKT/mTOR inhibitors like everolimus.[16] Lenvatinib is an anti-angiogenesis, multi-kinase inhibitor that has been approved for the treatment of DTC. It exerts an acceptable anti-cancer effect within 3 months, although later develops an obvious drug resistance. Notably, lenvatinib may cause hemorrhage, esophageal fistula and tracheal fistula.[17]

Immune checkpoint inhibitors (ICIs) like anti-PD-1, anti-PD-L1 and anti-CTLA-4 have been widely used in the treatment of solid tumors. At present, application of the anti-PD-1 antibody spartalizumab to ATC patients has been tested in clinical

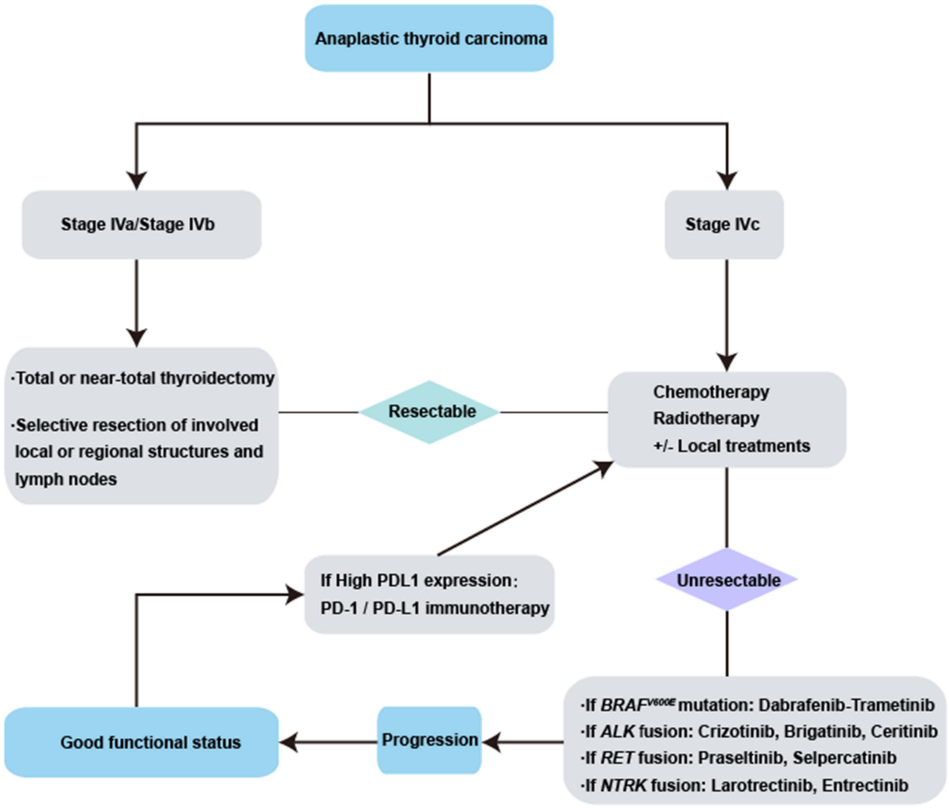

Figure 3 Flow diagram of clinical management of ATC.

trials, although the highest response rate is only observed in those with 50% of expression rate of PD-L1 or above.[10] The above-mentioned therapeutic strategies for ATC have their own limitations, and an effective treatment is urgently needed to improve the prognosis.

With the continuous development of nanomedicine, the role of nanomaterials becomes increasingly important in the prevention, diagnosis and treatment of tumors.[18] Because of the excellent properties of nanoparticles, including the scale effect, surface effect, quantum effect and properties of light, sound, electricity, heat, and magnetism, they are promising materials used in the imaging and treatment of tumors.[19] Since the size of nanomaterials is much smaller than that of tumor cells, they are capable of delivering drugs to target tumor cells.[20] Nanoparticles are stable in the physiological environment, which produce passive targeting of tumor cells via the enhanced permeability and retention (EPR) effect. Moreover, their surface is modifiable and functional to connect target molecules and functional groups, thus favoring the biocompatibility and targeting ability to tumor cells.[21–23] A series of clinical trials have been performed to analyze the treatment of solid tumors using nanoparticles, including colorectal cancer, non-small cell lung cancer (NSCLC), gastric cancer, breast cancer, and esophageal adenocarcinoma, which have achieved promising outcomes.[24] According to the chemical compositions, nanoparticles used in anti-cancer treatment can be classified into organic, inorganic and hybrid.[25] They are able to deliver diverse drugs like chemotherapeutic drugs, genes/siRNAs, photosensitizers, radioactive elements, optical materials and natural medicines to achieve the diagnosis and treatment.[26,27] The present review described the use of nanoparticles in the treatment of ATC via cancer cell targeting, enhancement of ^{131}I sensitivity, chemotherapy and phototherapy, thus providing references for opening up new avenues to the treatment of ATC (Figure 4 and Table 1).

Nanocarriers

Use of inorganic and organic nanoparticles in the treatment of ATC has been previously analyzed. Metallic and mesoporous hybrid silica are generally used in the delivery of conventional drugs and proteins, as well as photothermal therapy (PTT). Lipid nanoparticles and polymeric nanoparticles are used for the delivery of conventional drugs,

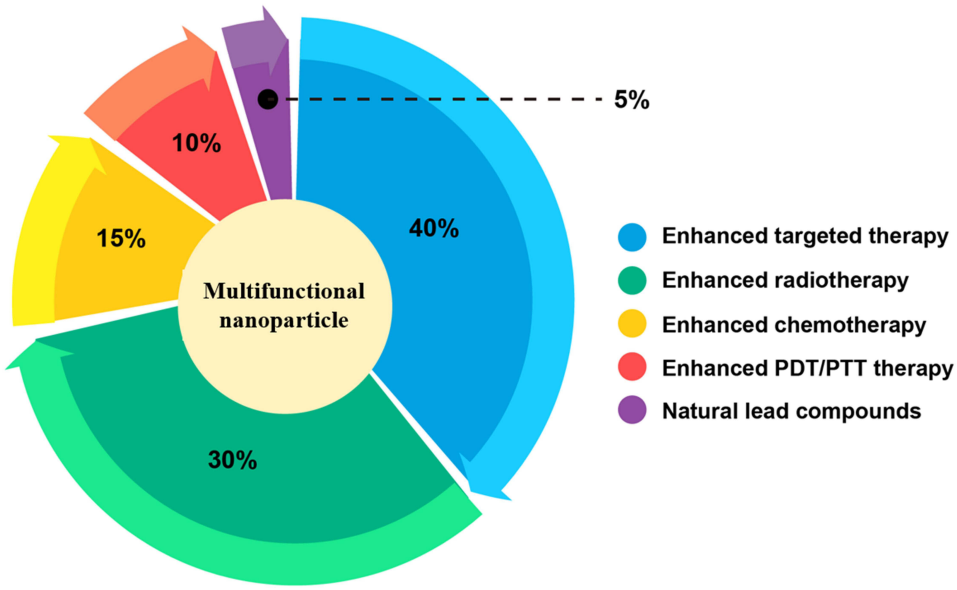

Figure 4 Composition of nanocomposites used in the treatment of ATC.

redifferentiation compounds, and siRNAs. Inorganic and organic nanoparticles have their own merits and demerits. The former can combine with other therapeutic strategies like photodynamic therapy, hyperthermia and EBRT, but they can be accumulated in human bodies. The latter can be rapidly degraded and provide multiple types of carriers, although they can barely combine with other anti-cancer treatment.

Organic Nanoparticles

Lipid Nanoparticles

Lipid nanoparticles (LNPs) are one of the frequently used and well-established bioactive nanocarriers for anti-cancer treatment, which are featured as excellent abilities to encapsulate drugs, and prolong the half-life and release time of drugs. The therapeutic efficacy enhances with the prolongation of drugs targeting tumor cells.[28] It is reported that the cytotoxicity of gemcitabine-loaded LNPs in ARO cells is significantly higher than that of free drugs. Moreover, the ammonium sulfate in the inner compartment of liposomes induces the protonation of gemcitabine and reduces the reverse diffusion of drugs in liposomes, resulting in a 90% of encapsulation effect.[29] Compared with those of free drugs, drugs loaded in LNPs present less photodegradation and stronger anti-proliferative ability against three thyroid cancer cell lines PTC1, B-CPAP and FRO.[30] LNPs are biocompatible and they can be functionalized with a variety of molecules and mRNAs. For example, a 4-fold higher accumulation of the thyroid-stimulating hormone (TSH)-conjugated polymer-lipid hybrid nanoparticles is detected in FTC 133 xenografts than that of the non-targeted nanoparticles, and the former presents a stronger anti-cancer role against thyroid cancer.[31] Li et al[32] developed liposome-peptide-mRNA nanoparticles (LPm NP) that are composed of mRNAs, peptide core and cationic lipid core-shell nanostructures. The optimal transfection rate and delivery effect can be obtained by adjusting the nitrogen/phosphorus (N/P) ratio in the core complex and mRNA adsorption, thus increasing the proportion of cells with positively expressed sodium iodide symporter (NIS) in the ATC cell line 8505C.[32] Liposomal delivery of miR-34b-5p significantly inhibits the proliferation, migration and angiogenesis in ATC cell lines 8505C and BHT-101, which also significantly suppresses the growth of BHT-101 xenografts in nude mice.[33]

PLGA

PLGA, or poly(lactic-co-glycolic acid), is a copolymer with a biodegradable shell that has been widely used in preparing polymeric nanoparticles due to the properties of surface modification, prolonged circulation, self-assembly and tumor targeting by combing with aptamers or antibodies. Wang et al[34] developed IR825-loaded PLGA nanoparticles (IR825@Bev-PLGA-PFP

Table 1 Overview of Nanoparticle Drug Delivery Systems for the Treatment of ATC

Nanoparticles	Particle Diameter (nm)	Zeta Potential (mV)	Biological Function	References
Nanocomposites for targeted drug delivery				
^{131}I-labeled anti-VEGFR2 targeted MSNPs	163±4.6	- 23.91	(A) Inhibiting tumor growth in ATC tumor-bearing nude mice; (B) Prolonging survival without apparent systemic toxic effects.	[28]
IR825 @Bev-PLGA-PFP nanoparticles	309±4	−11.5±0.2	(A) Sequential targeting; (B) Combined with synergistic antiangiogenic PTT; (C) Multimodal imaging-guided diagnosis for ATC.	[29]
(17-AAG+Torin2)@MSNs-antiVEGFR2	167	−5.04	(A) Inhibiting the growth of FRO cells; (B) Prolonging the median survival of FRO-bearing mice.	[30]
Prima-1@PEI-HA-Tyrs -^{131}I nanoparticles	91.01±0.51	−14.35±1.57	(A) Enhancing the sensitivity of ATC cells carrying p53 mutations to radiotherapy and inducing apoptosis; (B) Slowing down the growth of ATC.	[31]
AP-1-M-doxorubicin conjugates	-	-	(A) Inhibiting cell proliferation and induction of apoptosis; (B) Inhibiting tumor growth in FRO cell xenograft mice.	[32]
Anti-*hTERT* siRNA-loaded nanoparticles	130		(A) Inhibiting the viability and migration of CAL-62 and 8505C cells; (B) Inhibiting the growth of neoplasm with a minimal invasion of nearby tissues; (C) Inhibiting the vascularity of the xenograft tumor without signs of toxicity.	[33]
^{131}I-chitosan-pE9-hTERTp-yCDglyTK	80–120		(A) Upregulating suicide genes; (B) Cytotoxic effects on host cells.	[34]
Near-infrared nanoplatform for systemic delivery of siRNA	50	−6.4	(A) Long blood circulation; (B) High tumor accumulation; (C) Property of tumor imaging.	[29]
PAMAM-PEG-cRGD	Ranging from 91.7±7.1 nm to 133.7 ±6.0 nm with N/P ratio increases from 0.5 to 3.0	Ranging from 4.1±1.2 mV to 38.2 ±7.2 mV with N/P ratio increases from 0.5 to 3.0	(A) Inhibiting tumor activity; (B) Inducing apoptosis in ATC cells.	[35]
Pep-1-PEG3.5k-PCL4k@Res	-	-	(A) Delaying tumor growth; (B) Inducing extensive apoptosis (C) Causing obvious side effects and secondary drug resistance.	[36]

(*Continued*)

https://doi.org/10.2147/IJN.S429629

Table 1 (Continued).

Nanoparticles	Particle Diameter (nm)	Zeta Potential (mV)	Biological Function	References
Nanoparticles for improving the efficacy of ^{131}I radioiodine therapy				
Restoring the expression level of NIS				
Lipid-peptide-mRNA nanoparticles	100	-	(A) Increasing 1311 accumulation and NIS expression in subcutaneous ATC tumor tissues and ATC cells; (B) Inhibiting tumor growth.	[37]
In the combination treatment of ^{131}I radioiodine therapy and PTT				
^{131}I-HSA-ICG nanoparticles	25–45	−16	(A) Dual-modality imaging and treatment of ATC; (B) Ablation effect on tumor cells.	[38]
PEG-[^{64}Cu]CuS nanoparticles	11	-	(A) Pro-apoptotic effect; (B) Delaying tumor growth without causing acute toxicity.	[39]
Nanomaterials for improving the outcome of chemotherapy				
TSH-SiO_2@Dox nanoparticles	35		(A) Increasing the apoptotic rate in FTC-133 and TPC1 thyroid cells.	[40]
BSA-Dox-MONPs	224.3±21.2	−21.70±0.81	(A) Increasing drug uptake; (B) Inhibiting drug efflux.	[41]
Surfactant-coated doxorubicin-loaded PLGA nanoparticles	468±19	−11.2	(A) Enable delivery of doxorubicin across the blood–brain barrier.	[42]
CN-CPT	350	−27.4	(A) Inhibiting viability, clonogenic capacity and cell-cycle progression of ATC cells; (B) Inhibiting the growth, the metastatization and the vascularization of orthotopic ATC xenografts in SCID/beige mice without apparent toxic effects.	[43]
Au@MSNs	110	-	(A) Inhibiting the proliferation, migration and cell cycle progression, and induce apoptosis in FTC-133 and B-CPAP cells.	[44]

Abbreviations: MSNPs, mesoporous silica nanoparticles; Bev, bevacizumab; PLGA, poly(lactic-co-glycolic acid); PFP, perfluoropentane; ATC, anaplastic thyroid carcinoma; PTT, photothermal therapy; PEI, polyethyleneimine; HA, hyaluronic acid; PAMAM, polyamidoamine; PEG, polyethylene glycol; Res, resveratrol; HSA, human serum albumin; ICG, indocyanine green; Dox, doxorubicin; BSA, bovine serum albumin; MONPs, mesoporous organosilica nanoparticles; CN-CPT, camptothecin encapsulated in β-cyclodextrin-nanosponges.

NPs) for the synergistic antiangiogenic PTT under the guidance of the near-infrared (NIR) laser irradiation and multimodal imaging-guided diagnosis for ATC theranostics. Giovanni et al[35] induce the silence of hTERT using chitosan-coated PLGA nanoparticles encapsulating the anti-hTERT oligonucleotide. Their application does not influence the stability of genetic material and presents a good cell uptake rate. The poly[2,6-(4,4-bis-(2-ethylhexyl)-4H-cyclopenta[2,1-b;3,4-b′]dithiophene)-alt-4,7(2,1,3-benzothiadiazole)] (polyPCPDTBT) is used in creating polymeric nanoparticles for NIR imaging and BRAF siRNA delivery, the injection of which significantly silence BRAF and inhibit the proliferation of $BRAF^{V600E}$-mutated 8505C cells.[36]

Albumin

Bovine serum albumin (BSA) has been used as a mild biological template in nanoparticles. Serum albumin is widely used in drug delivery systems through coupling interactions due to its low cytotoxicity, low immunogenicity and good biocompatibility. Moreover, BSA enhances the concealment of nanoparticles in blood circulation, tumor-specific accumulation and the stability of loaded drugs. BSA-coated nanoparticles maintain a good dispersion in serum, which achieve the accumulation in tumor sites via the EPR effect.[37] BSA and hyaluronic acid (HA) loading remarkably enhances the targeting of drugs and their therapeutic efficacy. Sorafenib,[38] anti-VEGFR2 antibody,[39] indocyanine green,[40] and copper sulfide[41] loaded in mesoporous silica nanoparticles (MSNPs) coated with BSA present excellent outcomes in the treatment of targeted therapy, phototherapy and EBRT.

PDA

Polydopamine (PDA) and its coated nanoparticles have been widely used as near-infrared light absorbers at the wavelength of 700–1100 nm for PTT due to the benzoquinone structure.[42–44] NIR-induced PTT is a minimally invasive treatment that converts light energy into heat at 50–56°C to ablate tumors. Thermal ablation is a popular treatment of micropapillary thyroid carcinoma (mPTC). Microwave, laser or radiofrequency ablation causes coagulative necrosis of tumor cells, although the surrounding tissues may be potentially damaged.[45] PDA nanoparticles are capable of visualizing tumors by infrared thermography, which completely ablate tumor lesions without significant systemic toxicity.[46] Moreover, PDA nanoparticles containing phenolic hydroxyl groups are favorable to the conjugation of ^{131}I for RT.[47] Notably, mesoporous polydopamine nanoparticles with a cerebroid pore channel structure (CPDA) are excellent for the highest iodine-carrying capacity and higher photothermal conversion efficiency for acquiring high-quality tumor images owing to the maximum specific surface area and unique morphology, which can be synergistically applied with PTT and RT.[48]

Inorganic Nanoparticles

MSNPs and MONPs

MSNPs and metal oxide nanoparticles (MONPs) have been well concerned for drug loading and delivery because of the high loading capacity, excellent biocompatibility, large surface area, adjustable pore volume, and surface modification. A comparative study found that doxorubicin-loaded MSNPs are superior to melanin nanoparticles synthesized using dopamine hydrochloride. Although the latter provide 20% of doxorubicin loading capacity, mesoporous organosilica particles are composed of up to 47.02%.[49] Han et al[50] constructed BSA-coated MONPs as the carrier of doxorubicin, showing high loading efficiency and capacity and stronger anti-cancer effect on enhancing drug intake and reducing drug efflux in drug-resistant HTh74 cells. Wang et al[51] constructed MSNPs co-loading with 17-AAG and Torin2, and they found that the specificity and affinity of (17-AAG+Torin2)@MSNs-anti-VEGFR2 ab are significantly higher than those of (17-AAG+Torin2)@MSNs in FRO cells. It is confirmed that targeting VEGFR2 inhibits the growth of ATC cells.

Metal Ions

Nanoparticles containing metal elements are usually used for photodynamic therapy (PDT) and PTT. Using the single radioactive copper sulfide (CuS) nanoparticle platform, the radiotherapeutic property of ^{64}Cu combined with the plasmonic properties of CuS nanoparticles synergistically enhances the therapeutic outcome of RT combined with PTT in the orthotopic mouse model of ATC. Besides, the combination of RT and PTT significantly prolongs the survival of mice bearing Hth83 xenografts compared to those without any treatment or treated with laser treatment, or nanoparticle treatment alone, which does not produce acute toxic effects.[52] ^{131}I-labeled, BSA-modified CuS nanoparticles (131I-BSA@CuS) have the properties of both RT and PTT, showing the optimal anti-cancer effect in vitro. Moreover, MTT assay validated that BSA@CuS has negligible toxicity to ARO cells.[41] Cetuximab is a monoclonal antibody used to target

EGFR-expressing tumors like ATC. Cetuximab-conjugated perfluorohexane/gold nanoparticles enhance the efficacy of chemotherapeutic drugs by triggering their release through low-intensity focused ultrasound.[53] The paclitaxel prodrug CYT-21625 delivered together with TNF-α loaded in PEGylated gold nanoparticles reduces tumor burden in mice bearing metastatic FTC-133 and 8505C xenografts.[54] HA and oleic acid-coated gold nanoparticles functionalized with ATC-specific ligands like holo-transferrin and lapatinib present dual functional effect on human 8505C cells via PTT and targeting EGFR. Meanwhile, the anti-cancer effect of lapatinib targeting EGFR is not as effective as that of whole transferrin coating.[55]

Halloysite Nanotubes

Halloysite nanotubes (HNTs) are biocompatible aluminosilicate clay with a hollow tubular structure composed of silica on the outer surface and alumina on the innermost surface.[56] HNTs and functionalized-HNTs (f-HNTs) are capable of trapping active agents in lumens and external surfaces, followed by their retention and slow release. Due to their attractive properties, HNTs have been used as popular nanoparticles in gene delivery systems, cancer cell isolation, stem cell isolation, ultrasound contrast agents, bone implants, dental fillings, cosmetics, and controlled drug delivery.[57,58] Massaro et al[59] developed a novel nanocarrier composed of biodegradable HNTs-amphiphilic cyclodextrin hybrids for the co-delivery of silybin and quercetin, which is a potential combination treatment of thyroid cancer. Briefly, multicavity HNT materials are obtained by grafting amphiphilic cyclodextrin units onto the nanotube surface. Analysis of the interaction between cells and the carrier by fluorescence microscopy indicated that the nanomedicine is able to efficiently enter the cells and accumulate around the nucleus. In vitro cell experiments showed the anti-proliferative activity of the nanocarrier against the human ATC cell line 8505C.

Therapeutic Applications of Nanoparticles

Nanocomposites for Targeted Drug Delivery

ATC may derive de novo or from pre-existing DTC or long-standing goiter. Dedifferentiation of thyroid carcinomas can be caused by chromosomal gain and loss, gene mutations, and dysregulation of multiple signaling pathways that promote cell cycle progression and cell adhesion.[7] Inactivating mutations in *TERT, TP53, PTEN, TXNIP* and *RASAL1* and activating mutations in RAS are closely linked with dedifferentiation of thyroid carcinomas. The *BRAF V600E* activating mutations are the most common mutations leading to dedifferentiation of thyroid carcinomas, which are directly correlated with the downregulation of NIS. The *TERT* promoter mutations are linked with lymph node metastasis in ATC patients, and those carrying both *TERT* promoter mutations and activating mutations in *RAS* have a shorter survival. The *PI3KCA* gene amplification is frequently detected in ATC patients. Rearrangement of the *RET* gene can directly or indirectly activate the MAPK and PI3K/AKT pathways.[28] It directly impairs the activity of the cAMP/PKA signaling that is responsible for regulating thyroid-stimulating hormone receptor (TSHR) and NIS levels, thus lowering the sensitivity of ATC cells to radioiodine therapy. MicroRNAs (miRNAs) are involved in the autophagy and apoptosis of ATC.[60] So far, the p53, MAPK and PI3K/AKT/mTOR signaling pathways have been identified to participate in the progression of ATC[61] (Figure 5). Nanocomposites targeting the above signaling pathways have been applied to the preclinical research of ATC.

Targeting Angiogenesis

Accumulating evidence has validated the key role of VEGF in angiogenesis of malignant tumors. VEGFR is the main target for preventing or inhibiting tumor growth, angiogenesis and metastasis.[62] High-level VEGF is a predictive biomarker of ATC, and VEGF-targeted therapy contributes to inhibit angiogenesis and proliferation of ATC cells.[63] Previous clinical trials have evaluated some drugs with anti-VEGFR-2 properties in ATC. However, their application is limited by low bioavailability and inefficient delivery to the target site, which can be solved using nanomaterials to achieve targeted drug delivery.[64] Sorafenib is a multikinase inhibitor that has been approved by the US Food and Drug Administration for the treatment of local recurrence, metastasis and progression of DTC that are non-responsive to radioiodine therapy, but its therapeutic efficacy on ATC is poor.[13] Sorafenib is encapsulated in polycaprolactone (PCL)-coated BSA nanoparticles, which is labeled with ^{131}I by using chloramine T as the oxidizing agent (100% of labeling rate). In the ATC cell line 8305C, ^{131}I-BSA-PCL-sorafenib provides a 7.5 times higher uptake rate of ^{131}I than that of free

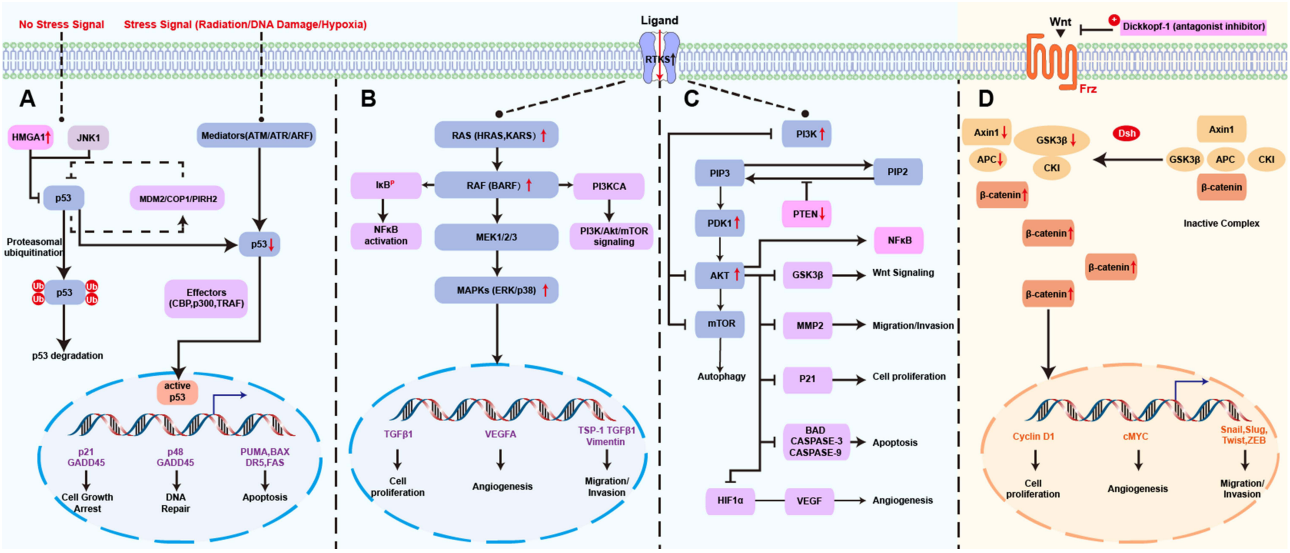

Figure 5 The p53 (**A**), BRAF (**B**), PI3K (**C**) and Axin1 (**D**) signaling pathways involved in the nanoparticle drug delivery systems for the treatment of ATC. The Axin1 signaling pathway has not been validated in clinical trials for its involvement in the treatment of ATC using nanomaterials.

^{131}I, which also assists the dynamic monitoring of drug distribution and metabolism in tumor tissues using single-photon emission computed tomography (SPECT)/CT.[65] Bevacizumab is an anti-VEGF monoclonal antibody with a unique affinity for VEGF.[66] It forms protein complexes on the surface of tumor cells, and therefore, bevacizumab is able to inhibit angiogenesis by blocking the VEGF signaling pathway and navigates nanomedicines to targeted sites. At present, bevacizumab is used for the treatment of metastatic colorectal cancer and advanced, metastatic and recurrent non-small cell lung cancer. Preclinical studies suggested that drug resistance induced by compensatory pathways of interrelated angiogenic factors leads to an unsatisfactory efficacy on ATC.[67,68] Wang et al[34] encapsulated PLGA nanoparticles loaded with IR825 and perfluoropentane (PFP, ultrasound contrast agent). IR825 nanoparticles are a type of photothermal agent with multiple functions of mitochondrial localization, and photoacoustic, fluorescence, and ultrasonic imaging. Using the carbodiimide method, bevacizumab is covalently attached to the shell of nanoparticles. Finally, IR825@Bev-PLGA-PFP nanoparticles are obtained, presenting the features of sequential targeting properties, synergistic therapeutic effect with anti-angiogenic PTT and multimodal imaging-guided diagnosis for ATC. In detail, serving as a sequential targeting nanoplatform, IR825@Bev-PLGA-PFP nanoparticles have biodegradable shells that are favorable to surface modification and extended circulation. The combination of bevacizumab and IR825 via linking amino and carboxyl groups achieves the VEGF-targeting anti-angiogenesis therapy and subcellular accumulation in mitochondria. Confocal laser scanning microscopy visualized a stronger and longer-lasting fluorescence signal in ATC cells induced with IR825@Bev-PLGA-PFP nanoparticles, suggesting its role in enhancing the targeting ability to blood vessels. They later tested the role of IR825@Bev-PLGA-PFP nanoparticles in the synergistic anti-angiogenic PTT. Owing to the high photothermal conversion efficiency of IR825, IR825@Bev-PLGA-PFP nanoparticles can be effectively accumulated in sensitive mitochondria to achieve the complete ablation of ATC cells. Moreover, IR825 favors the excellent fluorescence intensity and photostability, and PFP can be vaporized into microbubbles through phase-transformation NP-loaded liquid fluorocarbon. Therefore, IR825@Bev-PLGA-PFP nanoparticles present the properties of multimodal imaging (photoacoustic, fluorescence, and ultrasonic imaging). Importantly, they are highly biosafe that do not cause a significant change in the body weight. Their novel creation provides innovative references for the diagnosis and treatment of ATC.

Targeting the PI3K-AKT-mTOR Signaling Pathway

HSP90 is a chaperone with more than 400 client proteins, such as EGFR, MET, IGF21R, Akt, Raf21, p53, KIT, FLT3, CDK4, CDK6, etc. Some tumors that have already developed resistance to HSP90 inhibitors are still sensitive to HSP90 inhibitors, indicating that HSP90 is a potential target for overcoming drug resistance.[69–71] ATC cells are in an original state of dedifferentiation, in which the signaling transduction is very complicated. The crosstalk between signaling pathways involved

in ATC leads to the poor therapeutic efficacy of a single targeted drug.[72] Theoretically, HSP90 is featured as both the safety of a single target and the effectiveness of multiple targets. Its combination with other drugs has been validated to improve the anti-cancer effect.[73]

As a client protein of HSP90, the PI3K-AKT-mTOR signaling pathway is involved in regulating cell metabolism, motility, proliferation, growth, and survival. Its abnormal activation or inactivation is frequently detected in human cancers.[74] Mutations of *PIK3CA, PIK3R1, PTEN, AKT, TSC1, TSC2, LKB1, mTOR* and other key genes result in the abnormal activation of the PI3K-AKT-mTOR signaling pathway, thus leading to carcinogenesis. Therefore, inhibiting the PI3K-AKT-mTOR signaling pathway is a vital anti-tumor strategy.[75] At present, everolimus, temsirolimus, copanlisib and idelalisib are 4 inhibitors targeting the PI3K-AKT-mTOR signaling pathway that have been clinically applied. ATC patients carrying PI3K-AKT-mTOR mutations may benefit from everolimus, although its monotherapy is not ideal, and it is expected to achieve better outcomes in a combination treatment.[76] 17-allylamino-17-demethoxygeldanamycin (17-AAG) is the first HSP90 inhibitor that has been widely used as an anti-cancer agent.[77] Thyroid cancer cell lines are highly sensitive to 17-AAG. Torin2 is a second-generation mTOR inhibitor used in scientific research, which has been recently well concerned due to the dual inhibition of mTORC1 and mTORC2.[74]

Mesoporous silica can be used for the loading of chemotherapeutic drugs, genes/siRNAs and other biologically active substances. Drug loading of Torin2, anti-VEGFR2 antibody and 17-AAG by MSNPs contributes to fight against AST via targeting different signaling pathways. Wang et al[51] synthesized (17-AAG+Torin2)@MSNs-antiVEGFR2 by controlling the drug concentration and particle size. The loading capacity and encapsulation efficiency of 17-AAG are 7.29 ± 0.23% and 87.32 ± 1.36%, respectively, and those of Torin2 are 6.15 ± 0.64% and 86.23 ± 2.15%, respectively. Owing to the targeting effect on the anti-VEGFR antibody, (17-AAG+Torin2)@MSNs-antiVEGFR2 nanoparticles present the specificity to VEGFR2-positive FRO cells and a low cytotoxicity for normal cells. Histologically, cell necrosis is the typical manifestation, with reduced expression levels of Ki-67 and CD34. A quantitative analysis of HSP90 in ATC cells is expected to determine the selectivity and inhibitory effect of (17-AAG+Torin2)@MSNs-antiVEGFR2 nanoparticles on the PI3K-AKT-mTOR signaling pathway.

Targeting the p53 Signaling Pathway

The p53 signaling pathway is impaired in the pathogenesis of ATC due to inactivating mutations in the *TP53* gene or overexpression of its negative regulators like HMGA1 and MDM2. Loss-of-function mutations in the *TP53* gene and gain-of-function mutations in its negative regulators eventually lead to uncontrolled cell proliferation.[78] Loss of *p53* or *p53* mutations can be detected in more than 50% of ATCs.[79] CD44 is positively expressed in many malignant tumors. Tumor patients with high expression levels of CD44 are prone to vascular invasion and distant metastasis, presenting shorter disease-free survival and low survival rate.[80] It is reported that *TP53* mutations are detected in 9/12 ATC samples, showing a high positive rate of CD44 like other highly invasive tumors. Cancer cells carrying p53 mutations are insensitive to ^{131}I radioiodine therapy. As a result, reactivating p53 with drugs is promising in the anti-cancer treatment.[81] Prima-1 reactivates the transcriptional transactivation of mutant p53 by directly covalently binding to its core region. Based on the above findings, Huang et al[82] constructed Prima-1@PEI-HA-Tyrs-^{131}I nanoparticles that target CD44 and load Prima-1 as a p53 mutant restoring regent. In this CD44-targeted delivery system, HA is used as the hydrophilic material and the target ligand for CD44, and tyrosines (Tyrs) are modified on HA (HA-Tyrs) to provide sites for radiolabeling ^{131}I. Besides, polyethyleneimine (PEI) is conjugated to HA-Tyr, thus obtaining PEI-HA-Tyrs conjugates for self-assembly into nanoparticles and load Prima-1. The mean hydrodynamic diameter, polydispersity and zeta potential of Prima-1@PEI-HA-Tyrs are 91.01 ± 0.51 nm, 0.181 ± 0.008 and −14.35 ± 1.57 mV, respectively. Liquid chromatography-mass spectrometry (LC-MS) data revealed that the content of Prima-1 loaded in the nanoparticles is 4.62% (w/w). The drug release achieves 62.4% under an acidic condition after 24 h. Thin-layer chromatography (TLC) data revealed that an approximately 100% of radioiodine labeling rate, with a high stability. Compared with that of C643 cells, the uptake efficiency is significantly higher in 8305C cells expressing a higher level of CD44, suggesting that CD44 receptors are able to induce endocytosis. Moreover, compared with the monotherapy of ^{131}I treatment, PEI-HA-Tyrs combined with ^{131}I radioiodine therapy significantly enhances the sensitivity of ATC cells carrying p53 mutations to RT and induces apoptosis via upregulating p53, p21, Bax and SIPS, which may be attributed to the direct covalent binding of

Prima-1 to the p53 core domain and the re-activation of cell apoptosis or SIPS signaling pathway. In the in vivo ATC mouse model, the treatment of PEI-HA-Tyrs significantly increases the number of apoptotic cancer cells, slows down the tumor growth, and upregulates p21 and Bax.

Targeting Cancer Stem Cells

Cancer stem cells (CSCs) are of great significance in tumor survival, proliferation, metastasis and recurrence via the self-renewal and unlimited proliferation. The movement and migration of CSCs explain the metastasis of tumor cells because of the insensitivity to physical and chemical factors that kill tumor cells.[83] As a result, tumor recurrence occurs after the conventional anti-cancer treatment that kills the majority of tumor cells. Drug delivery through targeting highly expressed molecules on the surface of CSCs but lowly expressed in normal cells is a promising anti-cancer method.[84] CD133 is a well-known CSC marker that is positively expressed in ATC cells, indicating that ATC may have stem cell properties.[85–87] Ge et al[88] demonstrated that CD133 is overexpressed in ATC specimens and the ATC cell line FRO, which is barely expressed in normal thyroid tissues and cell lines, suggesting that CD133 may be a potential therapeutic target for ATC. They constructed a CD133-targeted aptamer AP-1 by cell-SELEX (systematic evolution of ligands by exponential enrichment), showing a high binding ability in Caco-2 and FRO cells. They further created AP-1-M-doxorubicin (AP-1-M-Dox) conjugates by inserting Dox at the 5′-end of AP-1-M, yielding higher drug loading rate, stability, drug endocytosis, apoptotic rate, and a lower proliferative rate of CD133-positive cells without a significant cytotoxicity in CD133-negative cells. It is suggested that AP-1-M-Dox conjugates precisely recognize CD133 and release Dox into intracellular compartments. Furthermore, AP-1-M-Dox conjugates significantly inhibit tumor growth and angiogenesis in mice bearing FRO xenografts in vivo. They present less toxicity to mouse liver and kidney compared with those of unconjugated Dox. Therefore, AP-1-M is a potential carrier for drug delivery to CD133-positive tumors, and the pharmacological efficiency of Dox can be significantly enhanced by binding to it. Aptamer-nucleic acid conjugates have been widely studied, which conjugate anti-cancer drugs by modifying chemically active groups at certain base positions base pairing or physical mosaic. They are featured by excellent serum stability, long circulation and anti-enzymolysis capacity, which have yielded acceptable outcomes in the treatment of breast cancer, prostate cancer, leukemia, etc. Aptamers conjugated with anti-cancer drugs are expected as a promising anti-cancer treatment of ATC in the future.

Targeting Nuclear Acids

TERT is overexpressed in thyroid cancers with lymph node metastasis. TERT promoter mutations have been detected in 75% of ATC tumor samples by next-generation sequencing.[7] Silence of hTERT by siRNA transfection significantly inhibits the growth, invasion and migration of ATC cells either carrying hTERT promoter mutations or not.[89] Hence, hTERT has become an optimal therapeutic target for thyroid cancer, and how to prevent the rapid degradation of siRNA by extracellular ribonucleases should be well concerned.

Giovanni et al[35] encapsulated anti-hTERT oligonucleotides (5′→3′ sequences of the hTERT-a-specific siRNA: AGGCACUGUUCAGCGUGCUCAACUA) using PLGA and chitosan. They analyzed the inhibitory effect of targeting TERT on the in vitro and in vivo ATC models, and the influence of silencing TERT on telomere length. Encapsulated by PLGA and chitosan, siRNA delivery does not influence the physical stability of anti-hTERT siRNA-loaded nanoparticles. The treatment of 20 nmol/L anti-hTERT siRNA-loaded nanoparticles reduces the viability of CAL62 and 8505C cells by 40%, and their migratory rate is reduced by 40% and 60%, respectively. In SCID mice bearing ATC, injection of 2.4 mg/kg PLGA-chitosan-Na-siTERT for 7 days significantly lowers the tumor mass, downregulates hTERT and Ki67, and reduces angiogenesis rate. Histological analyses on the liver, intestine, lung, kidney, heart, and spleen samples, and blood cell analysis do not provide evidence of toxicity. In addition, the telomere length is not significantly changed by the treatment of anti-hTERT siRNA-loaded nanoparticles, suggesting that the anti-cancer effect of silenced hTERT is independent of telomere length modification.

The suicide gene/prodrug system involving thymidine kinase (TK) and *Escherichia coli* cytosine deaminase (CD) has been analyzed in many types of cancer cell lines. The suicide gene system driven by hTERTp is highly specific to thyroid cancer cells,[90] although the driving efficiency in cancer cells is relatively low.[91] Chang et al[92] constructed ^{131}I-chitosan-pE9-hTERTp-yCDglyTK nanoparticles containing the radiation enhancer E9 and a dual-suicide gene system driven by hTERTp,

which are labeled with ^{131}I by using chloramine T. Under a weak radiation of ^{131}I, E9 significantly upregulating suicide genes by enhancing the activity of hTERTp. Besides, ^{131}I also has a certain killing effect after entering the host cells.

Targeting BRAF

The V600E mutation is a typical mutation of the *BRAF* gene, which can be detected in 15–44% of ATC patients. It is closely related to tumor growth, aggressiveness, and the development of drug resistance. In addition, mutations of downstream genes of BRAF affect 20–40% of ATC patients, and therefore, BRAF is an attractive target for ATC therapy.[93] At present, RNA interference (RNAi) targeting BRAF that delivers BRAF siRNA to ATC via nanocarriers has not been extensively analyzed. Previous studies usually assess the efficacy of gene silencing via measuring the protein expressions of target genes, while it is unable to assess the distribution of nanomedicines in tumor lesions. The thyroid gland is anatomically located in the superficial region. Hence, it is highly feasible to construct a non-invasive nanoparticle platform of NIR fluorescent polymers for siRNA delivery. Under the guidance of NIR, siRNA nanoparticles delivered to tumor tissues and metastatic lymph nodes can be visualized to reflect the anti-cancer effect.[94–96] Liu et al[36] constructed a nanoparticle polymeric platform for NIR imaging and siRNA delivery using polyCPDTBT, with the encapsulation efficacy of 50%. Owing to the use of polyethylene glycol as the surface coating, their innovatively constructed nanoparticles are highly stable. After nanoparticle injection for 4 h in mice, the fluorescence intensity of the NIR nanoparticles is relatively stable, with the decay at 12 h of only 14%. A clear contrast of tumor tissues with adjacent ones by NIR fluorescence contributes to determine the adjacent blood vessels surrounding the tumor and their potential infiltration. Moreover, a strong fluorescence intensity of sentinel lymph node can be rapidly detected within 10 min, which is featured as low cost, less exposure to radiation and high contrast ratio. In 8505C cells treated with the constructed nanoparticles, the number of invasive and metastatic cells decreases by 5 and 15 times than those of controls, respectively. In mice bearing BRAF^{V600E}-mutated 8505C xenograft tumors injected with BRAF siRNA nanoparticles, significantly downregulated BRAF and Ki67 in tumor tissues, smaller tissue volume and less pulmonary micrometastases all validated the anti-cancer capacity.

Targeting hERG

The hERG promoter region contains multiple binding sites of oncogenes like Sp1, NF-κB and p53.[97] Overexpression of hERG induces cell proliferation by accelerating cell cycle progression via altering the resting membrane potential of tumor cells. Silence of hERG is able to regulate the proliferation, adhesion and invasion of myeloid leukemia cells and glioma cells.[98–100] Li et al[101] synthesized a multivalent nanocarrier PAMAM-polyethylene glycol-cRGD (PAMAM-PEG-cRGD). Poly(amidoamine) (PAMAM) is a nanoscale polymer with a cationic surface environment that provides an electrostatic interaction with siRNA interaction and complexation, a better permeability and a higher siRNA loading. PEG encapsulation and cyclic Arg-Gly-Asp (cRGD) contribute to improve the biocompatibility and endocytosis of tumor cells, respectively. The treatment of PAMAM-PEG-cRGD in HTC/3 cells with an adjusted N/P results in a 68% of transfection efficacy, and hERG is downregulated to 26.3% of that in the control group. Knockdown of hERG inhibits tumor activity and induces apoptosis by suppressing the release of vascular endothelial growth factor and triggering the caspase-3 cascade in ATC cells.

Targeting IL-13Rα2

IL-13Rα2 is a 380-amino-acid glycoprotein located on the plasma membrane, which stimulates tumor development by activating relevant signal transductions like the PI3K, AKT and SRC signaling pathways.[102] IL-13Rα2 is overexpressed in ATC tissues but negatively expressed in adjacent normal thyroid tissues, suggesting the tumor specificity.[103] Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a non-flavonoid polyphenolic organic compound with a well-known anti-cancer property. However, a very low concentration of resveratrol is incapable of inhibiting tumor growth.[104] It is necessary to enhance the cell uptake of resveratrol. Xiong et al[105] constructed resveratrol nanoparticles Pep-1-PEG3.5k-PCL4k@Res with the drug loading rate and encapsulation efficiency of 6.81% and 40.84%, respectively. Compared with those injected with normal saline, subcutaneous tumor volume of nude mice injected with Pep-1-PEG3.5k-PCL4k@Res nanoparticles slowly grows (15.99% vs 4.92%), showing a similar anti-cancer effect with that of docetaxel and

doxorubicin. In vitro data revealed that resveratrol upregulates PTEN in ATC cells via targeting IL-13Rα2, which also inhibits the activation of the PI3K/AKT/mTOR signaling pathway by blocking the transformation of PIP2 into PIP3.

In addition to the above-mentioned targets used in nanoparticle drug delivery systems for the treatment of ATC, recent next-generation sequencing (NGS) analysis showed that the EIF1AX mutations have been detected in 14% of ATC cases, which is a novel target to be analyzed for the development of nanomedicines.

Nanoparticles for Improving the Efficacy of ^{131}I Radioiodine Therapy

Nanoparticles for Restoring the Expression Level of NIS

The barely expressed NIS on cell membrane causes the ineffective targeted radionuclide therapy for ATC.[106–108] The expression level of NIS decreases with the increased malignant level of ATC, predicting a poor prognosis. Therefore, restoring the expression level of NIS on the membrane of ATC cells is expected as a reliable way to enhance the sensitivity to ^{131}I radioiodine therapy. Li et al[32] developed lipid-peptide-mRNA (LPm) nanoparticles that deliver the mRNA encoding NIS into ATC cells, thus enhancing the sensitivity to ^{131}I. After the treatment of NIS-mRNA LPm nanoparticles for 24 h, the proportion of NIS-positive cells and iodine uptake in 8505C cells increase by 13% and 70 times, respectively. Moreover, the uptake of LPm nanoparticles is non-specific in either ATC cells, fibroblasts or macrophages. SPECT/CT visualized that ^{131}I is significantly distributed in ATC tissues of mice treated with NIS-mRNA LPm nanoparticles combined with ^{131}I radioiodine therapy, with a 4000-times higher radioactivity than other ^{131}I-treated groups. In conclusion, nanoparticles significantly enhance the efficacy of ^{131}I radioiodine therapy by restoring the expression level of NIS without causing damages to important organs (Figure 6).

Nanoparticles Used in the Combination Treatment of ^{131}I Radioiodine Therapy and PTT

Thermal therapy combined with ^{131}I radioiodine therapy prevents the repair of damaged DNA, leading to the residual of DNA double-strand breaks and cell apoptosis. Because of the adjustable composition and structure of nanoparticles,

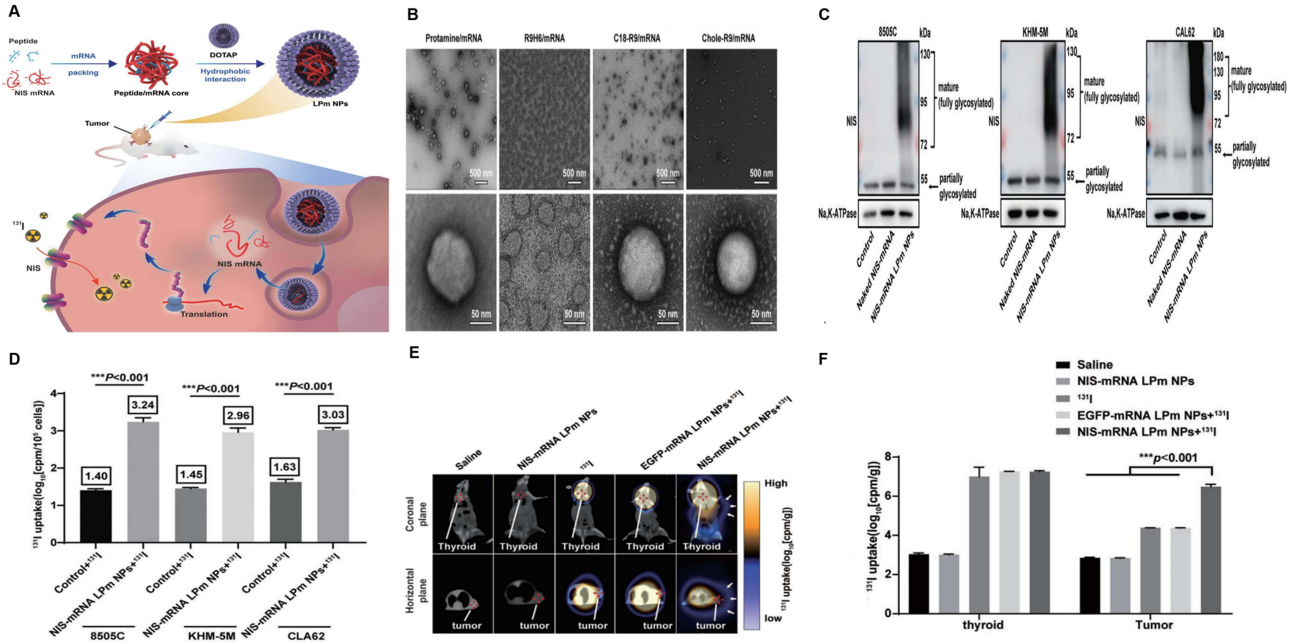

Figure 6 The design of lipid-peptide-mRNA (LPm) nanoparticles and their application in the treatment of ATC. (**A**) The design of LPm nanoparticles that deliver the mRNA encoding NIS into ATC cells. (**B**) TEM scans of Peptide/mRNA complexes (scale bar=500 nm and 50 nm). (**C**) NIS in ATC cells treated with naked NIS-mRNA or NIS-mRNA LPm nanoparticles by Western blot. (**D**) ^{131}I uptake in ATC cells treated with NIS-mRNA LPm nanoparticles. (**E** and **F**) SPECT/CT imaging of mice treated with saline, NIS-mRNA LPm nanoparticles, ^{131}I, EGFP-mRNA LPm nanoparticles + ^{131}I, or NIS-mRNA LPm nanoparticles +^{131}I for 24 h, and the quantitative analysis of the radioactivity of ^{131}I. White arrow indicates the SPECT/CT scans of the thyroid gland and tumor tissues in mice. ***P<0.001. Reprinted from Li Q, Zhang L, Lang J, et al. Lipid-Peptide-mRNA nanoparticles augment radioiodine uptake in anaplastic thyroid cancer. *Adv Sci*. 2023;10(3):e2204334. © 2022 The Authors. Advanced Science published by Wiley-VCH GmbH. Creative Commons..[32]
Abbreviations: LPm, lipid-peptide-mRNA; ATC, anaplastic thyroid carcinomas; NIS, sodium iodide symporter; TEM, transmission electron microscope; SPECT, single-photon emission computerized tomography; CT, computed tomography.

a nanoparticle system can be composed of different therapeutic strategies and imaging methods to achieve the synergistic anti-cancer treatment.[109] Zhang et al[40] constructed ^{131}I-HSA-ICG nanoparticles with ^{131}I labeled on human serum albumin (HSA) and indocyanine green (ICG) covalently bound to ^{131}I-HSA. The photothermal conversion efficiency of ^{131}I-HSA-ICG nanoparticles yields 24.25%, and they have the highest ablation effect on tumor cells under the irradiation of an 808-nm laser (2.5 W/cm^2) compared with that of other groups. Copper sulfide (CuS) has been well concerned for its application in PTT. 131I-BSA@CuS has the properties of both RT and PTT, with the ^{131}I labeling rate and photothermal conversion efficiency of 66–80% and 28.07%, respectively. The combination of PTT and ^{131}I radioiodine therapy presents the optimal anti-cancer effect. Huang et al[48] synthesized mesoporous polydopamine nanoparticles with a cerebroid pore channel structure (CPDA), serving as the nanocarriers to ^{131}I, the ^{131}I labeling rate (88.39%±5.17) and photothermal conversion efficiency (η=50.3%) of which are adjusted by optimizing their structure. CPDA-^{131}I nanoparticles exerts a 130-times higher cellular uptake rate than that of free ^{131}I. ^{131}I-labeled anti-VEGFR2 loaded in MSNPs coated with BSA (^{131}I-BSA-MSN-anti-VEGFR2) which are nanoparticles constructed to enhance the intracellular accumulation of ^{131}I and thus the RT outcome via targeting VEGFR-2 and MSNP-induced EPR.

In addition to ^{131}I, nanoparticles labeled by other radioactive metals like ^{186}Re/^{188}Re, ^{64}Cu, ^{90}Y and ^{198}Au have been synthesized as potential radiotherapeutic drugs. They are featured as small damages to non-targeted tissues due to the small range of radiation within millimeters.[110] The use of ^{64}Cu-labeled nanoparticles in RT has not been widely reported. Polyethylene glycol (PEG)-coated [^{64}Cu]CuS nanoparticles exert the properties of both RT and PTT via ^{64}Cu and CuS, respectively. Similarly, they present the optimal pro-apoptotic effect at 2.5 W/cm^2. PET/CT scans revealed the same metabolic form and in vivo radioactivity distribution of PEG-[^{64}Cu]CuS nanoparticles and ^{131}I-labeled nanoparticles. The absorbed doses and retention time of intratumorally injected PEG-[^{64}Cu]CuS nanoparticles are both superior to intravenous injection, which are comparable to those of ^{131}I-labeled nanoparticles. Importantly, combined RT/PTT remarkably delays tumor growth without causing acute toxicity.

Collectively, the acceptable efficacy of combined RT/PTT on ATC can be attributed to the suppression of RT-induced DNA damage repair by PTT, the increased intratumoral tissue blood flow and oxygenation, hypoxia and reoxidation of tumor cells, and non-selective effects on tumor cells and CSCs. In the future, the improvement of the accumulation of radioactive substances in tumor cells and the selection of radiation dose and administration methods that ensure the biological safety require further explorations.

Nanomaterials for Improving the Outcome of Chemotherapy

Currently, chemotherapy is still preferred to ATC patients without specific gene mutations. Paclitaxel plus carboplatin, cisplatin plus doxorubicin, docetaxel plus doxorubicin, paclitaxel alone or doxorubicin alone are recommended as the systemic treatment of ATC. However, the doubling time for tumor volume of ATC is as short as 3–12 days, and the very short dosing interval of chemotherapeutic drugs results in a high toxicity. ATC patients benefit less from a single chemotherapy, with the mean PFS of less than 3 months. Their poor prognosis is mainly attributed to the decreased drug uptake, increased efflux and the infiltration of tumor-associated macrophages.[12,13] Loading of chemotherapeutic drugs using nanomaterials contributes to enhance the intracellular drug uptake and the dosage. Li et al[111] constructed TSH-SiO_2@Dox nanoparticles that effectively deliver doxorubicin to tumor tissues and promote internalization via thyroid-stimulating-hormone receptor (TSHr) and acid induction. Through the targeting effect on TSH, the treatment of TSH-SiO_2@Dox nanoparticles significantly increases the apoptotic rate (79.0% vs 29.6%) in FTC-133 and TPC1 thyroid cells than that of free doxorubicin.[111] Nevertheless, TSHr is lowly expressed in ATC cells, and FTC-133 and TPC1 cells are lowly invasive. The inhibitory effect of TSH-SiO_2@Dox nanoparticles on the apoptosis of strongly invasive resistant cells remains unclear.

It is reported that the efficacy of doxorubicin loaded in dopamine-melanin nanoparticles on the drug-resistant ATC cell line, but the loading rate only ranges about 20.0%.[112] To further enhance the loading rate, Han et al[50] synthesized BSA-stabilized MONPs loaded with doxorubicin, which are excellent at the increased loading rate (47.02%), increased drug uptake rate in the drug-resistant cell line HTh74R, and decreased drug efflux.

Although the drug loading rate of doxorubicin can be significantly enhanced via nanomaterials, its toxicity should be well concerned. To reduce the cumulative dose, drug-loaded nanobubbles contribute to control the drug release in the

targeted area via extracorporeal shock waves (ESW). The combination of doxorubicin-loaded glycol chitosan nanobubbles and ESW therapy significantly reduces GI_{50} value by 40%. The toxicity of cardiomyocytes in rats treated with doxorubicin loaded in glycol chitosan nanobubbles combined with ESW therapy is much lower than those treated with free doxorubicin. Notably, ESWs trigger the intracellular drug release by targeting nanobubbles, leading to the highest nuclear drug dosage. A direct intranuclear drug delivery is found to overcome drug resistance.[113] Therefore, drug-loaded nanobubbles combined with ESW therapy are believed as a novel strategy to prevent drug resistance.

Camptothecin (CPT) is a type of topoisomerase 1 (TOP1) inhibitor with the anti-cancer activity. Irinotecan and topotecan are typical analogues of CPT, the dosage and anti-tumor effect of which are greatly limited by the time-consuming administration due to a low solubility, and severe myelosuppressive adverse events. β-Cyclodextrin-based nanosponges are characterized by the high encapsulation capacity. CN-CPT nanosponges are obtained by cross-linking β-Cyclodextrin-based nanosponges with CPT at 1:4 molar ratio and PEG encapsulation.[114] The treatment of CN-CPT nanosponges in ATC cell lines BHT-101 and CAL-62 significantly inhibit the cell viability, colony formation and cell cycle progression, showing a faster and stronger anti-cancer effect than that of free CPT. Moreover, CN-CPT nanosponges significantly inhibit the release of IL-8 and VEGFA in vitro, and xenograft growth, metastasis and angiogenesis in SCID/Beige mice in vivo without an obvious toxicity.

All-trans retinoic acid (ATRA) exerts its anti-cancer effect by regulating the expression level of RXR via activating the activating retinoic acid receptors (RARs) and retinoid X receptors on the nuclear membrane of cancer cells. However, it is unstable in the oxygen-rich and acidic environment, which can be protected by encapsulating them in nanoparticle drug delivery systems. Liposomes are able to embed hydrophilic, lipophilic, and amphiphilic substances, which can adjust the biopharmaceutical properties of encapsulated compounds and improve their stability, and even prevent photodegradation. ATRA loaded in DPPC/Chol/DSPE-mPEG2000 liposomes presents a stronger anti-proliferative effect against thyroid cancer cell lines PTC-1, B-CPAP and FRO than that of free ATRA.[115]

Synergistic Nanoparticle Platforms for Enhancing the Efficacy of PTT

PTT is a popular anti-cancer treatment, which can be applied to the synergistic treatment with photothermal agents, photosensitizers or chemical drugs loaded in nanoparticle platforms. The thyroid and its draining lymph nodes are superficial organs. Compared with other organs located in the abdominal cavity, PTT for thyroid diseases is simple and effective. However, a single PTT or PDT hardly yields a satisfactory outcome due to the heat shock effect of PTT and the obstruction caused by the hypoxic tumor microenvironment in PDT. At present, nanocomposites with the property of PTT combined with other anti-cancer treatment significantly improve the outcome.[116] Hypericin (Hyp) is an active ingredient of *Hypericum perforatum L*., which is used as a photosensitizer in PDT.[117] It is found that Hyp-assisted PDT significantly increases the level of intracellular reactive oxygen species (ROS) and mitochondrial damage in FRO cells in vitro and achieves tumor regression in FRO xenograft mice in vivo. It is found that carboplatin combined with radachlorin-PDT induces apoptosis in FRO cells and inhibits the growth of tumor xenografts in athymic mice by activating PTEN and deregulating EGFR/PI3K. Genistein is a major component in soybean, serving as a potential chemopreventive agent to enhance the anti-cancer efficacy in the combination of chemotherapy/radiotherapy.[118–120] The combination treatment of genistein and photofrin-PDT significantly induces apoptosis, increases ROS level and upregulates caspase 3/8/9/12 and cytochrome c.[121]

PDT has been widely reported in the treatment of superficially located skin tumors or deeply located digestive tract tumors. Its application to the treatment of malignant thyroid tumors, however, has been rarely reported. Generally, DTC has a good prognosis that can be effectively controlled by conventional therapeutic strategies, while ATC is rapidly aggravated that results in a limited sample size for further research. PDT for the treatment of ATC is able to overcome the disadvantages of insufficient laser wavelength and the requirement for a dedicated irradiation probe. Meanwhile, lymph node tracers can be loaded to achieve the goal of a combination treatment. A synergistic treatment of targeted therapy, immune therapy and chemotherapy with nanomedicines for PDT is a promising anti-cancer treatment in the future. Besides, the design of targeting optical probes and the control of laser irradiation are key factors to ensure the accuracy of PDT to minimize the damages to surrounding tissues. Currently, optical diffusers are used to deliver laser light uniformly and reduce laser dispersion by using circumferential light distribution and facilitating the physical interaction between photons and tissues.

Natural Drugs Delivered by Nanoparticles

The anti-cancer effect of natural drugs isolated from animals and plants has been concerned in recent years. Polyphenolic compounds in plants have been designed and developed as anti-cancer agents. Their disadvantages like the low solubility, low concentration in the circulatory system and unstable chemical properties are now can be largely solved by nanoparticle drug delivery systems.[122–124] Novel nanotube materials consisting of biodegradable HNT and functionalized amphiphilic cyclodextrin that co-deliver silybin and quercetin are designed to the treatment of ATC.[59] Yu et al[125] developed photo-triggered gold nanodots capped mesoporous silica nanoparticles Au@MSNs loaded with capsaicin for PTT. The anti-cancer effect of capsaicin on ATC cells is significantly improved by the loading of Au@MSNs nanoparticles, which inhibit the proliferation, migration and cell cycle progression and induce apoptosis.

Research Demerits

Due to the biological characteristics, ATC is poorly responsive to conventional treatment. Nanoparticle drug delivery systems are emerging tools to assist the treatment of ATC. However, they have the following demerits.

Demerits of Inorganic Nanoparticles

Inorganic nanomaterials like silica are suitable for the delivery of conventional chemotherapeutic drugs due to the expandable surface area and the property of PTT/PDT. However, it is unable to determine whether chemotherapy or PTT/PDT provides more clinical benefits. Currently, surface modification of inorganic nanomaterials and the exact drug loading by them have been rarely reported. Meanwhile, adverse events caused by the in vivo accumulation should be well concerned.[126]

Demerits of Organic Nanoparticles

Organic nanoparticles are more conducive to the delivery of targeted drugs and siRNAs due to their excellent biocompatibility and high cellular uptake. However, the poor stability and high rate of degradation in blood circulation should be highlighted in the future research.[127]

Demerits of the Combination Therapy

Calculation of the iodine uptake rate of ATC cells is essential for favoring the outcome of internal radiotherapy by the combination of nanomaterials and ^{131}I radioiodine therapy. Compared with papillary thyroid cancer cells, ATC cells have extremely poor iodine uptake due to downregulation of NIS and loss of radioactive iodine affinity for ^{131}I, which is unable to be solved by drug delivery systems that increase the cellular uptake.[92]

Research Gap of Endogenous Stimuli-Responsive Drug Delivery Systems in ATC Cells

At present, pH-responsive, enzyme-responsive, temperature-responsive and reduction-responsive nanomaterials have been widely analyzed in liver cancer, gastric cancer, intestinal cancer, lung cancer and breast cancer.[128] Because of the low incidence of ATCs, they have been rarely analyzed in tumor microenvironment of ATCs. Besides, sustained, controlled release, and highly specific drug delivery systems that have been extensively analyzed in tumors have not been fully elucidated in ATCs.

Lack of Clinical Trials

So far, nanoparticle drug delivery systems developed to the treatment of ATCs have been validated in in vitro cell models and in vivo animal models, and their application should be further explored in clinical trials. In addition, the potential of nanoparticle drug delivery systems in predicting the outcome of ATCs is a research gap. There is no comparability between the anti-tumor efficacy of intratumoral injection and intravenous injection.

Research Directions in the Future

We recommended the following aspects to future analyses of nanoparticle drug delivery systems to the treatment of ATCs.

Nanoparticle Drug Delivery Systems Targeting Anti-Angiogenesis

Anti-angiogenesis is a promising aspect for the design of nanoparticle drug delivery systems for ATC treatment, because the excessive angiogenesis is an indispensable factor in the dedifferentiation and evolution of ATCs. At present, nanotechnology-based anti-angiogenic drugs like bevacizumab and sorafenib have yielded acceptable outcomes in clinical trials. CA4P, also known as fosbretabulin, has been validated very effective in drug-resistant solid tumors in a phase III clinical trial.[129] How to increase the anti-angiogenesis ability of CA4P via loading in nanomaterials and its combination with chemotherapy and other anti-angiogenic agents to target key signaling pathways involved in the development of ATC are the future research highlights.

Nanoengineered Drug Delivery Systems for Target Gene Therapy

Nanoengineered drug delivery systems for target gene therapy are research hotspot, which not only target the specific gene in tumors but also provide a synergistic effect on the internal radiation via upregulating NIS and promoting the internalization of ^{131}I-labeled nanoparticles. With the great strides made on genome sequencing, gene targets of ATC (eg, TERT, TP53, BRAF, PIK3CA, PTEN) identified by this technology can be loaded in nanoparticle drug delivery systems. EIF1AX mutations have been frequently detected in ATC patients by the next-generation sequencing, and nanomedicines targeting it are expected to be explored in the future.[130]

In addition, nanoengineered drug delivery systems are expected to reduce chemotherapy resistance by enhancing drug internalization and reducing drug efflux. POLIVY, PADCEV and ENHERTU belong to the antibody-drug conjugates (ADCs), presenting dual functions of potent cytotoxicity as chemotherapy drugs and tumor targeting property as ADCs. They greatly enhance the efficacy of anti-tumor therapy and the survival of tumor patients.[131] Nanoengineered drug delivery systems for delivering ADCs contribute to enhance the targeting property in ATCs.

Nanoengineered drug delivery systems are capable of enhancing the labeling rate of ^{131}I and promoting the internalization of ^{131}I-labeled drugs in ATC cells like anti-TSHR antibodies by targeting subcellular structures.[101] Collectively, nanoengineered drug delivery systems may be a promising therapeutic strategy for ATCs.

Nanoengineered Drug Delivery Systems for PTT/PDT

Nanoengineered drug delivery systems for photodynamic therapy have been thoroughly analyzed, which are superior to the treatment of thyroid cancer because of the superficial location, simple procedures, high repeatability and recognition of tumor lesions, metastatic lymph nodes and other important anatomical structures like parathyroid glands and thoracic duct.[132] Improving the photoresponse and photothermal conversion efficiency of composite nanomaterials and modifying the irradiation range and intensity of the laser irradiator are future research fields in the treatment of ATC patients who are unable to achieve R0 resection.

Nanoengineered Drug Delivery Systems for Tumor Immunotherapy

Nanoengineered drug delivery systems for tumor immunotherapy via blocking PD-1 and PD-L1 have yielded acceptable outcomes.[133] In phase I/II clinical studies involving advanced/metastatic ATC patients, the response rate of PD-1-positive ATC patients treated with Spartalizumab (a monoclonal antibody against PD-1 receptor), especially those with the positive rate of greater than 50%, is significantly higher than those of negatively expressed patients.[134,135] Enhancing the response rate and inducing immunogenic cell death (ICD) by combining PTT/PDT are research directions in the future.

In vitro and in vivo evidence has shown encouraging findings in the application of nanoparticle drug delivery systems to the treatment of ATCs. Targeted drugs, genes/siRNAs, photosensitizers, radioactive elements, optical materials and natural medicines delivered by nanoengineered drug delivery systems are expected to be an alternative to ATC patients, especially providing clinical benefits to advanced patients who are unable to be surgically treated.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Janz TA, Neskey DM, Nguyen SA, Lentsch EJ. Is the incidence of anaplastic thyroid cancer increasing: a population based epidemiology study. *World J Otorhinolaryngol Head Neck Surg*. 2019;5(1):34–40. doi:10.1016/j.wjorl.2018.05.006
2. Amphlett B, Lawson Z, Abdulrahman GO, et al. Recent trends in the incidence, geographical distribution, and survival from thyroid cancer in Wales, 1985–2010. *Thyroid*. 2013;23(11):1470–1478. doi:10.1089/thy.2012.0573
3. de Ridder M, Nieveen van Dijkum E, Engelsman A, Kapiteijn E, Klumpen HJ, Rasch CRN. Anaplastic thyroid carcinoma: a nationwide cohort study on incidence, treatment and survival in the Netherlands over 3 decades. *Eur J Endocrinol*. 2020;183(2):203–209. doi:10.1530/EJE-20-0080
4. Hvilsom GB, Londero SC, Hahn CH, et al. Anaplastic thyroid carcinoma in Denmark 1996–2012: a national prospective study of 219 patients. *Cancer Epidemiol*. 2018;53:65–71. doi:10.1016/j.canep.2018.01.011
5. Wendler J, Kroiss M, Gast K, et al. Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: results of a multicenter study in Germany. *Eur J Endocrinol*. 2016;175(6):521–529. doi:10.1530/EJE-16-0574
6. Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A, Suzuki S. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC research consortium of Japan cohort study of 677 patients. *World J Surg*. 2012;36(6):1247–1254. doi:10.1007/s00268-012-1437-z
7. Xu B, Fuchs T, Dogan S, et al. Dissecting anaplastic thyroid carcinoma: a comprehensive clinical, histologic, immunophenotypic, and molecular study of 360 cases. *Thyroid*. 2020;30(10):1505–1517. doi:10.1089/thy.2020.0086
8. De Crevoisier R, Baudin E, Bachelot A, et al. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *Int J Radiat Oncol Biol Phys*. 2004;60(4):1137–1143. doi:10.1016/j.ijrobp.2004.05.032
9. Cabanillas ME, Williams MD, Gunn GB, et al. Facilitating anaplastic thyroid cancer specialized treatment: a model for improving access to multidisciplinary care for patients with anaplastic thyroid cancer. *Head Neck*. 2017;39(7):1291–1295. doi:10.1002/hed.24784
10. Capdevila J, Wirth LJ, Ernst T, et al. PD-1 blockade in anaplastic thyroid carcinoma. *J Clin Oncol*. 2020;38(23):2620–2627. doi:10.1200/JCO.19.02727
11. Maniakas A, Dadu R, Busaidy NL, et al. Evaluation of overall survival in patients with anaplastic thyroid carcinoma, 2000–2019. *JAMA Oncol*. 2020;6(9):1397–1404. doi:10.1001/jamaoncol.2020.3362
12. Molinaro E, Romei C, Biagini A, et al. Anaplastic thyroid carcinoma: from clinicopathology to genetics and advanced therapies. *Nat Rev Endocrinol*. 2017;13(11):644–660. doi:10.1038/nrendo.2017.76
13. Bible KC, Kebebew E, Brierley J, et al. 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2021;31(3):337–386. doi:10.1089/thy.2020.0944
14. Ryder M, Gild M, Hohl TM, et al. Genetic and pharmacological targeting of CSF-1/CSF-1R inhibits tumor-associated macrophages and impairs BRAF-induced thyroid cancer progression. *PLoS One*. 2013;8(1):e54302. doi:10.1371/journal.pone.0054302
15. Ito K, Hanamura T, Murayama K, et al. Multimodality therapeutic outcomes in anaplastic thyroid carcinoma: improved survival in subgroups of patients with localized primary tumors. *Head Neck*. 2012;34(2):230–237. doi:10.1002/hed.21721
16. Cabanillas ME, Dadu R, Iyer P, et al. Acquired secondary RAS Mutation in BRAF(V600E)-Mutated thyroid cancer patients treated with BRAF inhibitors. *Thyroid*. 2020;30(9):1288–1296. doi:10.1089/thy.2019.0514
17. Sparano C, Godbert Y, Attard M, et al. Limited efficacy of lenvatinib in heavily pretreated anaplastic thyroid cancer: a French overview. *Endocr Relat Cancer*. 2021;28(1):15–26. doi:10.1530/ERC-20-0106
18. Gleiter H. Nanostructured materials: basic concepts and microstructure. *Acta Mater*. 2000;48:1–29. doi:10.1016/S1359-6454(99)00285-2
19. Fagin JA, Wells SA. Biologic and clinical perspectives on thyroid cancer. *N Engl J Med*. 2016;375(11):1054–1067. doi:10.1056/NEJMra1501993
20. Webster TJ. Nanomedicine: what's in a definition?. *Int J Nanomedicine*. 2006;1(2):115–116. doi:10.2147/nano.2006.1.2.115
21. Martinelli C, Pucci C, Ciofani G. Nanostructured carriers as innovative tools for cancer diagnosis and therapy. *APL Bioeng*. 2019;3(1):011502. doi:10.1063/1.5079943
22. Navya PN, Kaphle A, Srinivas SP, Bhargava SK, Rotello VM, Daima HK. Current trends and challenges in cancer management and therapy using designer nanomaterials. *Nano Converg*. 2019;6(1):23. doi:10.1186/s40580-019-0193-2
23. Yao Y, Zhou Y, Liu L, et al. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. *Front Mol Biosci*. 2020;7:193. doi:10.3389/fmolb.2020.00193
24. Zein R, Sharrouf W, Selting K. Physical properties of nanoparticles that result in improved cancer targeting. *J Oncol*. 2020;2020:5194780. doi:10.1155/2020/5194780
25. Huynh E, Zheng G. Cancer nanomedicine: addressing the dark side of the enhanced permeability and retention effect. *Nanomedicine*. 2015;10(13):1993–1995. doi:10.2217/nnm.15.86
26. Thomas OS, Weber W. Overcoming physiological barriers to nanoparticle delivery-are we there yet?. *Front Bioeng Biotechnol*. 2019;7:415. doi:10.3389/fbioe.2019.00415
27. Golombek SK, May JN, Theek B, et al. Tumor targeting via EPR: strategies to enhance patient responses. *Adv Drug Deliv Rev*. 2018;130:17–38. doi:10.1016/j.addr.2018.07.007
28. Lopes MBS. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. *Acta Neuropathol*. 2017;134(4):521–535. doi:10.1007/s00401-017-1769-8
29. Celano M, Calvagno MG, Bulotta S, et al. Cytotoxic effects of gemcitabine-loaded liposomes in human anaplastic thyroid carcinoma cells. *BMC Cancer*. 2004;4:63. doi:10.1186/1471-2407-4-63
30. Cristiano MC, Cosco D, Celia C, et al. Anticancer activity of all-trans retinoic acid-loaded liposomes on human thyroid carcinoma cells. *Colloids Surf B Biointerfaces*. 2017;150:408–416. doi:10.1016/j.colsurfb.2016.10.052
31. Gao XJ, Li AQ, Zhang X, Liu P, Wang J, Cai X. Thyroid-stimulating hormone (TSH)-armed polymer–lipid nanoparticles for the targeted delivery of cisplatin in thyroid cancers: therapeutic efficacy evaluation. *RSC Adv*. 2015;5:106413–106420. doi:10.1039/C5RA12588J
32. Li Q, Zhang L, Lang J, et al. Lipid-Peptide-mRNA nanoparticles augment radioiodine uptake in anaplastic thyroid cancer. *Adv Sci*. 2023;10(3):e2204334. doi:10.1002/advs.202204334
33. Maroof H, Islam F, Dong L, et al. Liposomal delivery of miR-34b-5p induced cancer cell death in thyroid carcinoma. *Cells*. 2018;7(12):265. doi:10.3390/cells7120265

34. Wang Q, Sui G, Wu X, et al. A sequential targeting nanoplatform for anaplastic thyroid carcinoma theranostics. *Acta Biomater*. 2020;102:367–383. doi:10.1016/j.actbio.2019.11.043
35. Lombardo GE, Maggisano V, Celano M, et al. Anti-hTERT siRNA-loaded nanoparticles block the growth of anaplastic thyroid cancer xenograft. *Mol Cancer Ther*. 2018;17(6):1187–1195. doi:10.1158/1535-7163.MCT-17-0559
36. Liu Y, Gunda V, Zhu X, et al. Theranostic near-infrared fluorescent nanoplatform for imaging and systemic siRNA delivery to metastatic anaplastic thyroid cancer. *Proc Natl Acad Sci U S A*. 2016;113(28):7750–7755. doi:10.1073/pnas.1605841113
37. Tran S, DeGiovanni PJ, Piel B, Rai P. Cancer nanomedicine: a review of recent success in drug delivery. *Clin Transl Med*. 2017;6(1):44. doi:10.1186/s40169-017-0175-0
38. Heydari Z, Mohebbi-Kalhori D, Afarani MS. Engineered electrospun polycaprolactone (PCL)/octacalcium phosphate (OCP) scaffold for bone tissue engineering. *Mater Sci Eng C Mater Biol Appl*. 2017;81:127–132. doi:10.1016/j.msec.2017.07.041
39. Zhang R, Zhang Y, Tan J, et al. Antitumor Effect of (131)I-Labeled Anti-VEGFR2 targeted mesoporous silica nanoparticles in anaplastic thyroid cancer. *Nanoscale Res Lett*. 2019;14(1):96. doi:10.1186/s11671-019-2924-z
40. Zhang X, Yan Z, Meng Z, et al. Radionuclide (131)I-labeled albumin-indocyanine green nanoparticles for synergistic combined radio-photothermal therapy of anaplastic thyroid cancer. *Front Oncol*. 2022;12:889284. doi:10.3389/fonc.2022.889284
41. Zhang C, Chai J, Jia Q, et al. Evaluating the therapeutic efficacy of radiolabeled BSA@CuS nanoparticle-induced radio-photothermal therapy against anaplastic thyroid cancer. *IUBMB Life*. 2022;74(5):433–445. doi:10.1002/iub.2601
42. Liu Y, Ai K, Lu L. Polydopamine and its derivative materials: synthesis and promising applications in energy, environmental, and biomedical fields. *Chem Rev*. 2014;114(9):5057–5115. doi:10.1021/cr400407a
43. Wu D, Duan HX, Guan QQ, et al.. Mesoporous polydopamine carrying manganese carbonyl responds to tumor microenvironment for multimodal imaging-guided cancer therapy. *Adv Funct Mater*. 2019;29:1900095. doi:10.1002/adfm.201900095
44. Qi C, Fu LH, Xu H, Wang TF, Lin J, Huang P. Melanin/polydopamine-based nanomaterials for biomedical applications. *Sci China Chem*. 2019;62:162. doi:10.1007/s11426-018-9392-6
45. Min Y, Wang X, Chen H, Chen J, Xiang K, Yin G. Thermal ablation for papillary thyroid microcarcinoma: how far we have come?. *Cancer Manag Res*. 2020;12:13369–13379. doi:10.2147/CMAR.S287473
46. Hu JJ, Cheng YJ, Zhang XZ. Recent advances in nanomaterials for enhanced photothermal therapy of tumors. *Nanoscale*. 2018;10 (48):22657–22672. doi:10.1039/c8nr07627h
47. Liu X, Qin J, Zhang X, et al. The mechanisms of HSA@PDA/Fe nanocomposites with enhanced nanozyme activity and their application in intracellular H(2)O(2) detection. *Nanoscale*. 2020;12(47):24206–24213. doi:10.1039/d0nr05732k
48. Huang S, Wu Y, Li C, et al. Tailoring morphologies of mesoporous polydopamine nanoparticles to deliver high-loading radioiodine for anaplastic thyroid carcinoma imaging and therapy. *Nanoscale*. 2021;13(35):15021–15030. doi:10.1039/d1nr02892h
49. Wang K, Wang S, Chen K, Zhao Y, Ma X, Wang L. Doxorubicin-loaded melanin particles for enhanced chemotherapy in drug-resistant anaplastic thyroid cancer cells. *J Nanomater*. 2018;2018:1–6.
50. Han X, Xu X, Tang Y, et al. BSA-stabilized mesoporous organosilica nanoparticles reversed chemotherapy resistance of anaplastic thyroid cancer by increasing drug uptake and reducing cellular efflux. *Front Mol Biosci*. 2020;7:610084. doi:10.3389/fmolb.2020.610084
51. Wang C, Zhang R, Tan J, et al. Effect of mesoporous silica nanoparticles co-loading with 17-AAG and Torin2 on anaplastic thyroid carcinoma by targeting VEGFR2. *Oncol Rep*. 2020;43(5):1491–1502. doi:10.3892/or.2020.7537
52. Zhou M, Chen Y, Adachi M, et al. Single agent nanoparticle for radiotherapy and radio-photothermal therapy in anaplastic thyroid cancer. *Biomaterials*. 2015;57:41–49. doi:10.1016/j.biomaterials.2015.04.013
53. Liu Y, Ma Y, Peng X, et al. Cetuximab-conjugated perfluorohexane/gold nanoparticles for low intensity focused ultrasound diagnosis ablation of thyroid cancer treatment. *Sci Technol Adv Mater*. 2021;21(1):856–866. doi:10.1080/14686996.2020.1855064
54. Nilubol N, Yuan Z, Paciotti GF, et al. Novel dual-action targeted nanomedicine in mice with metastatic thyroid cancer and pancreatic neuroendocrine tumors. *J Natl Cancer Inst*. 2018;110(9):1019–1029. doi:10.1093/jnci/djy003
55. Amaral M, Charmier AJ, Afonso RA, et al. Gold-based nanoplataform for the treatment of anaplastic thyroid carcinoma: a step forward. *Cancers*. 2021;13(6). doi:10.3390/cancers13061242
56. Lvov Y, Abdullayev E. Green and functional polymer-clay nanotube composites with sustained release of chemical agents. *Prog Polym Sci*. 2013;38:1690. doi:10.1016/j.progpolymsci.2013.05.009
57. Vergaro V, Lvov YM, Leporatti S. Halloysite clay nanotubes for resveratrol delivery to cancer cells. *Macromol Biosci*. 2012;12(9):1265–1271. doi:10.1002/mabi.201200121
58. Kelly HM, Deasy PB, Ziaka E, Claffey N. Formulation and preliminary in vivo dog studies of a novel drug delivery system for the treatment of periodontitis. *Int J Pharm*. 2004;274(1–2):167–183. doi:10.1016/j.ijpharm.2004.01.019
59. Massaro M, Piana S, Colletti CG, et al. Multicavity halloysite-amphiphilic cyclodextrin hybrids for co-delivery of natural drugs into thyroid cancer cells. *J Mater Chem B*. 2015;3(19):4074–4081. doi:10.1039/c5tb00564g
60. Casali PG, Trama A. Rationale of the rare cancer list: a consensus paper from the Joint Action on Rare Cancers (JARC) of the European Union (EU). *ESMO Open*. 2020;5(2):e000666. doi:10.1136/esmoopen-2019-000666
61. Lai WA, Hang JF, Liu CY, et al. PAX8 expression in anaplastic thyroid carcinoma is less than those reported in early studies: a multi-institutional study of 182 cases using the monoclonal antibody MRQ-50. *Virchows Arch*. 2020;476(3):431–437. doi:10.1007/s00428-019-02708-4
62. Gule MK, Chen Y, Sano D, et al. Targeted therapy of VEGFR2 and EGFR significantly inhibits growth of anaplastic thyroid cancer in an orthotopic murine model. *Clin Cancer Res*. 2011;17(8):2281–2291. doi:10.1158/1078-0432.CCR-10-2762
63. Ding ZY, Huang YJ, Tang JD, Li G, Jiang PQ, Wu HT. Silencing of hypoxia-inducible factor-1alpha promotes thyroid cancer cell apoptosis and inhibits invasion by downregulating WWP2, WWP9, VEGF and VEGFR2. *Exp Ther Med*. 2016;12(6):3735–3741. doi:10.3892/etm.2016.3826
64. Nakayama M, Okano T. [Drug delivery systems using nano-sized drug carriers]. *Gan To Kagaku Ryoho*. 2005;32(7):935–940. Japanese.
65. Ke Y, Xiang C. Transferrin receptor-targeted HMSN for sorafenib delivery in refractory differentiated thyroid cancer therapy. *Int J Nanomedicine*. 2018;13:8339–8354. doi:10.2147/IJN.S187240
66. Zhu R, Wang Z, Liang P, et al. Efficient VEGF targeting delivery of DOX using Bevacizumab conjugated SiO(2)@LDH for anti-neuroblastoma therapy. *Acta Biomater*. 2017;63:163–180. doi:10.1016/j.actbio.2017.09.009

67. Missiaen R, Morales-Rodriguez F, Eelen G, Carmeliet P. Targeting endothelial metabolism for anti-angiogenesis therapy: a pharmacological perspective. *Vascul Pharmacol*. 2017;90:8–18. doi:10.1016/j.vph.2017.01.001
68. Zhao Y, Adjei AA. Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor. *Oncologist*. 2015;20 (6):660–673. doi:10.1634/theoncologist.2014-0465
69. Jolly C, Morimoto RI. Role of the heat shock response and molecular chaperones in oncogenesis and cell death. *J Natl Cancer Inst*. 2000;92 (19):1564–1572. doi:10.1093/jnci/92.19.1564
70. Porter JR, Fritz CC, Depew KM. Discovery and development of Hsp90 inhibitors: a promising pathway for cancer therapy. *Curr Opin Chem Biol*. 2010;14(3):412–420. doi:10.1016/j.cbpa.2010.03.019
71. Kim YS, Alarcon SV, Lee S, et al. Update on Hsp90 inhibitors in clinical trial. *Curr Top Med Chem*. 2009;9(15):1479–1492. doi:10.2174/156802609789895728
72. Ahmed M, Hussain AR, Bavi P, et al. High prevalence of mTOR complex activity can be targeted using Torin2 in papillary thyroid carcinoma. *Carcinogenesis*. 2014;35(7):1564–1572. doi:10.1093/carcin/bgu051
73. Beauchamp EM, Platanias LC. The evolution of the TOR pathway and its role in cancer. *Oncogene*. 2013;32(34):3923–3932. doi:10.1038/onc.2012.567
74. Tavares C, Eloy C, Melo M, et al. mTOR pathway in papillary thyroid carcinoma: different contributions of mTORC1 and mTORC2 complexes for tumor behavior and SLC5A5 mRNA Expression. *Int J Mol Sci*. 2018;19(5):1448. doi:10.3390/ijms19051448
75. Faustino A, Couto JP, Populo H, et al. mTOR pathway overactivation in BRAF mutated papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 2012;97(7):E1139–49. doi:10.1210/jc.2011-2748
76. Sidera K, Patsavoudi E. HSP90 inhibitors: current development and potential in cancer therapy. *Recent Pat Anticancer Drug Discov*. 2014;9 (1):1–20. doi:10.2174/15748928113089990031
77. Chen Y, Chen H, Shi J. In vivo bio-safety evaluations and diagnostic/therapeutic applications of chemically designed mesoporous silica nanoparticles. *Adv Mater*. 2013;25(23):3144–3176. doi:10.1002/adma.201205292
78. Tessier-Cloutier B, Kortekaas KE, Thompson E, et al. Major p53 immunohistochemical patterns in in situ and invasive squamous cell carcinomas of the vulva and correlation with TP53 mutation status. *Mod Pathol*. 2020;33(8):1595–1605. doi:10.1038/s41379-020-0524-1
79. Yoo SK, Song YS, Lee EK, et al. Integrative analysis of genomic and transcriptomic characteristics associated with progression of aggressive thyroid cancer. *Nat Commun*. 2019;10(1):2764. doi:10.1038/s41467-019-10680-5
80. Morgan MA, Lawrence TS. Molecular pathways: overcoming radiation resistance by targeting DNA damage response pathways. *Clin Cancer Res*. 2015;21(13):2898–2904. doi:10.1158/1078-0432.CCR-13-3229
81. Varinelli L, Caccia D, Volpi CC, et al. 4-IPP, a selective MIF inhibitor, causes mitotic catastrophe in thyroid carcinomas. *Endocr Relat Cancer*. 2015;22(5):759–775. doi:10.1530/ERC-15-0299
82. Huang S, Zhang L, Xu M, et al. Co-Delivery of (131) I and prima-1 by self-assembled CD44-targeted nanoparticles for anaplastic thyroid carcinoma theranostics. *Adv Healthc Mater*. 2021;10(3):e2001029. doi:10.1002/adhm.202001029
83. Najafi M, Mortezaee K, Majidpoor J. Cancer stem cell (CSC) resistance drivers. *Life Sci*. 2019;234:116781. doi:10.1016/j.lfs.2019.116781
84. Wang T, Shigdar S, Gantier MP, et al. Cancer stem cell targeted therapy: progress amid controversies. *Oncotarget*. 2015;6(42):44191–44206. doi:10.18632/oncotarget.6176
85. Zhu Z, Hao X, Yan M, et al. Cancer stem/progenitor cells are highly enriched in CD133+CD44+ population in hepatocellular carcinoma. *Int J Cancer*. 2010;126(9):2067–2078. doi:10.1002/ijc.24868
86. Cheng JX, Liu BL, Zhang X. How powerful is CD133 as a cancer stem cell marker in brain tumors?. *Cancer Treat Rev*. 2009;35(5):403–408. doi:10.1016/j.ctrv.2009.03.002
87. Yang ZL, Zheng Q, Yan J, Pan Y, Wang ZG. Upregulated CD133 expression in tumorigenesis of colon cancer cells. *World J Gastroenterol*. 2011;17(7):932–937. doi:10.3748/wjg.v17.i7.932
88. Ge MH, Zhu XH, Shao YM, et al. Synthesis and characterization of CD133 targeted aptamer-drug conjugates for precision therapy of anaplastic thyroid cancer. *Biomater Sci*. 2021;9(4):1313–1324. doi:10.1039/d0bm01832e
89. Maggisano V, Celano M, Lombardo GE, et al. Silencing of hTERT blocks growth and migration of anaplastic thyroid cancer cells. *Mol Cell Endocrinol*. 2017;448:34–40. doi:10.1016/j.mce.2017.03.007
90. Takeda T, Inaba H, Yamazaki M, et al. Tumor-specific gene therapy for undifferentiated thyroid carcinoma utilizing the telomerase reverse transcriptase promoter. *J Clin Endocrinol Metab*. 2003;88(8):3531–3538. doi:10.1210/jc.2002-021856
91. Shepelev MV, Kalinichenko SV, Saakian EK, Korobko IV. Xenobiotic response elements (XREs) from human CYP1A1 gene enhance the hTERT promoter activity. *Dokl Biochem Biophys*. 2019;485(1):150–152. doi:10.1134/S1607672919020200
92. Chang A, Ling J, Ye H, Zhao H, Zhuo X. Enhancement of nanoparticle-mediated double suicide gene expression driven by 'E9-hTERT promoter' switch in dedifferentiated thyroid cancer cells. *Bioengineered*. 2021;12(1):6572–6578. doi:10.1080/21655979.2021.1974648
93. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer*. 2013;13(3):184–199. doi:10.1038/nrc3431
94. Prabhakar U, Maeda H, Jain RK, et al. Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. *Cancer Res*. 2013;73(8):2412–2417. doi:10.1158/0008-5472.CAN-12-4561
95. Miller MA, Gadde S, Pfirschke C, et al. Predicting therapeutic nanomedicine efficacy using a companion magnetic resonance imaging nanoparticle. *Sci Transl Med*. 2015;7(314):314ra183. doi:10.1126/scitranslmed.aac6522
96. Arrieta O, Medina LA, Estrada-Lobato E, Ramirez-Tirado LA, Mendoza-Garcia VO, de la Garza-Salazar J. High liposomal doxorubicin tumour tissue distribution, as determined by radiopharmaceutical labelling with (99m)Tc-LD, is associated with the response and survival of patients with unresectable pleural mesothelioma treated with a combination of liposomal doxorubicin and cisplatin. *Cancer Chemother Pharmacol*. 2014;74(1):211–215. doi:10.1007/s00280-014-2477-x
97. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. *Nature* . 2006;440(7083):463–469. doi:10.1038/nature04710
98. Wadhwa S, Wadhwa P, Dinda AK, Gupta NP. Differential expression of potassium ion channels in human renal cell carcinoma. *Int Urol Nephrol*. 2009;41(2):251–257. doi:10.1007/s11255-008-9459-z
99. Masi A, Becchetti A, Restano-Cassulini R, et al. hERG1 channels are overexpressed in glioblastoma multiforme and modulate VEGF secretion in glioblastoma cell lines. *Br J Cancer*. 2005;93(7):781–792. doi:10.1038/sj.bjc.6602775

100. Pillozzi S, Brizzi MF, Balzi M, et al. HERG potassium channels are constitutively expressed in primary human acute myeloid leukemias and regulate cell proliferation of normal and leukemic hemopoietic progenitors. *Leukemia*. 2002;16(9):1791–1798. doi:10.1038/sj.leu.2402572
101. Li G, Hu Z, Yin H, et al. A novel dendritic nanocarrier of polyamidoamine-polyethylene glycol-cyclic RGD for "smart" small interfering RNA delivery and in vitro antitumor effects by human ether-a-go-go-related gene silencing in anaplastic thyroid carcinoma cells. *Int J Nanomedicine*. 2013;8:1293–1306. doi:10.2147/IJN.S41555
102. Bartolome RA, Martin-Regalado A, Jaen M, et al. Protein tyrosine phosphatase-1B inhibition disrupts IL13Ralpha2-Promoted invasion and metastasis in cancer cells. *Cancers*. 2020;12(2):500. doi:10.3390/cancers12020500
103. Gu M. IL13Ralpha2 siRNA inhibited cell proliferation, induced cell apoptosis, and suppressed cell invasion in papillary thyroid carcinoma cells. *Onco Targets Ther*. 2018;11:1345–1352. doi:10.2147/OTT.S153703
104. Tabeshpour J, Mehri S, Shaebani Behbahani F, Hosseinzadeh H. Protective effects of Vitis vinifera (grapes) and one of its biologically active constituents, resveratrol, against natural and chemical toxicities: a comprehensive review. *Phytother Res*. 2018;32(11):2164–2190. doi:10.1002/ptr.6168
105. Xiong L, Lin XM, Nie JH, Ye HS, Liu J. Resveratrol and its nanoparticle suppress doxorubicin/docetaxel-resistant anaplastic thyroid cancer cells in vitro and in vivo. *Nanotheranostics*. 2021;5(2):143–154. doi:10.7150/ntno.53844
106. Ravera S, Reyna-Neyra A, Ferrandino G, Amzel LM, Carrasco N. The Sodium/Iodide Symporter (NIS): molecular physiology and preclinical and clinical applications. *Annu Rev Physiol*. 2017;79:261–289. doi:10.1146/annurev-physiol-022516-034125
107. Schmohl KA, Dolp P, Schug C, et al. Reintroducing the sodium-iodide symporter to anaplastic thyroid carcinoma. *Thyroid*. 2017;27(12):1534–1543. doi:10.1089/thy.2017.0290
108. Landa I, Ibrahimpasic T, Boucai L, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. *J Clin Invest*. 2016;126(3):1052–1066. doi:10.1172/JCI85271
109. Raeesi V, Chan WC. Improving nanoparticle diffusion through tumor collagen matrix by photo-thermal gold nanorods. *Nanoscale*. 2016;8(25):12524–12530. doi:10.1039/c5nr08463f
110. Ku G, Zhou M, Song S, Huang Q, Hazle J, Li C. Copper sulfide nanoparticles as a new class of photoacoustic contrast agent for deep tissue imaging at 1064 nm. *ACS Nano*. 2012;6(8):7489–7496. doi:10.1021/nn302782y
111. Li S, Zhang D, Sheng S, Sun H. Targeting thyroid cancer with acid-triggered release of doxorubicin from silicon dioxide nanoparticles. *Int J Nanomedicine*. 2017;12:5993–6003. doi:10.2147/IJN.S137335
112. Qian CG, Chen YL, Feng PJ, et al. Conjugated polymer nanomaterials for theranostics. *Acta Pharmacol Sin*. 2017;38(6):764–781. doi:10.1038/aps.2017.42
113. Wohlfart S, Khalansky AS, Gelperina S, et al. Efficient chemotherapy of rat glioblastoma using doxorubicin-loaded PLGA nanoparticles with different stabilizers. *PLoS One*. 2011;6(5):e19121. doi:10.1371/journal.pone.0019121
114. Gigliotti CL, Ferrara B, Occhipinti S, et al. Enhanced cytotoxic effect of camptothecin nanosponges in anaplastic thyroid cancer cells in vitro and in vivo on orthotopic xenograft tumors. *Drug Deliv*. 2017;24(1):670–680. doi:10.1080/10717544.2017.1303856
115. Brierley J, Sherman E. The role of external beam radiation and targeted therapy in thyroid cancer. *Semin Radiat Oncol*. 2012;22(3):254–262. doi:10.1016/j.semradonc.2012.03.010
116. Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. *Nat Rev Cancer*. 2003;3(5):380–387. doi:10.1038/nrc1071
117. Kim H, Kim SW, Seok KH, et al. Hypericin-assisted photodynamic therapy against anaplastic thyroid cancer. *Photodiagnosis Photodyn Ther*. 2018;24:15–21. doi:10.1016/j.pdpdt.2018.08.008
118. Wang HZ, Zhang Y, Xie LP, Yu XY, Zhang RQ. Effects of genistein and daidzein on the cell growth, cell cycle, and differentiation of human and murine melanoma cells(1). *J Nutr Biochem*. 2002;13(7):421–426. doi:10.1016/s0955-2863(02)00184-5
119. Chodon D, Ramamurty N, Sakthisekaran D. Preliminary studies on induction of apoptosis by genistein on HepG2 cell line. *Toxicol In Vitro*. 2007;21(5):887–891. doi:10.1016/j.tiv.2007.01.023
120. Yang Y, Liu J, Li X, Li JC. PCDH17 gene promoter demethylation and cell cycle arrest by genistein in gastric cancer. *Histol Histopathol*. 2012;27(2):217–224. doi:10.14670/HH-27.217
121. Ahn JC, Biswas R, Chung PS. Combination with genistein enhances the efficacy of photodynamic therapy against human anaplastic thyroid cancer cells. *Lasers Surg Med*. 2012;44(10):840–849. doi:10.1002/lsm.22095
122. Huang WY, Cai YZ, Zhang Y. Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. *Nutr Cancer*. 2010;62(1):1–20. doi:10.1080/01635580903191585
123. Buhklari S, Memon S, Tahir MM, Bhanjer MI. Synthesis, characterization and investigation of antioxidant activity of cobalt–quercetin complex. *J Mol Struct*. 2008;892:39–46. doi:10.1016/j.molstruc.2008.04.050
124. Wei Y, Ye XL, Shang XG, et al.. Enhanced oral bioavailability of silybin by a supersaturatable self-emulsifying drug delivery system (S-SEDDS). *Colloids Surf A*. 2012;396:22–28. doi:10.1016/j.colsurfa.2011.12.025
125. Yu T, Tong L, Ao Y, Zhang G, Liu Y, Zhang H. Novel design of NIR-triggered plasmonic nanodots capped mesoporous silica nanoparticles loaded with natural capsaicin to inhibition of metastasis of human papillary thyroid carcinoma B-CPAP cells in thyroid cancer chemo-photothermal therapy. *J Photochem Photobiol B*. 2019;197:111534. doi:10.1016/j.jphotobiol.2019.111534
126. Janssen EM, Dy SM, Meara AS, Kneuertz PJ, Presley CJ, Bridges JFP. Analysis of patient preferences in lung cancer - estimating acceptable tradeoffs between treatment benefit and side effects. *Patient Prefer Adherence*. 2020;14:927–937. doi:10.2147/PPA.S235430
127. Xu M, Yim W, Zhou J, et al. The application of organic nanomaterials for bioimaging, drug delivery, and therapy. *IEEE Nanotechnol Mag*. 2021;15(4):8–28. doi:10.1109/MNANO.2021.3081758
128. Lechuga-Islas VD, Trejo-Maldonado M, Anufriev I, et al. All-aqueous, surfactant-free, and pH-driven nanoformulation methods of dual-responsive polymer nanoparticles and their potential use as nanocarriers of pH-sensitive drugs. *Macromol Biosci*. 2023;23(1):e2200262. doi:10.1002/mabi.202200262
129. Deng C, Zhao J, Zhou S, et al. The vascular disrupting agent CA4P improves the antitumor efficacy of CAR-T cells in preclinical models of solid human tumors. *Mol Ther*. 2020;28(1):75–88. doi:10.1016/j.ymthe.2019.10.010
130. Iqbal MA, Li M, Lin J, et al. Preliminary study on the sequencing of whole genomic methylation and transcriptome-related genes in thyroid carcinoma. *Cancers*. 2022;14(5). doi:10.3390/cancers14051163

131. Chudasama V. Antibody - Drug conjugates (ADC) - Drug discovery today: technologies. *Drug Discov Today Technol*. 2018;30:1–2. doi:10.1016/j.ddtec.2018.11.003
132. Lee S, Oudjedi F, Kirk A, Paliouras M, Trifiro M. Photothermal therapy of papillary thyroid cancer tumor xenografts with targeted thyroid stimulating hormone receptor antibody functionalized multiwalled carbon nanotubes. *Cancer Nanotechnol*. 2023;14(1). doi:10.1186/s12645-023-00184-9
133. Yu Y, Li J, Song B, et al. Polymeric PD-L1 blockade nanoparticles for cancer photothermal-immunotherapy. *Biomaterials*. 2022;280:121312. doi:10.1016/j.biomaterials.2021.121312
134. Liang J, Jin Z, Kuang J, et al. The role of anlotinib-mediated EGFR blockade in a positive feedback loop of CXCL11-EGF-EGFR signalling in anaplastic thyroid cancer angiogenesis. *Br J Cancer*. 2021;125(3):390–401. doi:10.1038/s41416-021-01340-x
135. Yin M, Di G, Bian M. Dysfunction of natural killer cells mediated by PD-1 and Tim-3 pathway in anaplastic thyroid cancer. *Int Immunopharmacol*. 2018;64:333–339. doi:10.1016/j.intimp.2018.09.016