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Review Article

Nanomaterials as targeted delivery system of therapeutics for inhibition of cancer

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Abstract

Cancer, a disease with complex pathological process, is the principal cause of mortality and morbidity throughout the world. Conventional chemotherapy faces drawbacks regarding its low bioavaiability, insolubility, high dose requirements, low therapeutic indices, cytotoxicity, multiple drug resistance-development, biological barriers related obstruction, and non-specific targeting. Cancer drug resistance includes over-expression of drug efflux transporters, hypoxic environment, and defective apoptotic pathways. To overcome these discrepancies, a lot of nanomaterials (NMs), as emerging delivery system, have attracted attention for carrying and delivering therapeutics to the desired sites of interest. For improving the targeting potential of the anticancer cargos, NMs are optimized for their sizes, shapes, and surfaces for enhancing their circulation time and targeting efficiency. The NMs through encapsulation or conjugation of cargos with ligands may target them to the cancer site/s with enhanced therapeutic efficacy in a controlled release manner. Generally, NMs, as cancer therapy, are utilized to target cancer cells, tumor microenvironment, and immune system mainly through enhanced permeability and retention (EPR) effect, stimuli-responsive targeting or modifying their surfaces with targeting ligands such as transferin, integrins, sugar, folic acid and antibodies for the enhancement of tissue targeting recognition and their internalization. This review demonstrates mainly the biomedical applications of NMs as delivery vehicles or systems functionalized with ligands and therapeutic agents to target cancer cells / tissues passively, actively or physically with higher inhibitory therapeutic efficacies against cancer.

Keywords: Cancer; Conventional chemotherapy; Nanomaterials; Biomedical applications; Therapeutic targeting; Inhibitory therapeutic efficacies

Introduction

Cancer includes a conjunction of different diseases owing to the consequence of gene mutations involving unregulated growth of cells through the interference with different cell processes such as attachment, division, or motility, and spreading into other tissues to form metastasis, leading to mortality [1-4]. Exposure of toxicants / pollutants, infections, poor diet, obesity, or lack of physical activity may damage genes and other bio-molecules, leading to carcinogenic mutations [5-7]. In general, surgery or radiation therapy or chemotherapy as well as gene therapy, as the primary therapeutic approaches, are utilized to target solid tumors or destroy cancerous cells respectively for the survival of patients [8-11]. However, chemotherapeutics / genes and radiation not only kill cancerous cells but also destruct normal healthy cells or surrounding cells respectively owing to their non-specificity to target diseased cells, associated with the requirements of high toxic drug dosages, toxic side effects, drug non-targeting for blood-brain barrier and other biological barriers, and emergence of drug resistance, aggravating the healthy condition of the patients [12-14].

The multiple factors for the developing of drug-resistance in cancerous cells include the evolution and spontaneous intrinsic mutations, and the consequence of the acquired or extrinsic uptake of drugs [15]. The chief mechanisms of drug resistance denote the drug inactivation, drug efflux, drug target alteration, reduced drug uptake, DNA damage repair and cell death -inhibition [16]. Epithelial-mesenchymal transition (EMT), a biological process to trigger tumors to metastatic forms, may induce apoptosis-resistant cancer progression through induction of over-expressed pre-mRNA processing factor (PRPF) [17-19]. Over-expression of tau, a microtubular-associated protein, has been disclosed to engage in drug inactivation in different cancer cells [20]. Different mutations in tyrosine kinase inhibitors (TKI) and epidermal growth factor receptor (EGFR) in lung cancer have shown their enhanced drug resistance accompanied by the amplification in the MET gene [21]. The alteration or over-expression of cell transporter proteins (ATP-binding cassette) or drug efflux protein (P-gp) may affect the drug uptake, export and accumulation, making chemotherapeutics unusable or pumping outside the cells, developing drug resistance [22]. Apoptosis and autophagy, comprehended as programmed cell death and necrosis, may be inhibited or modified to induce cancer cell-resistance. Apoptosis-resistance may be gained through receptors like the tumor necrosis factor family, or mitochondria, whereas autophagy is linked to hypoxic processes [23]. Changes in the programmed cell death ligand (PD-L1) may generate resistance in anaplastic lymphoma kinase proteins in lung cancer, while resistance to phosphoinositide 3-kinase (PI3K) may reduce oxidative stress and prevent cell death in a hypoxia micro-tumor environment [24]. DNA damage repair systems may be constrained by gene silencing or mutation to develop resistance in cancer cells,

resulting in further mutations and enhanced resistance [25]. Tumor heterogeneity and microenvironment can also take part in drug resistance through differential gene expression, motility or metastatic potential, relating to epigenetic, genetic, proteomic and transcriptomic factors, such as, chromosomal rearrangements or translocations of RNA and lesion-specific responses, and interfering and modifying cell communication by extracellular matrix growth factors and stromal cells [26-28].

Gene therapy involves the delivery, replacement or transfer of defective genetic materials with the functional and the healthy copies of that genes to cancerous cells or the surrounding tissue to cause cell death, or reduce / eliminate the growth of cancer cells, or to regulate the altered genes or genetic mutations of cancer by silencing or enhancing the expression of specific genes [10,11].

To overcome the conventional therapeutic obstacles against cancer-growth, nanotechnology-based NMs (organic, inorganic and lipid) have attracted attention and emerged as optimistic delivery systems as well as carriers for cancer therapy owing to their unique physicochemical and biological characteristics for specific targeting of therapeutics to diseased site/s [9,14,29-31].

It is reported that nanomaterials-conjugated cargos such as drugs including herbal, genes, sugars, proteins and antibodies may be selectively accumulated in tumors through EPR effect with reduced peripheral exposure, and may extravasate via enlarged pores of capillary endothelium as passive targeting [32-34]. Cancer cells can over-express a lot of tumor-specific receptors, such as for polyunsaturated fatty acids, monoclonal antibodies, folic acid, aptamers, oligopeptides, transferrin, and hyaluronic acid, utilized to target for delivering cytotoxic agents into tumors [35]. NMs are functionalized with various ligands such as peptides, proteins and antibodies for interacting with over-expressed receptors at the target site/s, and accumulated through active targeting, and controlled cargos-release, accompanied by triggering a change in different stimuli such as pH, temperature, response to enzymes or antigens, magnetic field, heat and light [36-38]. This review is focused chiefly on the recent advances of the significant targeted therapeutic efficacies of a lot of NMs conjugated with ligands and cargos against cancer through passive, receptor-mediated active and / or endogenous / exogenous stimuli -responsive targeting and release of cargos to the specific site/s of interest.

Nanomaterials used in cancer therapy

A few organic polymeric NMs include nanogel/hydrogel/aerogel -based polylactic acid (PLA), poly (amino acids), poly (lactic-co-glycolic acid) (PLGA), poly (ε-caprolactone) (PCL), polyacrylamide, polyacrylate, poly (styrene-maleic anhydride), N-(2-hydroxypropyl)-methacrylamide copolymer (HPMA), dendrimers, chondroitin sulfate (CS), gelatin, dextran (DEX), alignate, hyaluronic acid, chitosan, poly ethylene glycol (PEG), co-polymeric micelle, and graphene oxide, whereas lipid-based NMs include mainly liposomes, exosomes, solid lipid nanoparticles (SLNs), nano/micro lipid-micelle bubbles and lipid nano-emulsions (LNEs) or nanostructured lipid carriers (NLCs) [39-58, 31,34].

A few inorganic NMs include nanorod, quantum dots, layered double hydroxides, carbon dot/nanotubes, mesoporous silica, metallic and magnetic NPs [42,44,53,56,58-61,10]. A few other NMs include albumin-based nanocarriers, monoclonal antibody, and hybrid NPs [44,39,40,58,56,10,62-66].

Surface functionalization

Surface-functionalizations for targeted delivery of the NMs with ligands and cargos may be achieved through electrostatic adsorption, click chemistry or covalent attachment [67,68]. Hydrophobic drugs may be attached by the π-π stacking mechanism to improve dispersion and facilitate release of the drugs and genes [69-71]. A few targeting molecules to deliver selectively to cancerous cells may be anchored through click chemistry or covalent modifications [72-75]. Biological molecules such as proteins, peptides and nucleic acid may be anchored through electrostatic attraction, click chemistry or covalent interactions to enable ameliorated biocompatibility, solubility and enhanced shielding from uncontrolled degradation and cleavage [69,70]. A few ferromagnetic and magnetic particles may be entangled within the materials' cavities or anchored to their surfaces for magnetic field-assisted particular delivery [76].

Mechanisms of targeting

NMs / NPs mediated drug targeting to cancerous cells enhances the therapeutic efficacy of the delivery systems or nanocarriers specifically to protect normal cells from cytotoxicity. The targeting mechanisms may be divided into passive, active and stimuli-responsive targeting (Figures 1and 2).

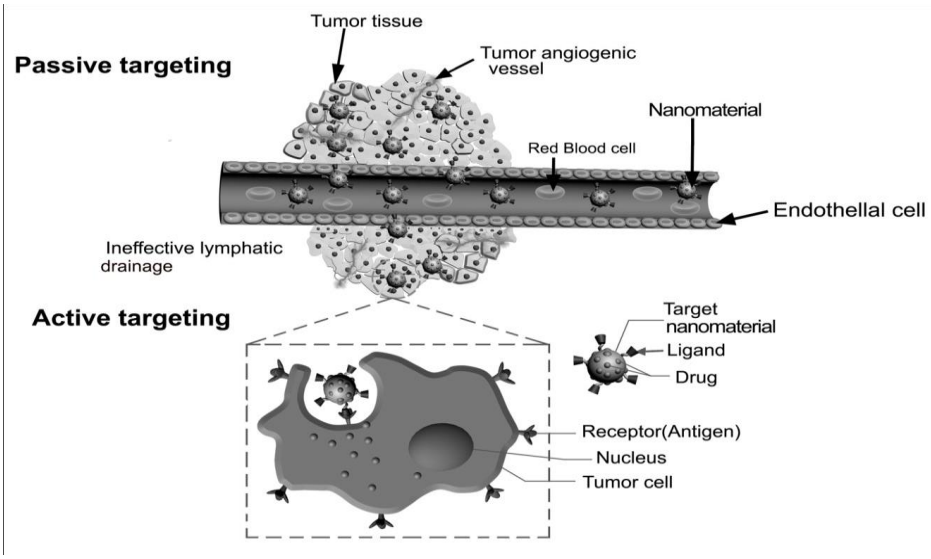

Figure 1. Passive targeting of nanomaterials in the target tissue through EPR effect, whereas active tissue targeting of ligand-conjugated nanomaterials through specific recognition of over-expressed receptor/s.

Passive targeting

In passive targeting of NMs, natural anatomical structures and physiological processes are taken into consideration, which direct their *in vivo* distribution and disposition. Passive targeting can be done by alteration of materials' composition, surface charge, and size.

Passive targeting is utilized considering the different characteristics of tumor and normal cells or tissues. High proliferation of cancerous cells inducts neovascularization, and enlarged pores in the vascular wall results in worsening particles-selectivity of tumor vessels in comparison to normal vessels [40]. The defective and rapid angiogenesis enables drug-loaded NMs to penetrate the leaky blood vessels and to supply, accumulate and release drug contents within tumor cells/tissues through EPR effect of NMs owing to also poor lymphatic cancerous drainage [40,41].

Active targeting

In active targeting, there is physical or chemical modifications of NMs' surface which help the NMs to be targeted towards a particular cell basically through a receptor mediated endocytosis.

Active targeting is utilized to target cancer cells through the direct interactions between receptors and ligands. The ligands on the NMs' surface are used to target the over-expressed receptor molecules of cancer cell-surface to internalize NMs and to release therapeutic cargos through receptor-mediated endocytosis distinguishing the non-targeted healthy cells [40]. The targeting ligand-moieties include chiefly amino acids, peptides, monoclonal antibodies, carbohydrates and vitamins, and the receptors include mainly folate, transferrin, glycoproteins, and the epidermal growth factor, while the ligands bind specifically to receptors on targeted cells [40].

Stimuli-responsive targeting

Target-specific deliveries of nanomaterial therapeutics may be performed on the basis of stimuli-responsive factors inducted by either endogenous (pH, enzyme, redox) or exogenous (light, temperature, acoustic) stimuli [42-44,77].

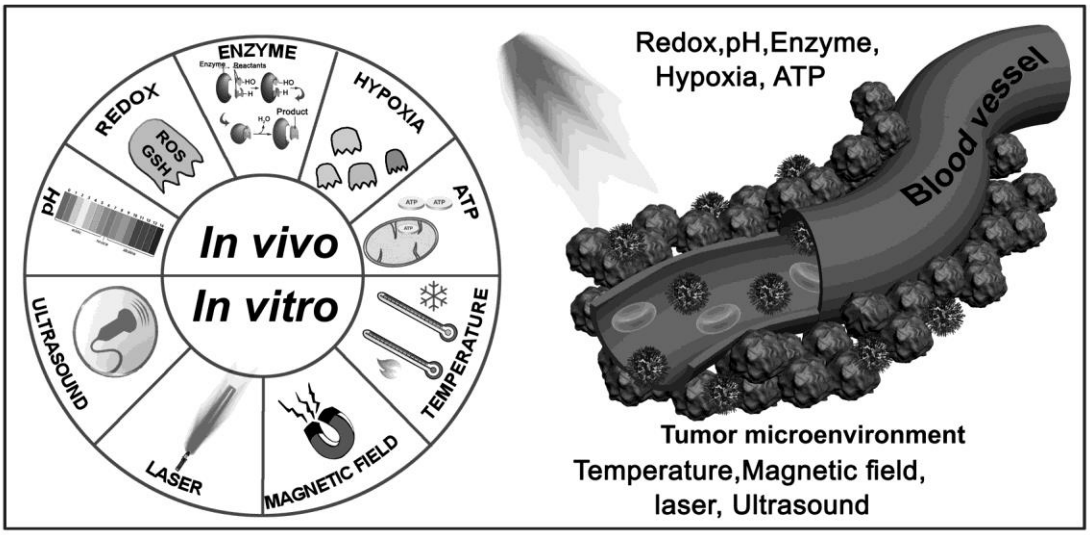

Figure 2. Schematic representation of endogenous and exogenous stimuli-responsive targeting to tumor tissue.

Biomedical applications of nanomaterials as delivery vehicles/systems

In general, NMs are utilized to deliver to targeted cells/tissues as cargos-carriers or systems to get effective therapeutic efficacy against diseases [59,78-82].

Targeting to cancerous cells

A few cargos-loaded NMs such as polymers, micelle, liposome, mesoporous silica, carbon nanotube, iron oxide, layered double hydroxide, protein, and PEI-modified nanographene oxide have been utilized to get higher therapeutic efficacies against multi/drug resistance, cancer cells / cancer, drug toxicity/side effect, neurotoxicity, and tumor proliferation through passive targeting to cancerous cells (Table 1).

A few investigators have utilized different polymeric NPs to trap various cargo molecules such as anti-miR10b/anti-miR-21, miR-34a/DOX, retinoic acid/DOX, CIS/RAPA, curcumin (CUR), CUR-anti-P-gp, CUR-5-FU, bortezomib, PTX, CPT, epigallocatechin gallate, green tea (Polyphenol EGCG), phytolaccaceae, polygalaceae, quercetin, resveratrol, noscapine or betulinic acid through electrostatic or hydrophobic bonding to target and release them against various cancer and cancer cells for getting higher anti-cancer efficacy [43,56,58] (Table 1). Several polymeric NMs such as cyclodextrin-PEG, γ-cyclodextrin-propylene diamine (GCD-PDA), PEG-PLGA, HA-PLGA, PAMAM dendrimers, poly-L-lysine dendrimers, PEG-PLL, FA-chitosan, nano gel, hydrogel and silica-polymer have been utilized to load / conjugate with CPT, BBR, DTX, CIS and BBR, DOX, epigallocatechin gallate/siRNA, CIS/DOX, PTX, CUR and P53 through covalent / electrostatic / chelation or π-π bonding for treating different cancer and cancer cells, solid malignancies, EAC tumors, solid tumor, the growth of tumor cells and adenocarcinoma cells to get higher anti-cancer efficacies [43,44,53,58,49] (Table 1, and Table 1. Contd. 1).

Table 1. A few nanomaterial therapeutics used in cancer therapy.

Nanomaterials	Therapeutics	Enhanced efficacy target against
Polymers	Anti-miR10b/anti-miR-21, MiR-34a/DOX, Retinoic acid/DOX	Breast cancer
	CIS/RAPA	Melanoma
	Curcumin	Human breast cancer cells (MDA-MB-231), prostate cancer, pancreatic cancer cells (BxPC3, MiaPaca), human epithelian cervical cancer cells (HeLa), drug resistant KB-V1 cervical cancer cells
	Curcumin-anti-P-gp	MDA-MB-231 cells
	Curcumin-5-FU	Colon cancer
	Bortezomib	TNBC(MDA-MB-468, HCC1937), proteasome function, tumor growth
	Paclitaxel	Lung cancer
	Camptothecin (CPT)	Breast cancer, glioma
	Epigallocatechin gallate	Prostate cancer
	Green tea (Polyphenol EGCG)	Prostate cancer cell growth
	Phytolaccaceae	Lung adenocarcinoma, A549 lung cancer cells
	Polygalaceae	A549 lung cancer cells
	Quercetin	HeLa cells, IGROV-1 tumors
	Resveratrol	NCI-H460 non-small lung cancer cells, prostate cancer
	Noscapine	MCF-7 breast cancer cells
	Betulinic acid	Lung cancer
Cyclodextrin-PEG	CPT	Lung and ovarian cancer
γ-cyclodextrin-propylene diamine (GCD-PDA)	Berberine (BBR)	4T1 cancer cells
PEG-PLGA	DTX	Solid malignancies
HA-PLGA	BBR	HeLa, MCF-7 cancer cells, EAC tumors
PAMAM dendrimers	CIS; BBR	Lung cancer cells (NCI-H460); Human breast cancer cells (MCF-7, MDA-MB-468)
Poly-L-lysine (PLL) dendrimers	DOX	Solid tumor
PEG-PLL	CPT	Murine C26, human colon carcinoma HT-29 tumors
FA-chitosan	BBR	Growth of CNE1 tumor cells

Graphene NMs such as GO-hydrogel, GO-aerogel, rGO, rGO-iron, rGO-polydomamine, GO-gold, amphiphilic graphene ethydium bromide, PEI-NGO and graphene quantum dot have been used to anchore or load DOX, 5FU, PTX, MTX, CPT, RV, CUR, BBR, polyphenolic green tea, glucose, hSET1 antisense, miRNA-101, pDNA, ADM/anti-miR-21 and cysteamine through hydrophobic/electrostatic bonding against various cancer and cancer cells, and tumors for achieving higher anti-cancer therapeutic efficacies [46,47,52,54,55,48,50,51,53,43] (Table 1. Contd. 1). Several investigators have exhibited the targeting capability of carbon dot and nanotube (CNT) through nanomaterial attachment of BBR, anti-P-gp antibody(Ab)/DOX or pRNA (TP53) via hydrophobic/electroststic bonding to overcome multi-drug resistance and to get higher biological efficiencies against tumor, leukemia and breast cancer cells [44,53,56] (Table 1. Contd. 1). A few polymeric micelles composed of core-shell structure formed by the self-assembly of amphiphilic polymers in aqueous solution for improving the bioavailability and hydrophobicity of drugs, have been used to load cargos such as THZ/DOX, DOX/PTX, msurvivin T34A gene/DOX, PTX/TR3siRNA, green tea catechin derivatives, protein herceptin and quercetin through hydrophobic or electrostatic bonding and to treat against breast, lung, melanoma or pancreatic cancer, and breast and ovarian cancer cells to reduce their carcinogenic severity, while methoxy-PEG-PLA, PEG-b-PAPA and PLGA-PEI NPs have been applied for the treatments of lung, breast, ovarian and gastric cancer, or breast cancer cells to get higher anti-carcinogenic efficacies [43,44,58,56] (Table 1. Contd. 1).

Table 1. Contd. 1

Nanomaterials	Therapeutics	Enhanced efficacy target against
Polymer		
Nano gel	Epigallocatechin gallate/siRNA, CIS/DOX	Breast cancer
Nano hydrogel	PTX, CIS; CUR	Lung cancer; A549 lung adenocarcinoma cells
Silica-polymer	P53	Lung cancer
Graphene		
GO-hydrogel	DOX, 5FU, PTX, MTX, CPT, RV, CUR, BBR	Breast cancer cells (MCF-7), Cancer
GO-aerogel	DOX	Stomach cancer, tumors
rGO	CUR; polyphenolic green tea	MDA-MB-231, SKBR3 breast cancer cells; Colon cancer cells (HT29, SW48)
rGO-iron	Glucose	Prostate cancer cells (LNCaP)
rGO-polydomamine	hSET1 antisense	Breast cancer cells (MCF-7)
GO-gold	miRNA-101	Breast cancer cells (MCF-7, MDA)
Amphiphilic graphene-ethydium bromide	Plasmid DNA(pDNA)	AGS cancer cells
PEI-nano graphene oxide (NGO)	ADM/anti-miR-21	Breast cancer
Graphene quantum dot	BBR, Cysteamine	HeLa, MDA-MB-231 cancer cells
Carbon		
Carbon dot	BBR	Growth of tumor cells
Carbon nanotube (CNT)	Anti-P-gpAb/DOX	Human leukemia cells (K562)
SWCNT: Ethylenediamine (CNT)	pRNA (TP53)	Breast cancer cells (MCF-7)
Micelle		
	THZ/DOX; DOX/PTX	Breast cancer; Lung cancer
	Msurvivin T34A gene/DOX	Melanoma
	PTX/TR3siRNA	Pancreatic cancer
	Green tea catechin derivatives, protein herceptin	Breast cancer cells (BT-474, SKBR-3), ovarian cancer cells (SKOV-3)
	Quercetin	Lung cancer
Methoxy-PEG-PLA	PTX	Lung, breast, ovarian cancer
PEG-b-PAPA	PTX	Breast, gastric cancer
PLGA-PEI	pDNA	Breast cancer cells (MCF-7)
Liposome	DOX	Karposi's sarcoma, multiple myeloma, ovarian cancer

A few researchers have utilized liposomes to encapsulate/load various cargos such as DOX, cytarabine, daunorubicin, ranGTP/DOX, VEGFsiRNA/PTX, PTX/TRAIL, DFO/YC1, BBR, BBR/BBR and PTX, curcumin, epigallocatechin-3-gallate, vincristine, quercetin, resveratrol, oleanolic acid, baicalein, combretastatin A4, betulinic acid, PTX/epigallocatechin gallate, curcumin and resveratrol or combretastatin and DOX through passive diffusion, hydrophobic or electrostatic bonding for the treatment of karposi's multiple myeloma, ovarian cancer, intrathecal lymphomatous meningitis, karposi's sarcoma, breast cancer, melanoma, pancreatic cancer, different cancer/carcinoma cells, drug resistant cancer cells, glioma cells, lung, colon and prostate cancer, and tumor cells, whereas magnetic, FA-PEG or anti-CD44-aptamer - liposomes loaded with artemisinin, C9-C16 BBR and DOX, or siRNA (protamine) for the threatment of different cancer cells, fibrosarcoma tumor growth and breast cancer to achieve significant anti-cancer efficacies [43,44,53,58,56] (Table 1. Contd. 1 and 2). A few investigators have used solid, 17β-estradiol cationic, PEI-stearic acid-g-chitosan, cationic PEG-PLA and Fab′-heparin binding EGF –lipids or nano/micro lipid-micelle bubbles, loaded or conjugated with docetaxel, PTX, artemisone, resveratrol, antisense oligodeoxynucleotide, pDNA, siRNA (CDK1), siRNA (polo-like kinase 1) or HSVtk gene/GCV to treat different cancer cells, cancer or tumor for availing higher therapeutic efficacies [56,58,57] (Table 1. Contd. 2).

Table 1. Contd. 2

Nanomaterials	Therapeutics	Enhanced efficacy target against
Liposome		
	Cytarabine; Daunorubicin	Intrathecal lymphomatous meningitis; Karposi's sarcoma
	RanGTP/DOX, VEGFsiRNA/PTX	Breast cancer
	PTX/TRAIL; DFO/YC-1	Melanoma; Pancreatic cancer
	BBR	HepG2 cancer cells
	BBR/BBR and PTX	Drug resistant breast cancer stem cells
	Curcumin (CUR)	Growth of B16BL6 melanoma cells
	Epigallocatechin-3-gallate	Breast cancer cells (MCF-7)
	Vincristine; Quercetin	Meth A sarcoma; C6 glioma cells
	Resveratrol	Resistant lung cancer cells
	Oleanolic acid	U14 cervical carcinoma cells
	Baicalein	Carcinoma cells (U14, HeLa)
	Combretastatin A4	Tumor vascular endothelial cells
	Betulinic acid	Growth of human lung, colon cancer
	PTX/epigallocatechin gallate	Breast cancer cells (MDA-MB-231)
	Curcumin and resveratrol	Prostate cancer
	Combretastatin and DOX	Growth of B16-F10 tumors
Magnetic liposome	PTX	Cancer cells (MCF-7, HeLa), fibrosarcoma tumor growth
	Artemisinin	Breast cancer
FA-PEG-liposome	C9-C16 BBR and DOX	MCF-7/ADR cancer cells
Anti-CD44- aptamer-liposome	siRNA (Protamine)	Gene expression (MDA-MB-231) in TNBC model
Lipid		
Solid lipid	Docetaxel	Breast cancer cells (MCF-7)
	PTX; Artemisinin derivatives artemisone	C6 glioma cells, A549 lung cancer cells; Melanoma cells
	Resveratrol	Cell proliferation and skin cancer
17β-estradiol cationic lipid	Antisense oligodeoxynucleotide (ERα and ERβ)	Breast cancer cells (MCF-7)
PEI-stearic acid-g-chitosan lipid	pDNA (PEDF)	Breast cancer cells (MCF-7)
Cationic lipid PEG-PLA	siRNA (CDK1)	Breast cancer cells (MCF-7) (TNBC cells)
Fab′-heparin binding EGF lipid	siRNA (polo-like kinase 1)	Polo-like kinase 1 expression, tumor growth (MDA-MB-231)
Nano/micro lipid-micelle bubbles	Herpes simplex thymidine kinase (HSVtk) gene / ganciclovir (GCV)	Lung adenocarcinoma cells (A549), colon carcinoma cells (HT29, C26), mammary carcinoma cells (EMT6), tumor

Several researchers have shown the targeted utilizations of mesoporous silica nanoparticles (MSNs) loaded with different cargos such as CUR, BBR and CPT, combretastatin A4 and DOX, CPT/DOX or P-gp siRNA/DOX or quercetin via hydrophobic/covalent or electrostatic/hydrophobic bonding against tumor spheroids, oral cancer cells, hepatocellular and breast carcinoma cells, HeLa tumor cells, tumor growth, cervical or breast cancer, whereas HA-MSN, or disulfide/cancer membranes-disulfide mesoporous organo silica, loaded with BBR and DOX / DOX, BBR with / without glutathione against hepatocarcinoma cells to get higher biological effectiveness [58,43,56,53] (Table 1. Contd. 3). A few scientists have utilized layered double hydroxide (LDH) NMs through their loading with 5-FU/siRNA by hydrophobic/electrostatic bonding to overcome drug resistance and to get higher anti-carcinogenic efficacies against various cancer cell lines [44] (Table 1. Contd. 3). A few investigators have shown the targeting and anti-metastatic

activities of PTX or noscapine -loaded (hydrophobic bonding) human serum albumin (HSA) NPs against metastatic breast cancer or breast cancer cells [44,58] (Table 1. Contd. 3). A few investigators have applied iron oxide (Fe_3O_4) and iron oxide-arginine NPs loaded/coated with DOX/CIS, phospholipid-PEG, epi-DOX, DOX, ODNs, GM-CSF, BBR, SAN, CUR, baicalein and methotrexate through covalent or electrostatic bonding to treat against breast, solid cancer, tumor cells and breast cancer cells for achieving higher anti-cancer efficacies [43,44,60,53,58,56] (Table 1. Contd. 3).

Table 1. Contd. 3

Nanomaterials	**Therapeutics**	**Enhanced efficacy target against**
Silica	CUR; BBR and CPT; Combretastatin A4 and DOX	Tumor spheroids and oral cancer cells (Nt-8e); Hepatocellular carcinoma cells (HepG2); Breast cancer cells (MCF-7, SK-BR-3), tumor growth, HeLa tumor cells
Mesoporous silica	CPT/DOX; P-gp siRNA/DOX	Cervical cancer; Breast cancer
(MSN)	Quercetin	Breast cancer cells (MDA-MB-231, MCF-7)
HA-MSN	BBR and DOX / DOX	Hepatocellular carcinoma cells
Disulfide / cancer membranes-disulfide mesoporous organo silica	BBR with / without glutathione	HepG2 hepatocarcinoma cells
Layered double hydroxide (LDH)	5-FU/siRNA	Cancer cell lines
Protein		
Human serum albumin	PTX	Metastatic breast cancer
	Noscapine	Breast cancer cells (SK-BR-3)
Iron oxide (Fe_3O_4)		
	DOX/CIS	Breast cancer
	Phospholipid-PEG coated	Solid cancer
	Epi-DOX, DOX, ODNs, GM-CSF	Cancer, tumor cells
	BBR, SAN	Solid tumors
	CUR, Baicalein	MDA-MB-231 breast cancer cells
Iron oxide-arginine	Methotrexate	Breast cancer cells (MCF-7, 4T1, HFF-2)
Silver (Ag)	*Andrographis paniculata* aqueous / methanol extract	HeLa carcinoma cells / Neuroblastoma cells
FA-PEG-Ag	BBR	Breast cancer cells (MDA-MB-231), tumor growth
Nickel oxide (NiO)	*Andrographis paniculata* extract (andrographolide, 14-deoxyandrographolide, neoandrographolide)	Breast cancer cells (MCF-7)
Zinc oxide (ZnO)	BBR	A549 lung adenocarcinoma cells
	CUR	AGS gastric cancer cells

A few researchers have used silver (Ag) or FA-PEG-Ag synthesized or loaded with *Andrographis paniculata* aqueous/methanol extract or BBR for treating HeLa carcinoma/neuroblastoma cells or breast cancer cells and tumor growth to get higher anti-cancer efficacy [61,53] (Table 1. Contd. 3). A few researchers have utilized nickel oxide synthesized with *Andrographilis paniculata* extract against breast cancer cells to achieve higher therapeutic efficacy [61] (Table 1. Contd. 3). Several researchers have used zinc oxide loaded with BBR or CUR against adenocarcinoma or gastric cancer cells to get higher anti-cancer efficacy [53,58] (Table 1. Contd. 3). A lot of other researchers have utilized different gold (Au) nanocomposites loaded with various cargos through hydrophobic/electrostatic bonding to target cancer cells or tumor growth for achieving higher anti-cancer therapeutic efficacies [10,53,56] (Table 1. Contd. 4).

Table 1. Contd. 4

Nanomaterials	Therapeutics	Enhanced efficacy target against
Gold (Au)		
MTX-AuNPs	MTX	Lewis lung carcinoma cells (LL2)
DOX-PEG-AuNPs	DOX	Multi drug resistant cancer cells (ADR/MCF-7)
DOX-Hyd@AuNPs	DOX, Hyd	ADR / MCF-7 cancer cells
CPP-DOX-AuNPs	CPP, DOX	A549 and HeLa cancer cells
FA-AuNPs	BBR	HeLa cancer cells
FA-Au-SMCC-DOX	SMCC, DOX	HDF, C0045C and HepG2-R cancer cells
DOX@PVP-AuNPs	DOX	H460, H520 and A549 lung cancer cells
DOX-BLM-PEG-AuNPs	DOX, BLM	Cervical carcinoma cells (HeLa)
Au-P(LA-DOX)-b-PEG-OH/FA NPs	DOX	4T1mouse mammary carcinoma cells
FA-BHC-AuNPs	BHC	HeLa and Vero cancer cells
PTX-RBC-EpCam-AuNPs	PTX, EpCam	4T1mouse mammary carcinoma cells
OPT-PEG-Carb-AuNPs	OPT	Lung/colon cancer cells (HCT15, HT29 / RKO)
(Pt(R,R-dach))-AuNPs	(Pt(R,R-dach))	A549, HCT116/15, HT29, RKO cancer cells
DAU-PA-AuNPs	DAU	U266 and Molt-4 lymphoblast cells
BLM-RGD-AuNPs	BLM	Metastatic MDA-MB-231 breast cancer cells
FA-CPA-AuNPs	CPA	Breast cancer cells
GMC-plectin1-peptide-Au	GMC	Pancreatic ductal adenocarcinoma cells (PDAC)
CPC/CIS/DOX-L-aspartate-AuNPs	CPC/CIS/DOX	Hepatocellular carcinoma cells
VCR-AuNPs@liposomes	VCR	HeLa cancer cells
ETP-HPMC/PVA-AuNPs	ETP	Lung carcinoma cells (NCI-H69)
6-MP-AuNPs	6-MP	K-562 leukemia cells
5-FU-glutathione-AuNPs	5-FU	Colorectal cancer cells
Tf pep-Au-prodrug Pc4	Pc4	LN229 and U87 glioma cancer cells
PEG-AuNPs	siRNA (c-Myc)	MCF-7 cancer cells
Polyethylene-AuNPs	siRNA (eukaryotic elongation factor 2 kinase)	Tumor growth (MDA-MB-231)

Receptor mediated active targeting

Recognition of the targeted cancer cell through the binding of over-expressed cancer cell-receptor by surface functionalized ligand to deliver therapeutics selectively to cancerous cells, is a desirable strategy for receptor mediated endocytic active targeting. Receptor-mediated NMs enhance accumulation of the cargos within cancerous cells and restrict their growth compared to non-targeted controls through increased site-specific cargo-concentration in cancerous cells and limited off-targeted drug-cytotoxicity in healthy cells/tissues [42,77,83]. A few over-expressed cancerous receptors as ligands-surface-functionalized nanomaterial therapeutic targets and delivery for cancer treatments are depicted below (Table 2) [25,42,44,77].

For availing growing requirements of iron (Fe) to maintain cell- division and growth, transferrin receptor (TfR), the membrane-associated glycoprotein, over-expressed on the tumor-surfaces, functions to mediate iron acquisition through binding iron-bound transferrin plasma protein with subsequent receptor-mediated endocytosis [42,77]. A few investigators have utilized TfRs with various ligand targets and drug cargos such as Tf and DOX/dihydroartemisinin/PTX, TfR ligand (7 pep) and DOX, Tf + TRAIL and DOX, Tf + Folate and DOX, T7 peptide + TAT and DOX, and TfR mAb and DNM, with different nanocarriers such as liposome, niosome, iron oxide, micelle and HSA to treat against breast, glioma and colon cancer for getting higher anti-cancer efficacies such as higher cellular uptake, enhanced intracellular cargos-delivery, and bypassing of drug-resistance, resulting in cancer cells-death [40,42,77] (Table 2). Several researchers have used transferrin/MMP-2 receptor with ligand target OX-26/CTX and cargo PC27 loaded with PEG-liposome for treating glioma to get higher anti-cancer efficacy [25] (Table 2).

The folate receptor (FR), named as vitamin B9 or folic acid receptor, over-expressed on cancer cells, composed of cysteine-rich cell-surface glycoprotein, functions to bind and internalize and transport folate into tumor cells through receptor-mediated endocytosis for the synthesis of nucleic acids [40,42,77]. A lot of investigators have exhibited that folate receptors have been utilized for ligand targets with cargos-loading such as folate with DOX/MTX/DOC/PTX/CIS, folate + Asp8 with DOX, and folate + transferrin with DOX, conjugated with different nanocarriers, such as liposome, organic, micelle, conjugate, BSA or liquid crystal for the treatment of several cancer diseases such as lung, cervical, prostate, breast, breast metastasis or glioma to get higher therapeutic anti-cancer

efficacies such as less side effect, reduced tumor burden and cancer cells-death [42] (Table 2).

Biotin receptor, known as vitamin B7 receptor, over-expressed on cancer cells, is related to the binding and internalization of biotin (the coenzyme for carboxylase enzymes), and its transport into the cancer cells via receptor-mediated endocytosis for utilization of cellular carbohydrates, fats and amino acids [84-89]. A few investigators have used biotin receptor for ligand target and drug application such as biotin and arginine modified hydroxypropyl-β-cyclodextrin (HCD) NPs with PTX to treat breast, lung, cervical and hepatocellular cancer for getting higher anti-cancer efficacies [89] (Table 2).

The human epidermal growth factor receptor-2 (HER-2), the transmembrane glycoprotein having an intracellular tyrosine kinase domain, over-expressed in various cancer cells, may function in dimerized form with other ErbB family receptors in the actuation of the HER signaling pathways for pathogenic tumor growth and progress [40,42,77]. A few researchers have utilized HER-2 receptors for ligand target conjugated with cargos-loaded different NPs such as anti-HER-2 humanized mAb trastuzumab (Herceptin) / anti-HER-2scFv / Neu peptide (FCDGFYACYADV) or KCCYSL (P_6.1peptide) conjugated with MTN/PTX or RAPA loaded conjugate or liposome, trastuzumab loaded gelatin+HSA, DOX, PTX or DOC loaded HSA, PEI/PLGA or PLGA, DOX loaded liposome, and gadolinium loaded liposome to treat breast cancer for getting higher anti-cancer efficacy with overcoming chemotherapeutic resistance [42] (Table 2).

Table 2. A few over-expressed receptors on cancer cell surface and their targeting by cargos-loaded nano-carriers/systems.

Receptor	**Ligand target**	**cancer**	**Nanocarrier/System**	**Cargo**
Transferrin	Transferrin (Tf)	Breast	Liposome, Niosome	DOX
			Iron oxide	Dihydroartemisinin
		Glioma	Micelle	PTX
	TfR ligand (7pep)	Breast	Micelle	DOX
	Tf + TRAIL	Colon	HSA	DOX
	Tf + Folate	Glioma	Liposome	DOX
	T7 peptide +TAT, TfR mAb	Glioma	Liposome	DOX, DNM
Transferrin/ MMP-2	OX-26/CTX	Glioma	PEG-Liposome	PC27
Folate	Folic acid	Lung, Cervical	Liposome, Organic	DOX, MTX and DOC
	Folate	Cervical	Micelle, Liposome	DOX, PTX
			Conjugate	DOX
		Prostate	BSA	PTX
		Breast	Micelle, Liquid crystal, Organic	PTX, DOC and CIS, DOX
			Liposome	DOX
	Folate + Asp8	Breast metastasis		DOX
	Folate + Tf	Glioma	Liposome	
Biotin	Biotin	Breast, Lung, Cervical, Hepatic	HCD	PTX
HER2	Trastuzumab	Breast	Conjugate, Liposome	MTN, PTX and RAPA
			Gelatin + HSA	Trastuzumab
	Anti-HER2 scFv	Breast	HSA, PEI/PLGA, PLGA	DOX, PTX, DOC
	Neu peptide (FCDGFYACYADV)	Breast	Liposome	DOX
	KCCYSL (P6.1peptide)	Breast	Liposome	Gadolinium
$\alpha_v\beta_3$*Integrin*	RGD	Endothelial, Glioma	Micelle	DOX, PTX
		Lung, Melanoma, Breast	Organic, Conjugate, Silica	PTX, DOX, CPT
	RGD + Estrone		Organic	PTX
	RGD + pHA	Breast	Liposome	DOX
	RGD + YPSMA-1mAb	Glioma	Micelle	PTX
		Prostate		

$\alpha_v\beta_3$ integrin receptor, the transmembrane glycoprotein receptor expressed highly in tumor neovascular endothelial cells, is related to intervene cell attachment via binding to extracellular matrix (ECM) proteins for attaching cells within tissue and perform a major role in cancer cell migration, invasion, and metastasis [40,42,77]. A few researchers have used $\alpha_v\beta_3$ integrin receptor for various ligand targets and cargos loaded NPs such as RGD (peptide), RGD+estrone, RGD+pHA or RGD+YPSMA-1mAb with DOX, PTX or CPT loaded micelle, organic, conjugate, silica or liposome for the treatment of cancer such as endothelial, glioma, lung, melanoma, breast or prostate to get higher anti-carcinogenic efficiencies such as higher endocytosis and improved tumor suppressed features [42] (Table 2).

Prostate-specific membrane antigen (PSMA) receptor, expressed in many prostate cancer cells, is used as receptor target against prostate cancer [42] (Table 2. Contd. 1). Several investigators have utilized PSMA receptor for various ligand targets with cargos loaded NMs such as A10PSMA aptaper (Apt), YPSMA-1mAb+RGD or anti-PSMA+anti-CD14mAb with CIS, DOC, shRNA, PTX, or fluorophore loaded PLGA, micelle or PAMAM NMs to treat against prostate cancer for getting higher anti-prostate cancer efficiencies with bypassing multi-drug resistance (MDR) [42] (Table 2. Contd. 1).

Asialoglycoprotein receptors (ASGPRs), the integral membrane proteins such as lectin / galactose receptors expressed on the surfaces of carcinoma cells, are used to bind asialoglycoprotein and glycoproteins to remove sialic acid and to expose galactose residues and to endocytose them [77,90,91]. Several investigators have utilized ASGPRs for different ligand targets and cargos loaded NMs such as lactobionic acid or galactose with QC/SRF or SRF/DOX loaded phospholipid-protein shell-oily core (PPSOC) NPs or janus gold nanorods (JGNs) to treat against hepatocellular carcinomas for getting higher receptor-mediated endocytosed anti-cancer efficiency [77] (Table 2. Contd. 1).

Lactoferrin receptor (LfR), a single-chain cationic iron-binding glycoprotein, expressed in glioma cells, has been utilized for ligand target lactoferrin with DOX loaded PEG-BSA NPs through LfR-mediated endocytosis in brain tissue to treat glioma for getting higher uptake of DOX against blood brain barrier (BBB) as well as enhanced therapeutic anti-cancer efficacy [25] (Table 2. Contd. 1).

Low density lipoprotein receptor (LDLR) composed of apolipoprotein B-100 (ApoB-100) forming hydrophobic core surrounded by a hydrophilic shell, has been used for ligand target peptide 22-decorated with PTX loaded PEG-PLA NPs against BBB-related glioma for getting LDLR-mediated endocytosed higher anti-glioma drug efficacy [25] (Table 2. Contd. 1).

Low density lipoprotein receptor-related protein (LRP), a transmembrane protein belonging to the LDLR family, expressed highly on glioma cancerous cells, has been utilized for ligand target angiopep-2 decorated with DOX or PTX loaded gold or PEG-PCL NPs to treat against glioma for getting higher anti-glioma efficacy [25] (Table 2. Contd. 1).

Insulin receptor, a membrane glycoprotein over-expressed in glioma cells, has been used for ligand target 83-14 murine monoclonal antibody decorated with PEGylated immunoliposomes (PILs) for targeting genes to brain tumors through insulin receptor-mediated endocytosis to get higher anti-glioma efficiency [25] (Table 2. Contd. 1).

Estrogen receptor (ER), a type of nuclear receptor over-expressed on breast cancer cells, binds to hormone estrogen (estradiol), and acts as transcription factor for regulating cell proliferation [42]. A few researchers have utilized ERs for ligand targets estrone/estrone+RGD/17β-estradiol, or estrogen analog tamoxifen conjugated with DOX/NOS/PTX, PTX/DOX, pCMV-β-Gal gene, or tamoxifen loaded liposome/gelatin/chitosan, organic/carbon nanotube, liposome, or gold (Au) NMs respectively to treat breast cancer for getting higher anti-cancer efficacies [42] (Table 2. Contd.1).

Table 2. Contd. 1

Receptor	Ligand target	cancer	Nanocarrier/System	Cargo
PSMA	A10PSMA Apt	Prostate	PLGA	CIS, DOC, shRNA
	YPSMA-1mAb+RGD	Prostate	Micelle	PTX
	Anti-PSMA+Anti-CD14mAb	Prostate	PAMAM	Fluorophore
ASGP	Lactobionic acid, Galactose	Hepatocellular	PPSOC, JGN	QC/SRF, SRF/DOX
Lactoferrin	Lactoferrin	Glioma	PEG-BSA	DOX
LDL	Peptide-22	Glioma	PEG-PLA	PTX
LRP	Angiopep-2	Glioma	Gold, PEG-PCL	DOC, PTX
Insulin	83-14 murine mAb	Glioma	PEG-Immunoliposome	-
Estrogen	Estrone	Breast	Liposome, Gelatin, Chitosan	DOX, NOS, PTX
	Estrone+RGD, 17β-Estradiol	Breast	Organic, Carbon nanotube, Liposome	PTX, DOX, pCMV-β-Gal
	Tamoxifen	Breast	Gold	Tamoxifen
Androgen	Testosterone	Prostate	Liposome	5-FU
	α and β-bicalutamide	Prostate	Gold	α and β-bicalutamide
LHRH	Peptide	Breast	HSA, Liposome	MTX, MXT
ICAM1	Anti-ICAM1mAb	Breast	Iron oxide, Liposome	N/A, Lcn2siRNA
	LFA-1	Cervical	Urethane acrylate nonionomer	PTX

CXCR4	LFC131 peptide	Lung, Breast	Chitosan, PAMAM	DOC, DOX
	Anti-CXCR4mAb	Breast	Liposome	DOX
	Peptide R	Lung	Liposome	DOX

Androgen receptor (AR), a nuclear receptor over-expressed on prostate cancer cells, binds testosterone and dihydrotestosterone for acting as master regulator of genes in castrate-resistant prostate cancer, and as a transcription factor in regulating cancer genes for tumor growth [42]. A few investigators have used ARs for ligand targets testosterone or α and β-bicalutamide conjugated with 5-FU or α and β-bicalutamide loaded liposome or gold NPs respectively against prostate cancer to get augmented anti-prostate cancer efficacies [42] (Table 2. Contd. 1).

Luteinizing hormone-releasing hormone receptors (LHRHRs), the transmembrane proteins over-expressed on a variety of cancer cells, have been explored with peptide modified NPs for the targeted delivery of therapeutics against cancer through receptor-mediated endocytosis [77]. A few investigators have utilized ligand target LHRH-peptide conjugated MTX or MXT encapsulated with HSA or liposome against breast cancer to get enhanced cellular uptake and augmented tumor suppression [77] (Table 2. Contd. 1).

Intracellular adhesion molecule-1 receptor (ICAM-1R), a transmembrane glycoprotein expressed on cancerous endothelial and immune cells, binds ICAM-1 to compose clusters in the cell membrane for inducting an intracellular signaling cascade to disrupt vascular junction and enhance endothelial permeability on inflamed endothelium [42]. A few researchers have utilized ICAM-1R for conjugated ligand targets such as anti-ICAM-1mAb or ICAM-1 ligand lymphocyte function-associated antigen-1(LFA-1) peptide with anti-angiogenic Lcn2siRNA or PTX encapsulated casein-coated iron oxide (IO), liposome or urethane acrylate nonionomer (UAN) NPs to treat against breast or cervical cancer for getting enhanced cellular uptake and higher anti-angiogenic efficacies [42] (Table 2. Contd.1).

The chemokine receptor type-4 ($CXCR_4$), a G-protein coupled receptor (GPCR) with seven trans-membrane domains over-expressed on cancerous cells, acts to regulate immune cell processes, proliferation, angiogenesis and metastasis [42]. A few researchers have utilized $CXCR_4$ for different ligand-targets such as LFC131 peptide, anti-$CXCR_4$ mAb, or peptide-4 conjugated with DOC or DOX loaded chitosan, PAMAM or liposome NPs to treat against lung or breast cancer for getting higher therapeutic efficacies such as enhanced cellular uptake and drug release with cancerous cell-death, decreased cancer migration and invasion, and reduced tumor growth and metastasis [42] (Table 2. Contd. 1).

The family of cluster of differentiation (CD) receptors, such as CD14, CD22, CD44 and CD133, a diverse set of immune-regulatory cell surface marker-proteins, over-expressed on cancer stem cells (CSCs), are functional for delivery-targets to inhibit tumor metastasis and improve survivability [42]. A few investigators have used CD14, CD22, CD44, or CD133for ligand-targets anti-CD14 mAb+anti-PSMA, anti-CD22 mAb, hyaluronic acid (HA) or aptamer respectively with fluorophore, CPM/BTM, PTX, DOX, or salinomycin loaded PAMAM, organic, micelle/organic, liposome or organic NMs to treat against prostate, lymphoma, breast, melanoma or bone cancer for availing higher anti-cancer efficacies [42] (Table 2. Contd.2).

The interleukin receptors (ILRs), a family of cytokine receptors belonging to the immunoglobulin super-family, are functional for the receptor-mediated cell internalization to deliver cargos to the targeted site/s for inhibiting cancer [42]. A few researchers have utilized IL-4 and IL-13 receptors for ligand-targets AP1 peptide, Pep-1, or IL-13 conjugated with DOX, or DOC loaded liposome/organic, liposome, or organic NMs for the treatment of colon/glioma, lung, or glioma cancer respectively to get higher anti-cancer efficacies [42] (Table 2. Contd. 2).

Table 2. Contd. 2

Receptor	**Ligand target**	**cancer**	**Nanocarrier/System**	**Cargo**
CD				
CD14	Anti-CD14 mAb+Anti-PSMA	Prostate	PAMAM	Fluorophore
CD22	Anti-CD22 mAb	Lymphoma	Organic	CPM, BTM
CD44	Hyaluronic acid	Breast	Micelle, Organic	PTX, DOX
		Melanoma	Liposome	DOX
CD133	Aptamer	Bone	Organic	Salinomycin
IL				
IL4	AP1 peptide	Colon,Glioma	Liposome, Organic	DOX
	Pep-1	Lung	Liposome	DOX
IL13	IL13	Glioma	Organic	DOC
EGFR	Anti-EGFR mAb	Breast	Liposome	DOX, ERB,VRB
		Lung	Liposome	Gemcitabine
	Cetuximab	Pancreatic	Inorganic	Gemcitabine
TNF	TRAIL+Transferrin	Colon	HSA	DOX

Glycyrrhetinic acid	Glycyrrhetinic acid	Liver	Organic	DOX
VEGF	Anti-VEGF mAb AR7+T7 peptide	Pancreatic Glioma	Conjugate Liposome	Gemcitabine DOX,Vincristine

The epidermal growth factor receptor (EGFR), the transmembrane glycoprotein over-expressed on various cancer cells, is functional for binding to EGF ligands to initiate intracellular signaling pathways for regulating cell proliferation, migration and apoptosis [42]. A few investigators have used EGFR for ligand-targets anti-EGFR mAb or cetuximab conjugated with DOX, ERB, VRB or gemcitabine loaded liposome or inorganic NPs to treat breast, lung or pancreatic cancer for getting higher anti-cancer efficacy [42] (Table 2. Contd. 2).

The tumor necrosis factor receptors (TNFRs), the transmembrane protein superfamily of cytokine receptors, expressed in leukocytes, are able to bind TNFs through an extracellular cysteine-rich domain, and involved in cellular inflammation, apoptosis and signal transduction pathways such as differentiation, survival and proliferation [42,92-94]. A few researchers have utilized TNFR for ligand-target TRAIL+transferrin conjugated with DOX loaded HSA against colon cancer to get higher anti-cancer efficacy [42] (Table 2. Contd.2).

The glycyrrhetinic acid receptor (GAR), over-expressed on cancerous cells, are used as the targeting moieties to deliver cargos to the targeted site/s for regulating inflammation and cancer [42]. A few investigators have used GAR for ligand-target GA conjugated with DOX loaded organic NPs to treat against liver cancer for getting higher anti-cancer therapeutic efficacy [42] (Table 2. Contd. 2).

The vascular endothelial growth factor receptors (VEGFRs), the signaling proteins over-expressed on cancerous cells, are involved in binding VEGF to target cargos to the specific site of interest for regulating vasculogenesis and angiogenesis [42]. A few researchers have utilized VEGFRs for ligand-targets anti-VEGF mAb or AR7+T7 peptide conjugated with gemcitabine, or DOX and vincristine loaded conjugate or liposome NPs to treat against pancreatic cancer or glioma for getting higher anti-cancer therapeutic efficacies [42] (Table 2. Contd. 2).

Stimuli-responsive targeting

Cancer cell proliferation is dependent on energy supply produced by metabolic glycolysis in cancer cells [40]. Enhanced glycolysis, in turn, yields acidic environment reducing the pH of the tumor microenvironment (TME). The pH-sensitive NPs are utilized to trigger them at low pH level and to release drug contents within the vicinity of cancerous cells [40]. The TME includes an acidic high concentration of ROS and GSH along with enhanced expression of specific enzymes, such as cathepsin B / MMP-2 [77]. In response to these endogenous stimuli, cellular alterations in molecular function, dispersion, degradation kinetics and morphology may induce / facilitate the intracellular internalization or escape from endosomal / lysosomal degradation, and liberation of nanoparticulated pharmaceutical therapeutics [77]. In addition to endogenous responsive nanosystems, a few exogenous stimuli-responsive NPs also exhibit beneficial targeting activities through utilization of controllable external factors, such as ultrasound, temperature, lasers and magnetism [77].

Redox-responsive targeting

Redox species, such as reactive nitrogen species (RNS) and reactive oxygen species (ROS), generated in tumor cells, may construct a complex antioxidant defense system and modulate redox homeostasis [77]. Hydrogen peroxide (H_2O_2) may either be utilized as an enzymatic substrate for oxygen (O_2) production to alleviate TME-hypoxia, or converted to other active ROS, including superoxide radical ($O_2^{\cdot-}$), singlet oxygen ($^1O_2$) and hydroxyl radical ($\cdot OH$), while cellular glutathione (GSH) may consume ROS to modulate redox homeostasis [77]. Carcinogenesis and its progression, caused by hypoxia, may be controlled by the over-production of hypoxia-induced factor (HIF-1α) and vascular endothelial growth factor (VEGF) in tumor cells, leading to reduced sensitivity of cancer to radiotherapy (RT), development of chemo-resistance, affecting the efficacy of O_2-related treatments such as sonodynamic therapy (SDT) and photodynamic therapy (PDT) [77]. Matrix metalloproteinases (MMPs), responsible for degradation of matrix proteins, are capable to deplete collagen via the activation of nitric oxide (NO) synthase-induced NO production. NO, can inturn react with $^1O_2$ to produce toxic peroxynitrite ($ONOO^-$) to kill tumor cells and induce DNA impairment and mitochondrial dysfunction, resulting in cellular apoptosis and tumor metastasis suppression [77]. A lot of investigators have utilized different nanoplatforms such as liposomes loaded with cisplatin-prodrug functionalized phospholipid and catalase (CAT), metallic nanocarriers (MOF, MnO_2, CeO_2, Pt, Pd and Au-Fe_3O_4), copper oxide (Cu_2O_2), mesoporous silica NPs (MSNs) loaded with arginine and glucose oxidase (Gox), and poly (propylene sulfide)-conjugated with PEG, accompanied with different therapeutic strategies to treat against various cancer diseases for getting higher anti-cancer efficacy with oxidative and nitrosative stress-induced enhanced tumor cell death or inhibition efficiency [77] (Table 3). A few researchers have utilized phenylsulfonyl furoxan as NO donor decorated with polymers loaded with prodrug using ester and disulfide bonds or folic acid, and other NO donors such as metal NO complexes, Roussin's black salt and S-nitrosothiols with PDT for targeting tumors to get higher anticancer efficacy [77].

Table 3. A few ROS-responsive building blocks for cancer treatment.

Type of chemical bonds	Nanoplatforms	Cancer models	Therapeutic strategies
Phenylboronate ester	G5.NHAc-Toy@TF	Breast	Chemotherapy, CDT
	pPBA(TL)-MN	Breast	Immunotherapy
Thioketal linker	Poly prodrug $NP_{DOX/Cy}$	Breast	Chemotherapy
Gallic acid-ferrous nanocomplex	BSO/GA-Fe(II)@liposome	Breast	CDT
Bilirubin	DOX@bt-BR NPs	Cervical carcinoma	Chemotherapy
	TH-302@BR-Chitosan NPs	Cervical carcinoma	Chemotherapy, PTT
Ru NP	HA-Ru NAs	Breast	PDT, PTT, CDT
FePt NP	FePt/MoS_2-FA	Breast	Immunotherapy, PTT
Manganese ferrite NPs	MFMSN-Ce6	Melanoma	SDT
Catalase (CAT)	CAT@Pt(IV)-liposome	Breast	Chemotherapy, RT
	CAT@HA-HMME	Colorectal	SDT
Horseradish peroxidase	Lipo@HRP, ABTS	Breast	PTT
	PEG-TiO_{1+X} NRs	Breast	SDT, CDT
Bis(3,4,6-trichloro-2-(pentyloxycarbonyl) phenyl oxalate	POCL	Cervical carcinoma	PDT

GSH-responsive targeting

A number of NPs composed of diselenide bonds, disulfide bonds, carbon-diselenide bonds or sulfonyl groups, may be prepared by cross-linking reactions, while over-produced GSH can break different disulfide bonds to disintegrate NPs and release cargos in cancerous cells [77]. A lot of investigators have utilized GSH-sensitive NPs such as trimeric prodrug functionalized FA decorated with PLGA-CPT with NIR coroconaine dyes through disulfide bonding, prodrug-based platinum (Pt-IV) or Pt-IV-PEG-lipid, multivalent metallic NPs for shifting their valencies in interactions, cerium oxide (CeO_2) NPs, MSNs and Cu-MOF NPs with or without NIR fluorescence and photothermal or chemodynamic therapies to treat against various tumors by regulating GSH and H_2O_2 in the TME for getting enhanced anti-cancer efficacy such as induction of DNA impairment and tumor cell apoptosis [77].

ROS and GSH dual-responsive targeting

In general, ROS generated from the catalytic oxidation of H_2O_2, may be consumed or removed by the over-produced cellular GSH, resulting in therapeutic interventions. For overcoming this obstacle, selective enhancement of oxidative stress via depletion of GSH concentrations and simultaneous elevation of ROS levels may be an effective strategy for cancer treatment [77]. A few researchers have used Au-anchored carbon dot NMs modified with triphenylphosphine and cinnamaldehyde to treat against tumors, while the dissociation of cinnamaldehyde by acidic endosomes favors the NMs to react with GSH, accompanied by ROS production, leading to the increment of ROS and simultaneous decrement of GSH, facilitating enhanced anti-cancer efficacy through oxidative-stress induced tumor cell killing [77].

pH-responsive targeting

In general, tumor cells consume more glucose for metabolic gycolysis with lactic acid production to get energy for maintaining their rapid proliferation, resulting in acidic TME [77]. A few researchers have changed the chemical structures in hydrophilicity via protonation and deprotonation acid-sensitive chemical bonds for designing pH-responsive NPs, which are capable of endosomal escape [77]. A lot of investigators have utilized different therapeutics-loaded NMs having pH-sensitive building blocks with different therapeutic applications to treat against various cancer cells for availing higher anti-cancer efficacies [42,77] (Table 4). A lot of researchers have used pH-responsive NMs including polyelectrolytes such as poly(aspartic acid-graft-imidazole), poly(histidine), PDMAEMA, anionic poly(Asp), cationic poly (β-amino ester), polysulfonamide, and poly(acrylic acid), and acid-sensitive bond cleavage-based (esters, imines and hydrazines) NMs, including liposomes and micelles, such as hydrazone bond-functionalized liposomes, formyl benzoic acid-PEG-maleimide-functionalized MSN, loaded with different cargos and combined with various therapeutic applications for treating against different cancers to get higher therapeutic anti-cancer efficiencies [42,77] (Table 4).

Table 4. A few pH-responsive building blocks for cancer treatment.

pH-sensitive building blocks	Therapeutic agents	Cancer models	Therapeutic applications
Poly(diisopropanol amino)ethyl methacrylate	GPDPA NPs	Glioblastoma	Chemotherapy, PTT
Poly(2-(hexametheleneimino)ethyl-methacrylate	siBRD4-loadedTCPA2-NPs	Prostatic	LNCaP-bearing mouse GT
	HR NMs	Glioblastoma	Chemotherapy
Poly N,N-dimethylamino ethyl methacrylate-co-2-hydroxyethyl methacrylate (DMAEMA/HEMA)	Trastuzumab, DOC	Breast	Chemotherapy
Benzoic-imine bond	CA-MTX NPs	Cervical carcinoma	Chemotherapy
	nBSA-DOX	Hepatocellular carcinoma	Chemotherapy
	$Nd^{IIII}IP$-N=CH-PEG	Cervical carcinoma	Chemotherapy, PTT
	Au@PP/RA/siRNA	Pancreatic	Chemotherapy
	DOX-ICM	Glioblastoma	Chemotherapy
Amide bond	DOX-CC-NP	Squamous cell carcinoma	Chemotherapy
	PDNBF NPs	Breast	Chemotherapy, PTT
Pyridine-2-imine	Gold nanomachine	Breast	PTT
	PMNP-DOX@RBC	Breast	Chemotherapy, CDT
Gadolinium oxide	Gd_2O_3 NSs	Melanoma	Chemotherapy
	FS-GdNDs	Breast	PTT
Nanodrug complex	MONCs	Breast	Chemotherapy, PDT
	B780/QuNPs	Breast	Chemotherapy, PDT, PTT
Triple DNA sequence	NLNs/DOX	Breast	Chemotherapy
	DNA conjugated AuNPs	Breast	Chemotherapy, PTT

Enzyme-responsive targeting

Owing to excellent catalytic characteristics of enzymes and their abnormal over-expressions (MMPs) on cancer cells, NPs modified with enzyme-responsive linkages, have been used to target cancer cells [77]. A few researchers have utilized MMP-2 and MMP-9 -responsive NPs such as octapeptide (AcGPLGIAGQ) conjugated PTX, gelatin-functionalized DOX-loaded MSNs, camptothecin-encapsulated MSNs functionalized with targeting cRGD, PTX-encapsulated PEG-PCL functionalized with protamine, Au grafted with complementary DNA strands functionalized with PEG-conjugated therapeutics, micelles conjugated with hydrophilic siRNA and hydrophobic drugs, lipoprotein conjugated PEG cleavable polymers loaded with Gem, and peptides conjugated copolymer loaded with curcumin to treat against various cancers with or without various stimuli applications for getting higher anti-cancer efficacies relating to degradation/hydrolysis of enzyme-cleavable peptides by the over-expressed MMPs (MMP-2 and MMP-9) and the release of cargos in TME [77].

A few investigators have utilized various heparanase-responsive NMs such as heparin-based nanogels, protamine and heparin nanocomplex, 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) cationic liposomes, loaded with various therapeutic agents, to treat against TME and metastasis for availing higher anti-cancer efficacy through cleavage of heparin or heparin sulfate proteoglycans (HSPGs) by over-expressed heparase-1 on cancerous cells, resulting in release of cargos for tumor cell-killing [77]. A few other researchers have used cathepsin-responsive NPs to treat against cancer for getting higher anti-cancer efficacy through degradation of Gly-Phe-Leu-Gly spacer in over-expressed cathepsin-B environments [77].

Hypoxia-responsive targeting

The abnormal vigorous metabolism and cell growth in tumor cells may deplete intracellular O_2, altering their hypoxic biological properties such as up-regulation of HIF-1α, carbonic anhydrase 1X and other enzymes, while tumor cells prefer aerobic glycolysis for obtaining energy rather than the conventional oxidative phosphorylation owing to the Warburg effect [77]. Many enzymes, involved in electron reduction or donation, such as nitroreductase, azoreductase, methionone synthase reductase, DT-diaphorase (DTD) and inducible nitric synthase, are over-produced in hypoxic tumor cells [77]. The hypoxia-responsive cargos-loaded NPs, utilizing hypoxia-responsive chemical bonds such as nitro, azo, N-oxide and quinine groups for changing their conformation as well as physicochemical properties such as hydrophobic characteristics and electrons-affinity by losing or gaining their electrons, have been developed and used for tumor treatment to get higher anti-cancer efficacy including prolonged blood-circulation, increased tumor penetration and accumulation, and enhanced cargos-release for tumor cell-killing [77] (Table 5).

In hypoxic environment, azobenzene (AZO) compounds utilized to link hydrophobic and hydrophilic moieties in amphiphilic molecules, may be reduced by NAD(P)H quinone dehydrogenase 1 (NQO1) and AZO reductase into two separate aniline groups which render them appropriate for preparing hypoxia-responsive NPs [77]. A lot of researchers have utilized different AZO-containing NPs such as hypoxic degradable NPs functionalized with AZO-containing

hydrophilic groups loaded with camptothecin and photo-sensitive chlorine e6 for laser-augmented therapy, CDT, PDT or SDT, supramolecular micelles loaded with photo-sensitizer and hypoxia-sensitive prodrug, AZO reductase-triggered NPs conjugated with DOX and siRNA, aptamer/antibody functionalized with hypoxia-sensitive AZO polymer NPs, MSN functionalized with β-cyclodextrin and 4-(phenyl AZO)benzoic acid, to treat against hypoxic tumors for getting higher anti-cancer efficacies through breakage of the AZO groups and simultaneous enhanced release of cargos in TME [77] (Table 5).

Table 5. A few hypoxia-responsive chemical bond-triggered nanoplatforms.

Type of chemical bonds	Therapeutic agents	Therapeutic methods	Cancer models
Azo	DOX@AMOFs@DRHC/CPPs	Chemotherapy	Breast
	DOX@NP	Chemotherapy	Lung
	ALN-HR-PMs/DOX	Chemotherapy	Prostate
	mPEG-AzoPAsp-IM micelles	PDT	Lewis lung carcinoma
	PEG-Azo-PEI DOPE	Chemotherapy	Cervical carcinoma
	CPs-CPT-Ce6 NPs	Chemotherapy, PDT	Cervical carcinoma
	CAGE	Chemotherapy, PDT	Melanoma
Nitro	DOX/CP-NI NPs	Chemotherapy, PDT	Cervical carcinoma
	DOX/FOBD liposome	Chemotherapy	Cervical
	DOX@HMs	Chemotherapy, RT	Breast
	HC/PN/DOX NPs	Chemotherapy, PDT	Lung
	ALP-(MIs)n/DOX	Chemotherapy, RT	Glioma
	NCs/DOX + Ce6 micelles	Chemotherapy, PDT	Breast
	Gd-Au DE NPs-Nit	RT	Nasopharyngeal carcinoma
	HR NP/siRNA	Chemotherapy	Breast
N-oxide	HSA-GOx-Fe^{3+}-TA (HGTFT)	Chemotherapy, CDT	Breast
	HA@AQ4N-Cu(II)-gossypol NPs	Chemotherapy	Prostatic
	TPZ/UCSs	Chemo / Photodynamic / Immuno therapy	Colorectal
	TENAB NPs	Chemotherapy, PDT, PTT	Cervical carcinoma
	UiO-66-H-P NMOFs	Chemotherapy, PDT	Glioblastoma
	YS-DMONs-AQ4N-GOx	Chemotherapy	Prostatic
	Mn-ADPMSF	Chemotherapy, PTT	Hepatocellular carcinoma
	Lip/Ce6/TPZ NPs	Chemotherapy, PDT	Breast
	AQ4N-^{64}Cu-hCe6-liposome	Chemotherapy, PDT	Breast

In hypoxic cancerous cells, polymeric -NO_2 groups (namely, 2-nitro imidazole and nitrobenzyl alcohol) are generally converted into –NH_2 through a series of biochemical interactions with nitro-reductase and NADPH. A lot of researchers have utilized different hypoxia-responsive -NO_2 containing NPs, such as nitroimidazole functionalized block co-polymers loaded with therapeutics, HA conjugated 6-(2-nitroimidazole)hexylamine loaded with lactate oxidase and virus, and 2-nitroimidazole-functionalized peptides decorated with cationic lipid like co-polymers loaded with siRNA, to treat against various hypoxic tumors for getting enhanced anti-cancer efficacy through reduced conversion of hydrophobic 2-nitroimidazole to hydrophilic 2-aminoimidazole, leading to degradation of NPs, O_2-depletion, silence of pro-tumorigenic gene (CDC20), and the release of loaded therapeutics in hypoxic tumor cells [77] (Table 5).

Tirapazamine, the aromatic N-oxide, and banoxantrone dihydrochloride, the aliphatic N-oxide derivative, exhibit higher cytotoxicity in hypoxic cancerous cells, while tirapazamine may generate radical species to break DNA via a single-electron reduction reaction catalyzed by different intracellular reductases, resulting in cellular damage and apoptosis, and banoxantrone dihydrochloride (AQ4N) may be reduced by various reductases and its protonated form (AQ4) may use DNA intercalation to suppress topoisomerase II-activity [77]. A lot of researchers have utilized various hypoxia-responsive conjugated N-oxide NPs such as glucose oxidase (GOx)-conjugated tirapazamine-loaded NPs, tirapazamine-encapsulated porphyrinic-based lanthanide-doped or anti-programmed death-ligand 1 (anti-PD-L1)-conjugated MOFs, banoxantrone dihydrochloride and ^{64}Cu-hCe6 encapsulated liposomes, banoxantrone dihydrochloride and GOx encapsulated MSNs, and near-infrared fluorescent banoxantrone dihydrochloride NPs, together with or without CDT, PDT, laser irradiation or image-guided therapy, to treat against various tumors for getting higher anti-cancer efficacies

through O_2-consumed enhanced hypoxic micro-environment creation, oxidative stress-induced higher ·OH generation or GSH-induced cleavage of tetrasulfide bonds of MSNs, and accumulation and release of therapeutics in hypoxic tumor cells leading to cellular death [77] (Table 5).

Quinone compounds and their derivatives, such as semiquinones or hydroquinones produced by one or two electron reduction, have been used for tumor treatment owing to their excellent chemical and electronic features, while the elimination of indolequinones may be achieved in hypoxic environment by the bio-reductive action of DT-diaphorase NQO1 over-expressed in cancer cells [77]. A few researchers have utilized enzyme-responsive conjugated prodrug (dopaquinone and 5-fluorodeoxy uridine) NPs and versatile NPs-functionalized with benzoquinone groups to treat against hypoxic tumors for availing enhanced anti-cancer therapeutic efficacy [77].

A lot of investigators have utilized different hypoxia-responsive conjugated NPs such as radio-sensitizer tantalum oxide (TaOx) NPs functionalized with PEG, conjugated manganese (Mn) NPs, FA-modified liposomal TiO-porphyrin NPs, NIR-laser-controlled O_2/Pt^{2+} self-generating prodrug (UCPP)-conjugated NPs, C_3N_4-based NPs, graphene oxide NPs, or pH-sensitive zinc(II) metalated porphyrin NPs, combined with or without laser irradiation/PDT, to treat against hypoxic tumors for getting higher anti-cancer efficacies through the production or release of O_2, and the generation of toxic ·OH and /or $^1O_2$ to kill cancer cells [77].

Interstitial fluid pressure (IFP)-related targeting

The delivery of therapeutics may be restricted due to elevated IFP for the drops in convection between intra-vascular and extra-vascular spaces [77]. A few scientists have utilized chemotherapeutic component-encapsulated liposomes applying single heating approach with the combination of hyperthermia and coagulative ablation (45 ◦ C for 2 min and 70 ◦ C for 3 min) to treat against 4T1 tumor bearing Balb/c mice for getting higher anti-tumor efficacy [77].

ATP-responsive targeting

The concentration gradients of ATP levels between tumoric intracellular and extracellular fluids have been utilized to develop ATP-responsive NPs for tumor treatments [77]. A lot of researchers have utilized different cargos-loaded/conjugated NMs such as siRNA-encapsulated ATP-responsive micelles, protein-based NPs conjugated with therapeutics, Mg^{2+} and chaperon, PEI hybridized with ATP-responsive ligands, DOX and siRNA, ATP-binding aptamer DNA functionalized with polymers, ATP-responsive nanogels/HA, to treat against various tumors for getting enhanced anti-cancer efficiencies through increased accumulation and degradation of NMs, and efficient release of the therapeutics into the TME for apoptotic cell death, cell cycle arrest at the G2 phase, as well as tumor inhibition [77].

Exogenous stimuli-responsive targeting

Temperature stimuli-responsive nanomaterials include poly-N-isopropylacrylamide (PNIPAAm), poly(2-oxazo line)s (POxs), poly(vinyl caprolactam) (PNVCL), poly(methyl vinyl ether) (PMVE), and liposomes for their solid-to-liquid phase transition characteristics in accordance with external conditions for having lower critical solution temperature (~30 ◦ C) [77]. A few researchers have utilized DOX-encapsulated temperature stimuli-responsive liposomes functionalized with iRGD peptide (CCRGDKGPDC) for the treatment against tumor for getting enhanced NPs-internalization by αVβ3-positive tumor cells and ultrasound mediated DOX-release in TME to kill cells [77].

A few investigators have used various magnetically responsive NPs such as encapsulated super paramagnetic Fe_2O_3 NPs (SPIONs), magnetic molybdenum disulfide ($mMoS_2$) modified liposomes, DOX-encapsulated tannic acid-Fe conjugate (TAFs) functionalized with fibronectin, and GSH-responsive MOF loaded with IDO inhibitor and NO donor s-nitrosothiol groups, to treat against tumors for getting higher anti-cancer efficacies such as enhanced NPs-accumulation and cargos-release to kill tumor cells, or improved anti-tumor immunotherapy [77].

Ultrasound-mediated external stimulus or sonodynamic therapy (SDT) is capable not only to disrupt NPs and release their cargos at the desired site/s, but also produce CO_2 to accomplish inertial cavitation and augment ROS accumulation to induce cancerous and immunogenic -cells death [77]. A few researchers have utilized various ultrasound-stimuli-responsive NMs such as cisplatin encapsulated solid lipid NPs, DOX-loaded MSNs, epirubicin-encapsulated micelles, piezoelectric NPs encapsulated with DSPE-PEG and decorated with anti-HER2 Ab, to treat against cancer for getting enhanced anti-cancer efficacies such as higher cellular uptake, enhanced drug-release, cancer cell killing, or suppression in tumor invasiveness and growth [77].

Laser (near infrared (NIR)) stimuli-responsive targeting may break light-sensitive functional groups or bonds such as truxylic acid, coumarinyl and pyrenyl methyl esters of the NPs at the lesions [77]. A few scientists have utilized different laser stimuli-responsive NPs such as photolabile spherical nucleic acid NPs decorated with antisense oligonucleotide and siRNA for their oxidized degradation to release cargos at the tumor site/s for availing enhanced anti-cancer therapeutic efficacy [77].

Hybridized and combined targeting

Generally, NMs may accumulate in the tumor site through passive or active targeting. Subsequently, such NMs tuned with endogenous stimuli may liberate cargos in controlled manner, and the release may be highly triggered under the cumulative action of multiple exogenous stimuli such as ultrasound, magnetic, laser, temperature or light at the targeted site [77]. A lot of researchers have utilized different stimuli-responsive targeting strategies for various therapeutic agents to treat against cancer for getting triggered anti-cancer efficacies such as the receptor or EPR -mediated NMs-internalizations in tumor cells, endosomal escape of the NMs from the acidic endo/lysosomal environment, endogenous stimuli-responsive cargos-release, and the synergistic killing efficiency in the TME through the exogenous stimuli [42,77] (Table 6).

Table 6. A few hybridized combinations of cancer nanomedicines.

Targeting strategies	Stimuli-responsiveness	Therapeutic agents	Cancer types/cells
Transferrin	Temperature	TMNP	Breast
	GSH	DMSN@PMAsh-Tf	Lung
	pH / Temperature	LF-PNIPAM-co-AA	Breast
Folic acid (FA)	pH	PEG-FA/(DOX+VER)@ZIF-8	Melanoma
	GSH	FA-S-S-PLGA NPs	Lung
	ROS	Lut/FA-Oxi-aCD NPs	Breast
	pH and GSH	PsEEL-DOX/PTX NMs	Lung
	pH and ROS	DT-NP	Breast
	pH and Laser	HM-Bi@PEG-FA NSs	Lung
	MMP-2	F/TMSP-NLC	Fibrosarcoma
Biotin	pH	B780/Qu NPs	Breast
	GSH	SS-Biotin-Ppy NWs	Breast
Hyaluronic acid (HA)	pH	HA/(R837+1MT)@ZIF-8	Melanoma
	GSH	HL/MOS@M780, LOD NPs	Breast
	pH and GSH	DOX/siGCN5@HPMSNs	Breast
	GSH and Hypoxia	PaHAsC	Melanoma
	Laser	DOX/ICG-CuS@MnO_2/HA NPs	Breast
RGD	pH	Met/GOx@His/ZIF-8~RGD	Breast
	GSH	RGD/MoS_2/DOX	Cervical
	pH and GSH	CuS DE NPs	Breast
	pH and esterase	IR825@IRI-ATRA/RGD NPs	Breast
	Laser	SPIOCs@HSA(PTX)-RGD	Glioma
	MMP-2	RHMH18@AuD NPs	Ovarian
RGD+FA	Thermal	Graphene oxide	Carcinoma
LHRH	pH, HIFU and ultrasound	LHRH-ELP-DOX	Breast
	GSH	PTX-LHRH-DCMs	Breast
EPR effects	P2, pH and ROS	SRF/Ce6-loaded PEG-M-PPMT NPs	Lung
	pH and cathepsin B	TNV	Melanoma, Colon
RGD and EPR effects	GSH and laser	RDG/shRNA	Breast

Table 6. Contd. 1

Targeting strategies	Stimuli-responsiveness	Therapeutic agents	Cancer types/cells
Hyperthermia (HT)	pH, PTT	GQD-ZIF-8-DOX	4T1 cells
HT	pH, PTT	GO-PEG/PAH-DA/DOX	MCF-7, MCF-7/ADR cells
IL-13Rα2, HT	pH, NIR, PTT	Graphene-silica-PEG-(IL-13 peptide)-DOX	Glioma cells
HA, HT	pH, NIR, PTT	GO-Au-HA-AHD-DOX	Huh-7, CHO cells
HA, HT	pH, NIR, PTT	rGO@MSN-HA-DOX	HeLa cells
Lf, HT	pH, NIR, PTT	rGO-Lf-DOX	RG2, MCR-5 cells
HT	pH, NIR, PTT, CT, PAT	rGO/Bi_2S_3-PVP-DOX	HeLa, MCF-7, Hep-G2, BEL-7402 cells
HT	pH, NIR, PTT	GQD-MSN-DOX	4T1 cells
HT	pH, GSH, PTT	GO-Alg-DOX	A549 cells

HT	pH, GSH, NIR,PTT	rGO-BPEI-PEG-DOX	PC3, HeLa cells
Ce6	660nm LED, PDT	GO-PEG-DOX/Ce6	SCC7 cells
Hypocrellin A	470nm LED, PDT	GO-SN-38-hypocrellin A	A549 cells
Ag	pH, 425nm LED, PDT	GQD-Ag-PEG-DOX	HeLa, DU145 cells
ZnPc	pH, 440nm light, PDT	Graphene-(poly-L-lysine)-DOX-ZnPc	HeLa, MCF-7, B-16 cells
HT	pH, 660nm light, PDT, PTT	rGO-Au-spinach extract-FU	HeLa, CHO cells
-	pH	rGO-PF-127-CUR-PTX	A549, MDA-MB-231cells
Magnetic, HT	pH, PTT	GO-Fe_3O_4-CPT-MTX	Hep G2 cells
HT	pH, PTT	GO-poloxamer 188-DOX-irinotecan	MDA-MB-231 cells
HT	pH, PTT	GO-PEG-DOX-rapamycin	MDA-MB-231, MCF-7, BT474 cells
TRAIL	pH	GO-PEG-furin cleavable peptide-TRAIL-DOX	A549 cells
Lf	NIR	Graphene-Lf-DTX, PFH	GR2 tumor
Bcl-2, GT	-	GO-PEI-DOX-siRNA	HeLa cells
Anti-miR21, GT	-	GO-PEI-PSS-ADR-(anti-miR-21)	MCF-7, MCF-7/ADR cells
DNA, GT	pH	rGO-chitosan-SPIO-DOX-DNA	A549, C4-2b cells
Magnetic	Laser	$ZnFe_2O_4$-rGO	LNCaP, U87MG
RGD, Cy7	Laser	rGONM-PEG-Cy7-RGD	U87MG cells
HA	Laser	PgP/HA-rGO	MDAMB231, A549
RGD, Cy3	Laser	rGONR-PEG-Cy3-RGD	U87MG cells

Table 6. Contd. 2

Targeting strategies	**Stimuli-responsiveness**	**Therapeutic agents**	**Cancer types/cells**
Let-7 g miRNA, GT	pH	GO-Gd-Polyamidoamine-EPI-miRNA	U87 cells
shRNA(shABCG2), GT	pH	GO-chitosan-Aco-PEG-PEI-DOX-shRNA	Hep G2 cells
FA, GT	pH, NIR	GO-PEI-PEG-FA-DOX-siRNA	MCF-7/MDR cells
Magnetic/photo hyperthermia	pH, AMF, NIR, MHT, PTT	GQD/MSN/Fe_3O_4-DOX	4T1 cells
Magnetic hyperthermia, ROS	NIR, magnetic field, PTT, PDT	GQD-Fe_3O_4/SiO_2-liposome-DOX	Eca-109 cells
ROS, Hyperthermia	660nm, 808nm light, PTT, PDT	GO-PEG-Ce6	KB, 4T1 cells
ROS, Hyperthermia	980nm light, PTT, PDT	GO-PEG-FA	B16F0 cells
ROS, Hyperthermia	775nm light, PTT, PDT	MFG-$SiNc_4$	HeLa cells
HA, ROS, Hyperthermia	365,808 nm light, PTT, PDT	rGO-ZnO-HA	MDA-MB-231 cells
HA, Ce6, ROS, Hyperthermia	Hadase, 670,810 nm light, PTT, PDT	GO-HA-Ce6	A549 cells
ROS, Hyperthermia	630,808 nm light, PTT, PDT	UCNPs-NGO/ZnPc	HeLa cells
Hyperthermia, pDNA, GT	808nm light, PTT	PEG-BPEI-rGO/pDNA	NIH/3T3 cells
FA, Hyperthermia, siRNA, GT	808nm light, PTT	GO/FA/siRNA	MIA PaCa-2 cells
Hyperthermia, siRNA, GT	808nm light, PTT	NGO-PEG-PEI	HeLa cells
Hyperthermia, CpG	808nm light, PTT	GO-PEG-PEI-CpG	RAW 264.7 cells
RT, Hyperthermia	808nm light, X-ray, PTT	^{131}I-rGO--PEG	4T1 cells
Hyperthermia, Magnetic	LFUS irradiation, pH, SHT	GO-PEG-EPI	GL261 cells
ROS, Hyperthermia	FUS irradiation, SDT, SHT	rGO@MSN-IONP-PEG-RB	SKBr3 cells
ROS, Hyperthermia	NIR, Ultrasound, SDT, PDT	GO-TiO_2-MnO_x-PVP	4T1 cells

A lot of investigators have used various stimuli-responsive targeting strategies for different graphene-based therapeutic agents for the treatment of cancer to avail higher anti-cancer efficacies [62-66] (Table 6. Contd. 1 and 2).

Table 6. Contd. 3

Targeting strategies	Stimuli-responsiveness	Therapeutic agents	Cancer types/cells
PSMA, X-ray CT	-	DOX-PSMA-AuNP	LNCaP cells
Photothermal, PET, Optical imaging	PTT, Thermal ablation	DOX@PEG-HAuNS	A431, MDA-MB-231 cells
FA, Hyperthermia	Cy3 luminescence	DOX-FA@AuNR	KB, HeLa cells
cRGD, PET, Optical imaging, CT	PTT	AuNR-DOX-cRGD	U87MG cells
Hyperthermia, TPL	Thermal	AuNR@SiO_2-DOX	A549 cells
B-cyclodextrin	Fluorescence (Rhodamine B)	PTX@PEG-AuNP	HeLa, A549, MG63 cells
Thermal ablation	Thermal	CIS@AuNR	OCI AML3, Jurkat T, MCF-7 cells
Optical imaging	PTT, NIR	CET-PEG-AuNR	A431, MCF-7 cells
PET, PAT	PTA, NIR	CET-HAuNS	A431 cells
Photothermal, US	PTT, NIR	AuNS	HeLa cells
Photothermal, X-ray CT	PTT, X-ray absorption	PEG-AuNR	MDA-MB-435 cells
Cy5.5-MMP	PTT, Cy5.5 fluorescence	MMP-AuNR	HeLa cells, SCC-7 tumors
Light scattering	-	siRNA-AuNR	Carcinoma cells
PET, PAT	PTT, Radiotherapy, NIR	siRNA-HAuNS	HeLa cells
MRI, X-ray CT	Radiotherapy	Au@DTDTPA-Gd	Solid tumors
US, X-ray CT	PTT	Au@PLA-$(PAH/GO)_2$	Tumors
MRI, Magnetic	PTT	SPIO@AuNS	A431 tumors
HER2, Optical imaging, MRI	PTT, Fluorescence of ICG	Anti-HER2-AuNS@Fe_3O_4@SiO_2-ICG	SKBR3, MDA-MB-231 cells
HER2, OCT	PTT, NIR	Anti-HER2-AuNS@SiO_2	SKBR3 cells
EGFR, Optical imaging, TPL	PTT	Anti-EGFR-AuNS/AuNR	OECM1, Cal27 cells
FA, X-ray CT	PTT, Radiotherapy	AuNR-SiO_2-FA	MGC803 cells
FA, MRI, Hyperthermia	PTT	Fe_3O_4@SiO_2@AuNR@mSiO_2-FA	KB cells

A lot of other researchers have applied different stimuli-responsive targeting strategies for various gold nanocomposites-based therapeutic agents to treat cancer for achieving higher therapeutic anti-cancer efficacies [10] (Table 6. Contd. 3).

Conclusions and future perspectives

In this review, different types of NMs have been demonstrated and designed with different characteristics to conjugate them with a variety of ligands and cargos for accumulating them at the desired site/s through passive, active and /or stimulus-responsive targeting/s to reduce the toxicity or other side effects and also to protect them from the deletion or clearance in blood circulation for getting higher therapeutic efficiencies against cancer. However, there are some caveats for their biomedical applications and needed to give further emphasize on optimization of the size and surface of NMs for membrane-protection, optimization of NMs-formulations with variable ligand clustering, multiple binding ligands, and various conjugation densities, scaling up of the NMs at commercial setting, high-throughput screenings, identifications of new receptors with corresponding ligands, and the explorations of suitable new and promising NMs. In addition, more extensive investigations regarding their interactions with cells, immunotoxicity, biodistribution, pharmacokinetics and elimination, routes of administration specifically oral and intravenous, successful scale-up of NMs-formulations with batch-to-batch contents uniformity, absence of residual organic solvents and surfactants, and effective biological efficacies are required to consider the conjugated NMs as well as NPs as potent nanomedicines for clinical translations.

Abbreviations:

NMs: Nanomaterials; NPs: Nanoparticles; PEG: Poly (ethylene glycol); PLGA: Poly (lactide-co-glycolide); PLA: Poly (D,L-lactide); PAMAM: Poly (amidoamine); PAPA: Poly (α, β-aspartic acid); PEI: Polyethylenimine; DOX: Doxorubicin; CIS: Cisplatin; RAPA: rapamycin; CPT: Camptothecin; DTX: Docetaxel; THZ: Thioridazine; PTX: Paclitaxel; VEGF: Vascular endothelial growth factor; TRAIL: Tumor necrosis factor related apoptosis-inducing ligand; DFO: Deferoxamine; YC1: HIF1α inhibitor lificiguat known as YC1; P-gp: P-Glycoprotein; 5-FU: 5-Fluorouracil; ADM: Adriamycin; MMP-2: Matrix

metalloproteinase-2; HER-2: Human epidermal growth factor receptor-2; PSMA: Prostate-specific membrane antigen; YPSMA: Mouse monoclonal PSMA antibody; pHA: p-hydroxybenzoic acid; RGD: Arginyl glycyl aspartic acid peptide; ASGP: Asialo glycoprotein; LDL: Low density lipoprotein; LRP: Low density lipoprotein receptor-related protein (LRP); TfR: Transferrin receptor; TAT: Transactivator of transcription; mAb: Monoclonal antibody; CTX: Chlorotoxin; Asp8: Aspartate-8; CD: Cluster of differentiation; HSA: Human serum albumin; BSA: Bovine serum albumin; HCD: Hydroxypropyl-β-cyclodextrin; PPSOC: Phospholipid-protein shell-oily core; JGN: Janus gold nanorod; PCL: Poly(ε-caprolactone); DNM: Daunomycin; MTX: Methotrexate; DOC: Docetaxel; MTN: Maytansinoid; QC: Quercetin; SRF: Sorafenib; NOS: Noscapine; LHRH: Luteinizing hormone-releasing hormone; ICAM1: Intracellular adhesion molecule-1; CXCR4: Chemokine receptor type-4; IL: Interleukin; EGFR: Epidermal growth factor receptor; TNF: Tumor necrosis factor; MXT: Mitoxantrone; CPM: Cyclophosphamide; BTM: Bortezomib; ERB: Epirubicin; VRB: Vinorelbine; CDT: Chemodynamic therapy; PTT: Photothermal therapy; PDT: Photodynamic therapy; SDT: Sonodynamic therapy; RT: Radiotherapy; MOF: Metal organic framework; NIR: Near-infrared; Au: Gold; Hyd: Hydrazone; CPP: Cell penetrating peptide; FA; Folic acid; SMCC: Succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate; PVP: Poly vinyl pyrrolidone; BLM: Bleomycin; PLA: Poly L-Aspartate; BHC: Berberine hydro chloride; RBC: Red blood cell (Membrane); EpCam: Epithelial cell adhesion molecule (Antibody); OPT: Oxaliplatin; Carb: Carboxylate; (Pt(R,R-dach)): Active ingredient of oxaliplatin; DAU: Daunorubicin; PA: Polyvalent aptamers; CPA: Cyclophosphamide; GMC: Gemcitabine; CPC: Capecitabine; VCR: Vincristine; ETP: Etoposide; HPMC: Hydroxypropyl methylcellulose; PVA: Polyvinyl alcohol; 6-MP: 6-mercaptopurine; Tf pep: Transferrin peptide; rGO: Reduced grapheme oxide; CUR: Curcumin; BBR: Berberine; ODNs: Anti-sense oligodeoxynucleotides; GM-CSF: Granulocyte macrophage colony stimulating factor; SAN: Sanazole; HT: Hyperthermia; GQD: Graphene quantum dots; GO: Graphene oxide; GT: Gene therapy; MHT: Magnetic hyperthermia therapy; SHT: Ultrasound hyperthermia therapy; NIR: Near-infrared; ZIF-8: Zeolitic imidazolate framework-8; PAH: Poly(allylamine hydrochloride); DA: 2,3-dimethylmaleic anhydride; IL-13: Interleukin 13; HA: Hyaluronic acid; ADH: Adipic acid dihydrazide; MSN: Mesoporous silica nanoparticles; Lf: Lactoferrin; PVP: Polyvinyl pyrrolidone; CT: Computed tomography; PAT: Photo acoustic tomography; Alg: Alginate; Ce6: Cholorin e6; SN-38: 7-ethyl-10-hydroxycamptothecin; ZnPc: Zn(II)-phthalocyanine; PFH: Perfluorohexane; ADR: Adriamycin; SPIO: Super paramagnetic iron oxide; EPI: Epirubicin; Aco: Aconitic anhydride; AMF: Alternating magnetic field; MFG: Magnetic and fluorescent graphene; SiNc4: Silicon napthalocyanine bis (trihexyl silyloxide); LFUS: Low-power focused ultrasound; RB: Rose benga; CpG: Cytosine-phosphate-guanine; AuNP: Gold nanoparticle; HAuNS: Hollow gold nano-sphere; AuNR: Gold nanorod; SiO_2: Silica oxide; CET: Cetuximab; MMP: Matrix metallo-proteinase; DTDTPA: Diethylene triamine penta acetic acid; Gd: Gadolinium; ICG: Indocyanine green; EGFR: Epidermal growth factor receptor; PET: Positron emission tomography; TPL: Two photon luminescence; PTA: Photo thermal ablation; US: Ultrasound; MRI: Magnetic resonance imaging; OCT: Optical coherence tomography.

Conflict of interests

The author declares no conflicts of interest.

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