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Engineered nanoparticles against MDR in cancer: The state of the art and its prospective

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Abstract

Cancer is a highly heterogeneous disease, both within a single patient as well as between patients, and is the leading cause of death worldwide. A variety of mono and combinational therapies, including chemotherapy, have been developed and refined over recent years for its effective treatment. However, the evolution of chemotherapeutic resistance or multidrug resistance (MDR) in cancer has become a major challenge to successful chemotherapy. MDR is a complex process that combines multifaceted non-cellular and cellular-based mechanisms. Research in the area of cancer nanotechnology over the past two decades has reached the point where smartly designed nanoparticles with targeting ligands can aid successful chemotherapy by preferentially accumulating within the tumor region through means of active and passive targeting to overcome MDR, and simultaneously reduce the off-target accumulation of their payload. Such nanoparticle formulations – sometimes termed nanomedicines - are at different stages of cancer clinical trials and show promise in resistant cases. Nanoparticles as chemotherapeutics carriers provide the opportunity to have multiple payloads of drug and/or imaging agents for combinational and theranostic therapy. Moreover, nanotechnology has the potential to combine new treatment

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DECLARATION OF INTEREST

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strategies, such as near-infrared (NIR), magnetic resonance imaging (MRI), and high intensity focused ultrasound (HIFU) into cancer chemotherapy and imaging. Here we discuss the cellular/non-cellular factors that underpin MDR in cancer, and the potential of nanomedicines to combat MDR, along with recent advances in combining nanotechnology with other approaches in cancer therapy.

Keywords

Multidrug resistance; MDR; efflux transporter; Nanoparticles; passive targeting; active targeting; pH-sensitive; HIFU; Combinational drug targeting

1. INTRODUCTION

Cancer, a complex series of fatal diseases, is a huge health crisis faced by both developed and developing countries. In the coming years, more than 15 million new cancer patients are predicted worldwide by 2020, which will no doubt stretch social, economic and healthcare resources across countries. In a majority of cases, treatment failure and death ensues with the systemic spread and growth (metastasis) of malignant cells from their original site to vital organs. Generally, cancer treatment involves single and/or a combinational approach of surgery, radiation therapy, chemotherapy, and biological therapy [1-2]. Over the past decades, remarkable progress has been visible in cancer therapy toward its cure. Yet the integral component of cancer treatment, chemotherapy, faces numerous limitations. Non-targeted and limited delivery of chemotherapeutics to the tumours, failure of drug accumulation, and non-responsiveness by the tumours are the major constraints. Considering the tumour pathophysiology, multi-resistance or multidrug resistance (MDR) is judged the main cause of the penultimate and last constraint [3-6]. MDR is a complex mechanism involving abnormal vasculature, localized area of hypoxia, low pH environment, up-regulated ABC-transporters, enzymatic degradation, aerobic glycolysis, elevated apoptotic threshold, and increased interstitial fluid pressure as well as numerous other factors that reduce drug actions. [5-10]. In recent years, many potential strategies have been evaluated to mitigate MDR, modification of chemotherapeutic combinations, inactivation of MDR-related mRNAs, monoclonal antibodies against an extracellular epitope of a MDR efflux transporter, use of chemo-sensitizers, the application of nanoparticles, and others [1, 3, 5, 8, 11-15]. Among these approaches, smartly designed nanoparticles create an opportunity to overcome the MDR for the established chemotherapy associated with the development of resistance to cancer treatment. When successful, this allows the effective use of established chemotherapeutics [1, 3, 5, 8, 11-15]. A wide variety of nanoparticles are currently under investigation, including polymeric/non-polymeric nanoparticles, dendrimers, quantum dots, carbon based nanoparticles, and lipidic nanoparticles as carriers for anti-cancer drugs in MDR tumors [15-18]. Targeted nanomedicines in MDR cases can improve the therapeutic index of chemotherapeutics by providing improved pharmacokinetics consequent to their preferential accumulation within the tumor region via the 'enhanced permeability and retention' (EPR) effect (i.e., passive targeting), or by specific cell targeting through targeting ligands (i.e., active targeting), and suppressing the efflux and other resistance mechanisms [19-21]. MDR targeted nanocarriers should optimally possess prolonged systemic

circulation, reduced non-specific cellular uptake, active and passive targeting potential, controlled drug release, and multidrug encapsulation for instance for chemotherapeutic drugs, nucleic acids and inhibitors of MDR causing enzymes etc. [5,8,12,22-24]. The work presented here offers insight into the factors responsible for the MDR of cancer that eventually leads to the failure of chemotherapy. Moreover, the progress made in the development of different nanoparticle designs against MDR, including multiple payload nanocarriers and stimulus responsive nanoparticles are discussed.

2. MDR IN CANCER

The specificity of drug, tumor and host, collectively, characterizes resistance to chemotherapy that ultimately results in failure of anticancer drugs in treating tumor [25]. The principal barrier to effective anticancer therapy is acquisition of natural (inherited) and acquired resistance [5,9,25]. Natural resistance is the unresponsiveness of a tumor towards an anticancer drug, whereas acquired resistance is unresponsiveness of tumors that develops over the time against chemotherapeutics that are initially effective [12, 22, 25]. Over the years, a large number of elements have been discovered as factors claimed for MDR in cancer [23]. They can be classified into two major categories; cellular and physiological factors. Cellular factors include molecular targets, genetic defects like polymorphisms and gene deletions, an over-expression of efflux pumps, reduced apoptosis and increased drug metabolism; while physiological factors include inter-cellular interactions, higher interstitial fluid pressure, a low pH environment, a hypoxic area within the tumor, irregular tumor vasculature, and the presence of cancer cells in areas difficult to penetrate [5,8,12,22-25].

2.1. Factors responsible for MDR in cancer

As classified above, key cellular factors include efflux pump activity e.g. ATP-dependent transporters and/or reduced influx of drugs, the activation of detoxifying proteins, defective apoptotic machineries, and altered DNA repair pathways [23-27]. ATP binding cassette transporters or ABC transporter membrane proteins (including nucleotide binding domain (NBD) and transmembrane domain (TBD)) can efflux molecules out of cells against a concentration gradient by hydrolyzing ATP at NBD [26-29]. Until now, a large number of anticancer molecules have been identified as the substrate for this protein family, including taxols, anthracyclines, topotecan, and etoposides [29-31]. Another important cellular factor, apoptosis, plays a significant role in the life cycle of a cell [34]. It is characterized by the process of development of cell membrane blebs, DNA condensation and fragmentation, and leads towards the organized death of a cell [32, 33]. Two interlinked pathways, extrinsic and intrinsic, activate this form of cell death by the binding of ligands to cell surface receptors and by direct stimuli at mitochondria, respectively [35]. A cancer cell can develop adaptations against this complex cell death programming. Most common among these are upregulation of anti-apoptotic proteins, like Bcl-2, Bcl-XL and Mcl-1, and downregulation of Bcl-2 family proteins, like bax, which provide cellular mechanisms to avoid apoptosis [36,37]. Moreover, endogenously, inhibitor of apoptosis (IAP) and the PI3K/Akt pathway are also considered processes to mitigate apoptosis [38]. Other factors, such as death receptors and p53 genes, are known to make cancer cells resistant to paclitaxel and cisplatin [39]. DNA repair mechanisms provide another feature responsible for resistance

development against the drugs (as found for alkylating agents, anthracycline analogues and platinum-based compounds) whose anti-cancer activity is directly related to their interaction with DNA [40, 41]. The microenvironments of tumors (particularly high interstitial fluid pressure (IFP), hypoxia and a low extracellular pH (pHe)) play a key role in tumor progression and are considered one of the important extracellular contributors in MDR of cancer [42]. Unlike normal tissues, altered regulation of angiogenesis leads to leaky unorganized vasculature development in tumor tissues that allows leakage of protein from blood vessels into their interstitium, and eventually raises interstitial fluid pressure (IFP>100mm of Hg) [43, 44]. Such unorganized vasculature may, on the other hand, aid in the passive tumor targeting of cancer whereby nanoparticles of sizes under 100 nm can accumulate [1]. However, this IFP together with the unorganized vasculature often causes the poor accumulation of conventionally i.v delivered chemotherapeutics [45]. Decreased blood flow, transcapillary fluid flow, and convective transport are the essential mechanisms accounting for this [43]. Moreover, deep localization of tumors can make drug delivery difficult in conventional chemotherapy [43]. Linked to these extracellular factors, hypoxia, which is a common event with tumors, represents another key element behind the resistance that develops in many cancers [46]. Perfusion and diffusion limited oxygen delivery, due to abnormalities in microvessels and altered diffusion mechanisms and sometime anemic hypoxia, are considered as mechanism of tumor hypoxia [47]. Hypoxia forces the cells to rely on for their energy needs sources that later cause the excess production of lactate and carbonic acid [48]. These acid byproducts eventually reduce the extra-cellular pH (normally 5.5 to 7) [49]. Therapy and drugs whose action are dependent on the presence of oxygen; for example, radiation therapy (requiring oxygen to generate reactive oxygen species), and drugs such as melphalan, bleomycin and etoposide etc., face resistance development in a case of hypoxia [50, 51]. Moreover, activation of hypoxia inducible factors (HIF1) eventually leads to the over expression of vascular endothelial growth factors (VEGF), nitric oxide synthase (NOS), transforming growth factor beta (TGF- β), interleukin-8, and ultimately induce resistance for some chemotherapeutics, like cisplatin and doxorubicin [52]. Under the harsh environment of anoxia, the cell cycle may become arrested in either G1/G2 or S phase, as well as induce an increase in DNA repair enzymes to result in resistance to cycle-selective cytotoxic drugs (5-FU, paclitaxel) and to the DNA-damaging agents (alkylating agents, cisplatin) [51]. Fourthly, the most important indirect effect of hypoxia is the induction of the ABC transporters [53]. Additionally, the presence of acidic products of glycolysis also leads to generation of a pH gradient, which causes an 'ion trapping' phenomenon, characterized by a permeability difference between ionized and non-ionized forms of anticancer drugs. This mechanism is of particular importance for weakly basic drugs like doxorubicin and vincristine, which remain ionized and therefore trapped in the acidic extracellular environment [54]. This ion trapping is thus dependent on the pH, as well as the pKa of the drugs. Besides these most common factors responsible for MDR development, researchers have noted that some further adaptive mechanisms also play a role. These include the expression of survivin, inhibition of apoptosis, autophagy, and alterations in receptors and enzymes (for example; folate transporters and tyrosine kinase, etc.) [55-57].

3. Engineered nanoparticles against MDR in cancer

In current scenarios, nanotechnology is explored in relation to cancer chemotherapy - with the focus of overcoming MDR. The anatomy and physiology of tumor blood vessels is markedly different from that of normal ones. They exhibit rather large fractions of proliferating endothelial cells, an augmented tortuosity, a deficit of pericyte and an unusual basement membrane. Furthermore, lymphatic drainage is also impaired in tumors, which is attributable to greater retention of extra-vascular macromolecules. Such a series of events is collectively denoted as the “enhanced permeation and retention (EPR) effect” [12,58, 59]. This effect favors the uptake of nanocarriers by accelerating the passive targeting in tumors. The other approach used for tumor targeting in nanotechnology is active targeting, which is based on ligand-tagged nanoparticles for specific receptor binding. However, delivering a payload to specific tumor tissues and cells face many challenges, or in other words, may be considered as factors responsible for the off-target and failure of chemotherapy with conventional therapeutic delivery. Unorganized tumor vasculature and impeded lymphatic flow generate high interstitial fluid pressure that leads to a tremendously hydrophilic ambience that restricts the access of drugs into solid tumors [12]. In addition to this, the extracellular matrix of tumors, fibrillar collagen, and necrotic non-supporting regions are other significant hindrances that impact the clinical efficacy of anticancer agents [6-9]. Here we discuss advances in nanoparticle-based chemotherapeutics delivery that have been made over the recent decade. In this regard, we give attention to the factors that describe how the nanoparticles were engineered to overcome MDR factors, along with tumor specific targeting. A wide spectrum of nanoparticles have been synthesized from different organic and inorganic materials. Materials from these two categories in nanotechnology have their own pros and cons. Most of the nanoparticles used in anti-cancer drug delivery can be classified as vesicular and particulate nanocarriers. Those most commonly studied in relation to targeting MDR in cancer are liposomes, micelles, and nanoemulsions. Within this category, liposomes are most the extensively investigated nanocarrier and also are established as an anti-cancer pharmaceutical in the form of Doxil[®]. These are vesicular structures that have an aqueous core surrounded by a lipid bilayer, which commonly are made by film hydration and the ethanol injection method [1]. Liposomes can encapsulate drugs within their aqueous compartment or in their lipid bilayer depending on the physicochemical nature of the drug. Liposomes as nanoparticles, provide the opportunity to be tailored to the carrier by the way that it can offer active or passive targeting and, thereby, overcome MDR factors [60]. Recently, active targeted liposomes of Doxorubicin (mAb 2C5 as ligand) and Paclitaxel (anti-HER2 mAb targeting ligand) are under clinical study [61-63] and seem promising. The approach of combining physical method and stimulus responsive liposomes has resulted in the design for localized targeting to overcome MDR issues with cells. Based on this idea, ThermoDOXO[®] (thermosensitive DOX loaded liposome) was developed, and has now successfully reached a phase III clinical study [60, 64, 65]. Some further interesting liposomal formulation have likewise been developed and are providing promising results in MDR cases at a preclinical level. Recently, a neutral DOPC (1,2-dioleoyl-sn-glycero-3-phosphatidylcholine) liposome-siRNA delivery system was designed that can work against resistance to cisplatin by siRNA-dependent silencing of the cisplatin resistance transporter mRNA of ATP7B [66]. The modulation of Pgp by liposomes marks

another important method of enhancing the therapeutic efficacy of anticancer drugs in MDR cancer cells [67]. The appearance of multiple mechanisms that simultaneously account for the development of MDR encouraged the need of a multi-targeted design in nanoparticles. Recently, Minko and co-workers developed a liposome system to simultaneously carry DOX (chemotherapeutics) and antisense oligonucleotides targeting MDR1 mRNA and BCL-2 mRNA [68]. This complex nanoparticle system was found to effectively kill resistant A2870/AD human ovarian carcinoma cells. A further example is a dual-functional liposome that is based on the synthetic polymeric nano-biomaterial (Gal-P123) for reversal of MDR in hepatocellular carcinoma (HCC) cells against mitoxantrone [69]. The combined effect of active targeting and chemosensitization (by Gal-P123) were found to be the main contributors for its improved tumor growth suppression [69]. In another study, Kobayashia et al., demonstrated the potential of transferrin receptor targeted liposomes to overcome MDR against DOX [70].

Polymeric micelles represent a potential nanoparticle system that allows efficient delivery of chemotherapeutics in non as well as resistant cancers [71, 72]. A polymeric micelle is principally formed when the hydrophobic part of a block copolymer is driven to the interior of the aqueous phase, whereas the hydrophilic portion faces outwards to form a shell. This supports high drug loading for hydrophobic drugs, and tailoring of the structure to permit multiple functions; making this nanocarrier attractive for drug delivery. Many polymeric micelles are currently in different phases of clinical studies, including examples from cancer therapy. Recently, Yang et al. developed FG020326 (P-gp blocking imidazole derivative) and vincristine (anti-cancer molecule) loaded folate-functionalized polymeric micelles from diblock copolymers of poly(ethylene glycol) (PEG) and biodegradable poly(ϵ -caprolactone) (PCL) [73]. This resulted in the occurrence of a 5-fold higher re-sensitization of resistant KB-V200 cells [73]. Moreover, cellular efflux was significantly reduced for rhodamine 123, which was used a marker of P-gp drug efflux in the study [73]. Recently, in a further interesting micelle design, TNF-related apoptosis inducing ligand (Apo2L/TRAIL) and self-assembled micelles of DOX containing a cationic copolymer of poly{N-methyldietheneaminesesbacate)-co-[(cholesteryloxocarbonylamido ethyl) methyl bis(ethylene) ammonium bromide]sebacate} (P(MDS-co-CES)) was developed that showed improved cytotoxicity in resistant tumor cells [74]. A caveat of these exciting studies is that whereas these multiple payload carrying, multi-targeted particles look attractive and illustrate good results, these presently are limited to cells based assay. It is possible that such complex design at the nanoscale level, may not be easily reproducible or translatable. Hence, further studies are awaited.

Nanoemulsions represent another vesicular nanocarrier system that are being studied as anti-cancer drug carriers against MDR cancer cases Nanoemulsions are either of water in oil or oil in water, and there are multiple emulsion carrying oil droplets dispersed at the size of 1-200 nm. It is the oil in water type that is commonly used consequent to their high solubilisation capacity for lipophilic drugs in their oily phase. A majority of the investigations that have used nanoemulsions as anticancer drugs highlight their obvious potential for bioavailability enhancement of orally administered lipophilic chemotherapeutics [75, 76]. Recently, a few studies emphasized that nanoemulsions can be designed to overcome MDR in cancer. In this regard, Ganta et al., reported that the co-

administration of paclitaxel and curcumin resulted in inhibition of NF κ B activity and down regulation of P-glycoprotein expression in resistant cells (wild-type SKOV3 and resistant SKOV3_{TR} human ovarian adenocarcinoma cells) [76]. In this case, curcumin inhibited NF κ B and caused ABC transporter down-regulation.

Among the particulate nanocarriers, polymeric nanoparticles, solid lipid nanoparticles, inorganic nanoparticles, polymeric conjugates, carbon nanotubes, and dendrimers have been widely explored to overcome MDR in cancer. Biodegradable polymer-based nanoparticles have been well received in cancer nanotechnology owing to their satisfactory safety, controlled drug release capacity, and opportunity for multi-functionalization [77, 78]. Koziara et al. has investigated the in-vivo efficacy of paclitaxel (PAX) NPs in a PAX-resistant human colorectal tumor HCT-15 xenograft model, and had found the marked inhibition of tumor growth in mice that were treated with PAX-NPs [79]. Yang et al. formulated chitosan NPs - containing shRNA that targeted MDR1 - and found a significant reversal of paclitaxel resistance in A2780/TS cells, in a time-dependent manner [80]. Recently, stearylamine-modified dextran nanoparticles of DOX have been designed, and demonstrated success by improving the intracellular delivery of DOX in resistant osteosarcoma cells [81]. However the mechanism behind this effect remains to be more fully characterized, and is presumed to involve the suppression of P-gp. In another study, Misra et al. developed DOX and curcumin loaded into a single PLGA nanoparticle system [82]. The curcumin within the nanoparticles was described to facilitate the retention of DOX with in the cell nucleus and to also down-regulate the expression of P-gp and BCL-2 in K562 cells. This co-incorporation of curcumin into nanoparticle formulations of DOX resulted in better in-vitro cytotoxicity, in comparison to DOX nanoparticles alone [82]. In another interesting design, Lei formulated HER2 antibody conjugated DOX-loaded PLGA nanoparticles and studied cellular uptake and cytotoxicity in resistant ovarian SKOV-3 and uterine MES-SA/Dx5 cells [83]. The results revealed an increased cellular uptake of targeted nanoparticles, as compared to free DOX and non-targeted nanoparticles. Furthermore, Shieh et al. designed DOX loaded nanoparticles in which they co-encapsulated DOX and a photosensitizer in 4-armedporphyrin-poly lactide nanoparticles, whose surface was coated with D- α -tocopheryl polyethyleneglycol1000succinate (TPGS) - which is a potential P-gp inhibitor [84]. The study findings indicated that such a combination of agents exhibited a synergistic effect in relation to DOX intracellular delivery to resistant MCF-7/ADR cells. Yet another potential nanoparticle system design used for anticancer delivery in MDR cases are Dendrimers [85]. These structures are characterized by a central core, an inner dendritic structure of highly branched polymers, and an outer surface of multivalent functional groups [85]. The functional groups present on their surface can incorporate charged polar compounds by electrostatic interaction, whereas their hydrophobic interior is able to efficiently harbor uncharged, non-polar compounds. Potentially valuable, exterior functional groups can enable modulated drug release that is governed by specific pH, specific enzymes, or by targeting moieties - such as the RGD peptide or mAbs, etc. In the area of chemotherapeutics, many hydrophobic drugs such as Doxorubicin and Paclitaxel are frequently targeted as dendrimers [86, 87]. Lee et al. designed DOX dendrimers through hydrazone linkage [88]. This study demonstrated that these DOX-dendrimers exhibited a controlled drug-loading via multiple attachment sites, a modulated solubility profile

consequent to PEGylation, along with a characteristic drug release that was influenced by their pH-sensitive hydrazine dendrimer linkages. The developed polyester dendrimer-PEO-doxorubicin conjugate significantly blocked the growth of a DOX-resistant C-26 tumor. Furthermore, in-vivo studies in tumor bearing mice that involved intravenous delivery showed a 9-fold higher uptake of DOX-dendrimers by tumor cells, as compared to free DOX, and resulted in complete tumor regression [88].

Cyclodextrin, which has a long history of use in pharmaceuticals as a solubility-enhancing agent, has been evaluated in the design of nanoparticles for chemotherapeutic delivery in normal and resistant cancers. Qiu and co-workers developed an advanced cyclodextrin-based formulation of DOX (sPEL/CD) for which they reacted methoxy polyethylene glycol and poly lactic acid to obtain linear mPEG-PLA. This produced a branched three-dimensional star-like structure of arms around a central β -cyclodextrin core [89]; providing hydrophobic and hydrophilic fragments that coexisted within each single star-like structure. This delivery system was found to exhibit an improved drug loading and entrapment efficiency that was attributable to the presence of the poly lactic acid, which increased hydrophobic interactions between the polymer and DOX, together with a superior loading of DOX within the inner space of β -cyclodextrin. The study findings revealed that there was 3-fold decrease in the IC50 value by DOX-loaded sPEL/CD, as compared to free DOX, in resistant MCF-7/ADR cells. The authors concluded that the mPEG-PLA block segment of the sPEL/CD complex likely was having identical actions as do Pluronic block copolymers in averting MDR in cancer cells, owing to their contrasting structural resemblance [90]. Moreover, it was presumed that suppression of P-gp by the polymers might also provide a probable mechanism to account for the reversal of MDR by sPEL/CD.

Gold nanoparticles (Au-NPs) are being extensively evaluated for cancer theranostics, biomedical imaging, and bio-sensing. Their biocompatibility, high stability and tissue permeability make them a promising carrier system for delivery of anticancer drugs. Anticancer agents can be formulated as Au-NPs by physical adsorption, ionic bonding, and/or covalent bonding [91-93]. Au-NPs can be also utilized for delivery of large highly hydrophilic molecules, including proteins, DNA, or RNA. More recently, TNF α has been integrated with colloidal gold for treating advanced solid tumors, as epitomized by sarcomas and melanomas, is in phase I clinical trials [94]. Gu et al. prepared Au-NPs of DOX by integration of DOX into PEG-Au-NPs via a disulfide bond (Au-PEG-SS-DOX). This resulted in increased intracellular drug uptake in resistant HepG2-R cells [95]. Of interest, it was observed that DOX uptake was confined to cytoplasm only, which indicates that the cytotoxic activity of Au-PEG-SS-DOX was not due to its interaction with nuclear DNA. The authors hypothesized that these NPs caused MDR reversal via mechanisms that altered cell membrane properties and impaired mitochondria to thereby induce cell apoptosis. Wang et al. designed DOX Au-NPs using a hydrazone linker (DOX-Au-Hyd-NPs). Their study demonstrated uptake of nanoparticles via active caveolae- and clathrin-mediated endocytosis, and the subsequent release of DOX from the nanoparticles into the cytoplasm and nucleus [96]. The DOX-Au-Hyd-NPs markedly increased DOX intracellular uptake and minimized efflux, and resulted in a significantly enhanced cytotoxicity in comparison to free DOX in resistant MCF-7/ADR cells.

Magnetic nanoparticles have also received significant attention from scientists working on designing metallic nanoparticles against MDR, and as theranostics in cancer. In magnetic targeting, a strong magnetic field is applied within the tumor area that guides the local targeting and controls the release of drug in the blood circulation. Various magnetic materials with a wide range of magnetic properties are available, such as magnetite, iron, nickel, cobalt, neodymium-iron-boron, and samarium-cobalt. Moreover, there are liquids that can become intensely magnetized in the presence of a magnetic field, which are known as ferrofluids. Ferrofluids are basically nano-dimension ferromagnetic particles (~10 nm diameter) suspended in a liquid medium. Currently, the most frequently applied magnetic NP is iron oxide NPs that offer biodegradability, biocompatibility, super-paramagnetic effects, and the ability to serve as a contrast agent in MRI [97]. At present, superparamagnetic iron oxide (Fe_3O_4) nanoparticles, which involve local hyperthermia or oscillation strategies to deliver conjugated drugs, are being intensely investigated. Furthermore, magnetic fields can also be utilized for targeted delivery of drugs inside the body [98]. Chen et al. studied the role of Fe_3O_4 magnetic nanoparticles in daunorubicin mediated prevention of MDR (in-vitro) in resistant K562 cells [99]. The coating of tetraheptylammonium (THA) on the NPs was undertaken to improve interaction between NPs and the lipid portion of cell membranes. The study revealed a significant interaction of THA-coated Fe_3O_4 NPs with cell membranes and a substantial enhancement in the uptake of daunorubicin into resistant K562 cells. The control formulation, that comprised comparable sized THA capped Ni magnetic nanoparticles, did not much influence daunorubicin cellular uptake into sensitive or resistant cells, which suggests that THA capped Fe_3O_4 nanoparticles selectively accelerate daunorubicin uptake.

The use of inorganic carriers in nanotechnology to aid delivery of anticancer agents likewise appears to be expanding. One of the most important among them are silica NPs, which are broadly utilized as a non-metallic inorganic chemotherapy carriers. Huang et al., designed DOX silica nanoparticles (MNSP) by covalently linking DOX in mesoporous silica by hydrazone bonding to improve DOX delivery into resistant MES-SA/Dx-5 cells [100]. In a different study, Meng et al., formulated MNSP by co-incorporating DOX and MDR1 siRNA [101]. In this example, the MNSP surface was activated with a phosphonate group that facilitated DOX binding within the MNSP by electrostatic action, and the coating of cationic polyethylenimine (PEI) on this functional group supported the complexation with anionic MDR1 siRNA. The co-delivery of DOX and MDR1 siRNA by means of MNSP notably improved the intracellular and intranuclear uptake of DOX into resistant KB-V1 cells, as compared to free DOX or DOX MNSP without siRNA. Endosome escape for DOX in this NP system was facilitated by the proton sponge induced by PEI [101]. In a further study, Shen et al. also formulated DOX MNSP, which exhibited 8-fold greater potency and a significantly increased intracellular and intranuclear concentration of DOX, in comparison to free DOX in-vitro in resistant MCF-7/ADR cells [102]. The authors claimed that MNSP inhibited P-gp expression by down-regulating P-gp levels. They proposed that intracellular uptake of MNSP occurred through micropinocytosis and after becoming entrapped inside the cell, MNSP proved able to circumvent P-gp due to its extremely large size. In a more comprehensive study, Chen et al., co-engineered DOX and BCL-2 siRNA as MNSP by the entrapment of DOX inside the MNSP pores and complexation of BCL-2 siRNA within the

modified polyamidoaminedendrimers of MNSP [103]. The study provided a dramatic 132-fold increase in cytotoxicity by the MNSP preparation, in contrast to free DOX in resistant A2780/AD human ovarian cancer cells. The suppression of BCL-2 mRNA together with the perinuclear localization of DOX, by means of MNSP, likely accounted for this noticeably improved antitumor efficacy.

Carbon-based nanoparticles in the form of a carbon nanotube have been extensively exploited as a drug carrier to overcome MDR in cancer. Carbon nanotubes are thin sheets of benzene ring carbons that are evenly rolled to form a smooth, seamless rod-like tubular structure [104]. They possess a very large surface area that offers abundant attachment sites for integrating targeting ligands along with an interior space for incorporating therapeutic or diagnostic agents. These carbon nanotubes additionally possess electrical and thermal conductivity, which may be of value in chemotherapeutics in relation to thermal ablations. Recent strategies in the context of nanotube developmentss comprise the integration of important anticancer drugs, exemplified by doxorubicin and paclitaxel, nucleic acids including antisense oligonucleotides, and SiRNAs [105]. Li et al., designed DOX carbon nanotubes by linking a P-gp antibody onto functionalized carbon nanotubes by a diimide-activated amidation reaction, followed by loading DOX through physical adsorption [106]. This physical adsorption of DOX into nanotubes kept the molecular integrity intact by preventing chemical bonding. Moreover, a modified DOX release from nanotubes was observed following exposure of DOX nanotubes under near-infrared radiation. The authors proposed that the controlled and sustained release of DOX via near-infrared radiation and specific P-gp targeting were major contributors in successfully mitigating MDR in resistant human leukemia K562R cells. Furthermore, it was concluded that coupling of the P-gp antibody on nanotubes offers substantial steric hindrance for P-gp recognition of DOX - resulting in inhibition of its efflux.

Among currently available lipid-based nanoparticles, solid lipid nanoparticles (SLNs) are considered as potential carriers for poorly water-soluble drug. They offer improved properties by combining the benefits of liposomes, NPs, and lipid emulsions. They are usually prepared by high-pressure homogenization or microemulsification techniques, whereby drug is efficiently entrapped in a lipid matrix [107]. To exploit these features of SLNs for effective targeting in cancer, Kang et al., formulated DOX-loaded SLNs using glycerylcaprate (Capmul MCM C10) as the lipid phase, polyethylene glycol 660 hydroxystearate (Solutol HS15) as the surfactant, and curdlan as the shell forming material [108,109]. The resulting DOX SLNs demonstrated a 17.1- and 21.6-fold increased cellular uptake at 1 and 2 h, respectively. In addition, a greater apoptotic cell death was found in comparison to free DOX in resistant MCF-7/ADR cells. Of note, these SLNs did not induce hemolysis of human erythrocytes, which contributed to their safety. In another study, Shuhendler et al., prepared polymer-lipid hybrid SLNs by co-incorporating DOX and mitomycin C using myristic acid, HPESO, pluronic F68, PEG100SA, and PEG40SA [110]. In this case, the resulting SLNs showed a 20- to 30-fold increased toxicity in resistant MB435/LCC6/MDR1 cells, as compared to free DOX.

Hydrophilic polymers conjugated to proteins and anticancer drugs are one of the most extensively explored approaches for drug delivery – establishing these polymer therapeutics

as one of the first classes of anticancer nanomedicines. The prospect of using more sophisticated polymer-based vectors in chemotherapeutics is continuously expanding [111]. For protein drugs, conjugation with synthetic polymers - predominantly PEG - by covalent linkage, enhances their residency time in plasma, decreases their protein immunogenicity, and widens their therapeutic index. Presently, many PEGylated enzymes, such as L-asparaginase, and cytokines that include interferon- α and granulocyte colony-stimulating factor are being frequently utilized. In addition to these examples, polymer conjugation can play a crucial role in anticancer drug delivery by optimizing the bio-distribution of low-molecular-weight drugs, and facilitation of tumor-specific targeting with minimization of toxicity. Polymeric conjugates can be delivered either via passive targeting, by the enhanced permeability for lysosomotropic delivery following the EPR effect, or by active targeting by binding cell-specific ligands for receptor-mediated targeting. A prime example of a polymeric conjugate chemotherapeutics is polyglutamic acid-paclitaxel nano-conjugate which is currently being evaluated in phase III trials for non-small-cell lung cancer. At a preclinical level interesting studies have been reported by Sirova M et al., investigating the in-vivo efficacy and safety of HPMA-based copolymers of DOX possessing a spacer containing pH-sensitive linkage in murine tumor models bearing T cell lymphoma EL4 or B cell lymphoma 38C13 [112]. This study showed that conjugates with 10-13% weight of bound DOX produced remarkable anti-tumor effects. In-vivo outcomes of a representative number of interesting nanomedicines as an approach to overcome MDR across different types of malignancies are summarized in Table 1. Nowadays, drug delivery utilizing pH sensitive material-based nanocarriers represents an active targeting approach in cancer chemotherapy. Many studies have been undertaken to try to exploit mechanisms to overcome efflux-dependent MDR via acidic pH-activation. The basic idea of cellular targeting in this context is disruption of the endosomal membrane, and burst release of nanocarrier-loaded drugs into the cytoplasm [134]. In this regard, the pH difference between the extracellular (not < 6) and lysosomal milieus (not > 5) can be explored in order to design a specific pH responsive drug release system to target the lysosomal rather than the endosomal compartment, to thereby reduce undesirable drug release in the tumor stroma [135, 136]. In this scenario, it is extremely important to design lysosomal pH responsive pK_b of polymers sensitive to accomplish the precise pH dependent drug release. In order to trigger drug release, these nanocarriers should be sufficiently sensitive to structural transformations and solubility changes in the acidic lysosomal compartments. Nevertheless, such pH-responsive polymers can cause disruption of endosomal membranes, most probably by proton absorption and by interacting with these membranes [118,137]. The proton absorption leads to osmotic swelling and rupturing of the membranes, likely the result of the nanocarriers generating endosomal membrane defects by creating pores or channels. The acidic milieu of endosomes/lysosomes is quite possibly a factor in the unresponsiveness of some weakly basic drugs. For example, DOX becomes protonated and turns hydrophilic and positively charged. This water-soluble charged DOX is then unable to cross the endosomal/lysosomal membrane and thus can become entrapped. A similar phenomenon accounts for resistant cancer cells that sequester cytosolic DOX and forms the basis of the proposed protonation, sequestration and secretion (PSS) model. This PSS model has been proposed to explain the sensitivity of some tumor cells and resistance of MDR cells towards weakly basic chemotherapeutic drugs. If correct, a nanoparticle design should be able to aid endosomal

escape of such drugs. In one report, Lee et al., engineered pH-sensitive polymeric micelles of Doxorubicin targeting resistant solid tumors [118]. The surface of these DOX loaded pH-sensitive micelles was coated with folate (PHSM/f). This PHSM/f was designed using a mixture of two block copolymers of poly(l-histidine)-*b*-PEG-folate (75 wt.%) and poly(l-lactic acid)-*b*-PEG-folate (25 wt.%). The resulting PHSM/f preparation demonstrated more than 90% cytotoxicity in DOX resistant MCF-7 (MCF-7/DOX^R). A series of events likely supported this activity that included folate-receptor mediated endocytosis, the ionization of histidine residues resulting in micelle destabilization, the disruption of endosomal membranes, and Pgp inhibition [118]. Further in-vivo study of this NP preparation in mice bearing s.c. MCF-7 or MCF-7/DOX^R xenografts demonstrated a substantial reduction in tumor volumes in mice administered PHSM/f, in comparison to both free DOX or an identical micelle formulation without folate (PHSM). In addition to this, the accumulation of PHSM/f DOX was 20-fold greater in solid tumors, as compared to free DOX. Likewise, He et al., formulated pH-responsive drug-surfactant micelles-co-loaded mesoporous silica nanoparticles via in situ co-self-assembly of DOX, surfactant micelles-CTAB (chemosensitizer), and silica [138]. This system provided a precise pH-responsive drug release both in-vitro and in-vivo, with significant anti-cancer and MDR actions. The mechanism for overcoming MDR was demonstrated to be a synergistic cell cycle arrest/apoptosis-inducing effect as a consequence of the chemosensitization property of the surfactant, CTAB. In another study, Kim et al. evaluated a DOX-loaded second generation pH-sensitive micelles system that was composed of poly(L-histidine-*co*-L-phenylalanine(16 mol%))(MW: 5K)-*b*-PEG(MW: 2K) and poly(L-lactic acid)(MW: 3K)-*b*-PEG(MW: 2K)-folate (80/20 wt/wt%) to support early endosomal pH targeting (pH 6.0) as evaluated in-vivo in a MDR ovarian tumor-xenograft mouse model [139]. The study demonstrated a prolonged circulation of the drug carrier, a higher tumor-selective accumulation, as well as an increased intracellular drug delivery. Moreover, the prepared micelle formulation successfully suppressed the growth of existing MDR tumors within the mice. The authors concluded that this micelle formulation was superior to first generation formulations targeting pH 6.8 and folate receptors. Overall, pH responsive nanoparticles appear to be highly promising in regard to chemotherapeutic delivery and cancer targeting in resistant tumors consequent to pH controlled drug release.

Ultrasound-and temperature responsive nanoparticles have received considerable attention in relation to optimizing cancer chemotherapy, and provide an example of how NPs can be designed to be responsive to external physical stimuli.. The application of ultrasound energy (oscillating pressure wave frequency > 20 kHz) is best known in relation to its use in imaging and diagnostics. For therapeutic application, ultrasound energy can readily be focused on a small region of tissue with higher intensity to achieve deeper penetration efficiency, as is accomplished with high intensity focused ultrasound (HIFU). Initially, therapeutic ultrasound was primarily restricted to thermal ablation of tumors, but more recently its use has been applied to attain specific accumulation of NPs and instant release of their payload. Ultrasound energy has the potential to increase localized delivery of drug and/or nanoparticles to a specific biological area by three mechanisms; heat generation, acoustic cavitation, and acoustic radiation forces. The important parameters in relation to nanoparticle design to achieve ultrasound mediated heat-induced delivery are the

optimization of the time of ultrasound use, the nature of the ultrasound (whether continuous or pulsed), and its frequency and power [140-142]. In addition, microbubble technology has been broadly studied for ultrasound-related drug delivery and imaging. A microbubble is a gas filled microsphere that has a core of water insoluble gas (e.g. perfluorocarbons, sulfur hexafluoride) whose surface is stabilized by protein, lipid, surfactant, or a biocompatible polymer. Initially, this technology was established for contrast development in ultrasound imaging. In the presence of microbubbles, ultrasound exposure can lead to acoustic cavitation at low frequency, whereas at a higher frequency it causes a loss of structural integrity. In a cellular environment, ultrasound exposed microbubbles can significantly change the permeability of cells (a process commonly called sonoporation), to facilitate the absorption of a drug or drug carrier across the cell membrane [143]. Alternatively, microbubbles can potentially be used as a direct delivery system of a drug or gene carrier following ultrasound energy mediated microbubble disruption [144,145]. There are multiple reports of the beneficial application of HIFU to drug targeting with nanoparticles, including the development of ultrasound responsive micellar polymeric particles [140, 146]. The logic behind this particular approach involves the synthesis of drug-loaded pluronic micellar nanoparticles, which can be restricted within the tumour cell by passive targeting, followed by the controlled focusing of an ultrasound pulse. In vitro studies have demonstrated that such as a micellar delivery system can quickly liberate its payload following a 15-30 s short HIFU pulse [140,146,147], to generate higher intracellular concentration of DOX in sensitive and MDR cancer cell lines [148,149]. In translational animal studies, an increased drug accumulation and distribution in intraperitoneal (i.p.) and subcutaneous (s.c.) ovarian tumors was achieved with a focused 30 s ultrasound pulse [150]. This resulted in the improved efficacy of a DOX micellar preparation that was activated by ultrasound, as compared to DOX administered as a solution form in the i.p. ovarian carcinoma model [151]. Moreover, the use of the ultrasound pulse provided a uniform distribution of drug throughout the tumor volume, whereas distribution was non-uniform in its absence. In relation to the s.c. tumor model, the micelle-based DOX delivery system combined with a focused ultrasound pulse resulted in a significant delay in tumor growth [151].

4. NANOCARRIERS WITH COMBINATIONAL PAYLOAD AGAINST MDR

The idea of utilizing combination therapy to increase the therapeutic efficacy of drug treatment and simultaneously maintain a tolerable toxicity profile has greatly evolved over recent years. The logic behind this therapy lies in appropriately targeting different biochemical pathways to overcome MDR in heterogeneous tumors. In a one-dimensional mode of action utilizing single drug chemotherapy, activation and strengthening of alternative pathways can lead to the appearance of a MDR phenotype and the likelihood of tumor recurrence [152]. The key rational supporting combination therapy is to concurrently impact diverse molecular mechanisms so that tumor cell death probability is increased and the opportunity of MDR development and overlapping resistance is reduced [153]. The development of technologies to achieve accurate and restricted delivery of multiple agents should enhance the effectiveness of combination therapy. In this regard, multifunctional nanoparticle delivery systems have proved useful in reversing MDR cellular and in vivo cancer models by allowing co-administration drug combinations that synergistically

induce tumor cell death [154,155,156]. The combination of a chemotherapeutic agent, along with an MDR modulator, will more effectively impact tumor cells that have acquired MDR. In the case of apoptotic pathway dependent MDR, prosurvival mutations - as occur in the deregulation of BCL2 and NFkB - permit tumor cells to withstand drug insults and, thereby, limit their entry into apoptotic pathways. This feature of MDR cancer can potentially be exploited by numerous therapies, such as co-administering pro-apoptotic modulators or inhibitors to restore apoptotic signaling [157,158] to increase the sensitivity of MDR cells to chemotherapeutic agents and, thereby, reduce the re-occurrence of tumors [159-161]. As a consequence, multi-targeted payload in a single nanomedicine (MTPNs) are being increasingly studied for treating cancers as, if appropriately optimized, they should be less prone to resistance development. Clearly for MTPNs to work most effectively, they should combine agents that possess a different yet complimentary mechanism of action, and can combine small synthetic chemotherapeutics with biological molecules such as siRNA, miRNA [162-164]. Representative examples of MTPNs in preclinical and clinical studies are summarized in Table 2. Research outcomes thus far appear quite promising for MTPNs against resistant cases of cancers; supporting their further development as a potential cancer therapy option.

It should be noted, however, that combining synergistic drugs and/or proteins as a payload in single nanoparticle systems provides significant challenges in designing formulations that can optimize each of the sometimes very different individual components in relation to their pharmacokinetic profile within the tumor as well as the systemic circulation, as well as dose titration and dosing frequency [164-166]. Such optimization of combinational payloads appears to be feasible, and has been aided by pharmacokinetics models and a sound knowledge base built by both scientists and regulatory authorities in relation to more conventional drug delivery systems [170,171], whose principles can be applied to the continued development of MTPNs.

5. FUTURE SCOPE AND CONCLUDING REMARK

Nanotechnology-based chemotherapeutic targeting approaches are gaining increasing interest in cancer drug therapy and particularly in relation to MDR cases. Preferential accumulation of chemotherapeutics in the tumor region can be attained by the combination of active and passive targeting that can further help in reducing the off-target accumulation of cytotoxic agents, and therefore, toxic effects to healthy tissues/organs. Doxil[®], Marqibo[®] and Abraxane[®] are representative names of successfully marketed nanomedicines for cancer chemotherapy. These nanomedicines, because of their size (<200 nm), passively target poorly vascularized tumor tissues and efficiently overcome the non-cellular factor of MDR for their payloads. We have summarized, above, the diverse nanotechnology-based formulations that are being evaluated across different preclinical and clinical stages of cancer therapy, theranostics, and diagnostics, and suggest for further reading our recently published review [1]. Notably, the development of multi-targeted payloads of MDR inhibitors combined within a single nanomedicine holds promise to result in successful chemotherapy. Recently, substantial work has been undertaken using nanoparticles as drug carriers for the local targeting of organ specific cancers. This offers the potential for high accumulation of chemotherapeutics within the cancer-affected organ, to thereby reduce the

unwanted exposure to healthy tissue. In this regard, the treatment of lung cancer with nanomedicines to provide local delivery and improve the outcome of chemotherapy appears an area of high focus [193]. As an important challenge to achieve effective cancer therapy, an key present therapeutic interest is to target cancer stem cells that have the property of self-renewal and initiation of tumor growth. These stem cells are normally resistant to chemotherapy and radiotherapy, and hence their effective elimination is critical and can potentially be aided by the described nanotechnologies, if creatively applied.

Abbreviations

ABC	ATP binding cassette
ASOs	Antisense oligonucleotides
Au-NPs	Gold nanoparticles
BCRP	Breast cancer resistance protein
DOPC	1,2-dioleoyl-sn-glycero-3-phosphatidylcholine
DOX	Doxorubicin
EPC	Egg phosphatidylcholine
EPR	Enhanced permeation and retention
HCC	Hepatocellular carcinoma cells
HIF	Hypoxia inducible factors
HIFU	High intensity focused ultrasound
MDR	Multidrug resistance
MNSP	Mesoporous silica nanoparticles
MRI	Magnetic resonance imaging
MRP	Multidrug resistance-associated protein
MTPNs	Multi-targeted payload in single nanomedicine
MX-LPG	Mitoxantrone incorporated liposome
NBD	Nucleotide binding domain
NFκB	Nuclear factor kappa B
NIR	Near-infrared
NOS	Nitricoxide synthase
NP	Nanoparticle
PAX	Paclitaxel

PCL	Poly(ϵ -caprolactone)
PEG	Poly(ethylene glycol)
P-gp	P-glycoprotein
pHe	Extracellular pH
PHSM/f	pH sensitive micelles with folate
PLGA	Poly(lactic-co-glycolic acid)
PSS	Protonation, sequestration and secretion
RES	Reticuloendothelial system
ROS	Reactive oxygen species
siRNA	Small interfering RNA
SLN	Solid lipidnanoparticle
TBD	Transmembranedomain
Tf-R	Transferrin receptor
TGF-β	Transforming growth factor beta
TNF	Human tumor necrosis factor
TRAIL	TNF-related apoptosis inducing ligand
VEGF	Vascular endothelial growth factor

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Table 1

Nanomedicines investigated against MDR in cancer: preclinical studies.

S.No.	Nanomedicine	Drug	Targeting Ligand	Cancers	Model	Outcome	Refs.
1.	Liposome	Topotecan		Breast cancer	MCF-7/adr cell xenografts, and naturally resistant B16 melanoma metastatic model in nude mice	exhibited the strongest inhibitory and anti-metastatic effect on investigated model; furthermore, mitochondrial targeting effects were demonstrated by enhanced drug content and co-localization in mitochondria, dissipated mitochondrial membrane potential, opening of mitochondrial permeability transition pores, release of cytochrome C, and activation of caspase 9 as well as 3.	[113]
		Mitoxantrone	Gal-P123	Hepatocellular carcinoma (HCC)	HCC Huh-7 cells and MDC-K11/BCRP cells; HCC xenograft BALB/c mice	Mitoxantrone loaded liposome had 2.3-fold higher cytotoxicity in Huh-7 cells and 14.9-fold increase in mitoxantrone accumulation in MDCK11/BCRP cells; furthermore improved antitumor activity in-vivo in orthotopic HCC xenograft BALB/c mice.	[69]
		Paclitaxel	TPGS 1000-TPP	Lung cancer	A549 cells, A549/cDDP cells and A549/cDDP cells xenografted nude mice	In comparison with taxol and regular paclitaxel liposomes, the mitochondria targeting paclitaxel liposomes exhibited the strongest anticancer efficacy <i>in vitro</i> and in the drug-resistant A549/cDDP xenografted tumor model; Furthermore, have the potential to treat drug-resistant lung cancer.	[114]
2.	Polymeric Micelles	Doxorubicin and siRNA	Passive and active cancer targeting/ RGD4C and TAT peptide	Breast cancer	MDA-MB-435 tumor model	Multifunctional polymeric micellar system was shown to be capable of DOX and siRNA delivery to their intracellular targets, leading to the inhibition of P-gp-mediated DOX resistance <i>in vitro</i> and targeting of $\alpha v \beta 3$ -positive tumors <i>in vivo</i>	[115]
		Paclitaxel	folic acid	Oral epidermal carcinoma	BALB/c mice bearing KBv MDR tumor xenografts	stronger antitumor efficacy was shown in folic acid functionalized Pluronic P123/F127 mixed micelles encapsulating paclitaxel in KBv MDR tumor xenografts	[116]

S.No.	Nanomedicine	Drug	Targeting Ligand	Cancers	Model	Outcome	Refs.
						model, with good correlation between <i>in vitro</i> and <i>in vivo</i> results	
		Docetaxel	Passive targeting	Oral epidermal carcinoma	KB and KBv cells; KBv xenograft BALB/c mice	Cytotoxicity studies in KB and KBv cells revealed that the mixed micellar formulations were more potent than the commercial docetaxel formulation (Taxotere). Moreover, antitumor activity assessed in KBv cancer xenograft BALB/C nude mice models showed that the mixed micelles significantly reduced the tumor size than Taxotere.	[117]
		Doxorubicin	folate	Breast cancer	MCF-7/DOXI cells and MCF-7/DOXI xenografts model	Doxorubicin loaded pH-sensitive micelles decorated with folate showed more than 90% cytotoxicity of DOX resistant MCF-7 cells <i>in vitro</i> . Moreover, in the MCF-7/DOXI xenograft model accumulated doxorubicin level in solid tumor was 20 times higher than free doxorubicin.	[118]
		Paclitaxel	folate	Breast cancer	MCF-7 tumor bearing mice	Dual-targeting micellar demonstrate excellent MDR overcoming ability and improved tumor distribution <i>in vivo</i> .	[119]
3.	Nanoemulsion	Paclitaxel and 17AAG or tanespimycin	Passive targeting	Cervical cancer, Breast cancer, Ehrlich ascites carcinoma	HeLa, MCF-7 cells and Ehrlich ascites carcinoma in mice	Co-encapsulation of paclitaxel and 17AAG into the oil-in-water nanoemulsions cause synergistic cytotoxicity effect in cancer due to overcoming the P-glycoprotein-mediated multidrug resistance as well as functional inhibition of Hsp90 with 17AAG.	[120]
4.	Polymeric nanoparticles	Paclitaxel	Passive targeting	Human colon adenocarcinoma	HCT-15 cells and HCT-15 xenograft model	Paclitaxel encapsulated nanoparticles was shown to overcome drug resistance in HCT-15 cell line. Moreover, significant inhibition in tumor growth was observed in HCT-15 mouse xenograft model.	[79]
		Doxorubicin and curcumin	Passive targeting	Myeloma, prostate and ovarian cancer	NCI/ADR, P388/RPMI8226 cells and its xenograft model	A composite doxorubicin-curcumin nanoparticle that overcomes both MDR-based doxorubicin chemoresistance and doxorubicin-induced cardiotoxicity	[121]

S.No.	Nanomedicine	Drug	Targeting Ligand	Cancers	Model	Outcome	Refs.
		Doxorubicin	Passive targeting	Breast cancer	MCF-7/ADR	Polyethylene glycol anchored doxorubicin nanoparticles bypassed the P-gp mediated effluxing and exhibited potent antitumor activity <i>in vitro</i> and <i>in vivo</i> as well as significantly increased <i>in vivo</i> safety than free doxorubicin.	[122]
		Doxorubicin and cyclosporin A	Passive and active targeting	Lung cancer	A549 cells and A549-bearing mice	Antitumor drug and drug efflux pump inhibitor co-loaded nanoparticles offer advantages to overcome the drug resistance of tumors and highlight new therapeutic strategies to control drug resistant tumors.	[123]
		Vincristine	Active targeting/ folic acid and R7 peptide	Breast cancer	MCF-7, MCF-7/Adr cells and <i>In vivo</i> model	Significantly enhance cellular uptake and cytotoxicity <i>in vitro</i> as well as exhibited the strongest antitumor efficacy <i>in vivo</i> ; Furthermore, effective nanocarrier for delivering antitumor drug and overcoming multidrug resistance.	[124]
5.	Dendrimers	Doxorubicin	Passive targeting	Colon carcinomas	C-26 cells and C-26 tumors bearing BALB/c mice	In cytotoxicity test, dendrimer-doxorubicin was 10 times more toxic than free doxorubicin toward C-26 cells. Moreover, its tumor uptake was nine fold higher than i.v. administered free doxorubicin in C-26 bearing BALB/c mice.	[88]
6.	Gold nanoparticle	Pc4	Passive targeting	Non-specific tumor	Tumor-bearing nude male mice	With the gold nanoparticle-Pc 4 conjugates, the drug delivery time required for photodynamic therapy has been greatly reduced to less than 2 h, compared to 2 days for the free drug.	[126]
		Tiopronin	Passive targeting	Breast cancer	Female Balb/c nude mice-bearing MCF-7S cells	Both 2 and 6 nm Gold@tiopronin nanoparticles were distributed throughout the cytoplasm and nucleus of cancer cells <i>in vitro</i> and <i>in vivo</i> , whereas 15 nm Gold @tiopronin nanoparticles were found only in the cytoplasm as aggregates.	[127]
7.	Magnetic nanoparticle	Doxorubicin	Passive targeting	Breast cancer	Mice with xenograft MDA-MB-231 breast tumor	Inhibited tumor growth efficiently and showed no significant toxicity for mice organs after 24 days treatment	[128]

S.No.	Nanomedicine	Drug	Targeting Ligand	Cancers	Model	Outcome	Refs.
8.	Silica nanoparticle	Doxorubicin and siRNA	Active targeting/ siRNA	Breast cancer	MCF-7/MDR cells and MCF-7/MDR xenograft model	Achieve 8% enhanced permeability and retention effect at the tumor site and analysis of multiple xenograft biopsies demonstrated significant Pgp knockdown at heterogeneous tumor sites.	[129]
9.	Carbon nanotube	Doxorubicin	Active targeting/ anti-P-gp	Leukemia	K562R cells	It expressed 2.4-fold higher cytotoxicity compared with free Doxorubicin and specifically localize on the cell membrane of K562R cells	[130]
10.	Solid lipid nanoparticle	Doxorubicin and mitomycin C	Passive targeting	Breast cancer	MDR human mammary tumor xenografts	Demonstrated enhanced efficacy compared to liposomal Doxorubicin with up to a 3-fold increase in animal life span, a 10-20% tumor cure rate, undetectable normal tissue toxicity and decreased tumor angiogenesis.	[131]
		Doxorubicin	Active targeting/ glycosaminoglycan hyaluronan	Ovarian cancer	human ovarian adenocarcinoma cell line and xenograft model	Dramatically decreased cell viability in P-gp-overexpressing human ovarian adenocarcinoma cell line compared to Doxil. Furthermore, showed a superior therapeutic effect over free DOX in a resistant human ovarian adenocarcinoma mouse xenograft model	[132]
11.	Polymer conjugate	Doxorubicin	Active targeting/ RGD4C	Breast cancer	Female SCID mice bearing MDA-435/LCC6 ^{WT} and MDA-435/LCC6 ^{MDR} tumors	Multifunctional polymeric nano-conjugates are capable of cancer targeting, receptor-mediated cellular uptake, pH-triggered drug release and controlled subcellular delivery of carried anticancer drug in sensitive and resistant cancers <i>in vitro</i> as well as yielded parallel results in xenograft mouse model.	[133]

Table 2

Multi-targeted payload in Nanomedicines against cancer MDR at their different stage of preclinical and clinical studies.

Nanomedicines	Multi-targeted payload	Cancer	Preclinical/Clinical	Refs.
Liposomes	Cytarabine + Daunorubicin	Hematologic Cancer	Phase II	[167]
	Irinotecan + Floxuridine	Colorectal Cancer	Phase II	[168]
	siBcl-2-lipoplex+ S- 1(5-FU) pro-drug	Colorectal cancer	Preclinical	[169]
	Irinotecan and Cisplatin	NSCL cancer	Preclinical	[172]
	Doxorubicin+ Msurvivin T34A plasmid	Lung carcinoma	Preclinical	[173]
	Topotecan + Vincristine	Brain cancer	Preclinical	[174]
	Topotecan + Amlodipine	Leukemia	Preclinical	[175]
	Vincristine + Quinacrine	Leukemia	Preclinical	[176]
	6-Mercaptopurine + Daunorubicin	Leukemia	Preclinical	[177]
	Doxorubicin + Verapamil	Leukemia	Preclinical	[178]
	Paclitaxel + Tariquidar	Ovarian cancer	Preclinical	[179]
	siMcll+Suberoylanilidehydroxamic acid	Cervical cancer	Preclinical	[180]
	PD0325901 +siMcll	Cervical cancer	Preclinical	[181]
	Taurocholate+ Suberoylanilidehydroxamic acid	Oral cancer	Preclinical	[182]
	Ceramide+ Sorafenib	Breast Cancer	Preclinical	[183]
	Gemcitabine+Tamoxifen	Breast cancer	Preclinical	[184]
	Combretastatin A-4+ Doxorubicin	Melanoma	Preclinical	[185]
	siB-Raf+ siAkt3	Melanoma	Preclinical	[163]
Dendrimer	Doxorubicin + siRNA	Glioblastoma	Preclinical	[186]
	Antisense-miRNA21 + 5-Fluorouracil	Glioblastoma	Preclinical	[187]
	Paclitaxel + Alendronate	Bone metastases	Preclinical	[188]
	Methotrexate + Trans-retinoic acid	Leukemia	Preclinical	[188]
	Unmethylated CpG-ONTs + Doxorubicin	Prostate	Preclinical	[189]
Magnetic nanoparticles	Paclitaxel + Rapamycin	Breast cancer	Preclinical	[190]
Polymeric (PLGA) nanoparticles	Vincristine + Verapamil	Hepatocellular carcinoma	Preclinical	[191]
Polymeric micelle	Doxorubicin+p53 gene	Hepato-carcinoma	Preclinical	[192]