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A Review of Newer Technologies in Development of Nanomedicines for Cancers

Timothy Allen, MD, Ph.D*[1], Giridhar M.N.V, MD,MBA[1], Ghazaleh Shoja E Razavi MD[2]

[1]*Global Allied Pharmaceutical, Center for Excellence in Research & Development, USA.*

[2]*Dir. Clinical Development- Oncology and Respiratory, Global Allied Pharmaceutical, USA.*

**Corresponding author:* *Dr. Timothy Allen, MD, PhD, Global Allied Pharmaceutical, Center for Excellence in Research and Development, USA, Tel: 321-945-4283; Email: Timothy.Allen@gapsos.com*

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Abstract

Cancer is the leading cause of morbidity and mortality worldwide. Advances in nanotechnology have contributed to the development of nanoparticles used for medical applications and optimized therapy. Due to unique features of nanoparticles like a large surface area, structural properties, and along circulation time, many nanomedicines were prepared that have the potential to revolutionize the diagnosis and treatment of many diseases. Nanomedicines in cancer were designed and developed to overcome the limitations of the conventional chemotherapeutic agents that include unfavorable bio-distribution upon intravenous administration, rapid clearance from the circulation, only a small fraction of the drug reaching the tumor site, and development of multi drug resistance. Many strategies that were employed in the development of nanomedicines include passive drug targeting, active drug targeting, triggered drug delivery, multi stage drug delivery and nano-hybrids. In-spite of many advances in strategies for the development of various formulations of nanomedicines, several issues need to be addressed before translation from preclinical to clinical development including the physicochemical characteristics of nanoparticles that dictate the in vivo efficacy, evading particle clearance mechanisms, and controlling drug release. However, these progress made in development of nanomedicine formulations by various technologies strongly suggests the potential role of nanomedicines in improvement of cancer therapeutics.

Keywords: Nanomedicines; Nanotechnology; Nanohybrids; Nanoparticles; Targeted Drug Delivery; Multidrug Resistance; Pluronics; MDR Modulators; siRNA; Cancer Therapeutics

Abbreviations:

HER2: Human epidermalgrowth factorreceptor 2;
RES: ReticuloendothelialSystem;
PEG: Polyethyleneglycol;
MDR: Multidrug resistance;
MSP: Mesoporous Silicon Particles;
MTX-LDH: Methotrexate-Layered DoubleHydroxide;
LPN: Lipid-polymer hybrid nanoparticles;
UDCA: Ursodeoxycholicacid CSS: cholesterylsuccinylsilane;
DOX: Doxorubicin;
FB-LDH: Flurbiprofen-Layered DoubleHydroxide

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide. In-spite of many advances in therapeutic aspects, it only resulted in modest impact on patient's survival. Increased understanding of the underlying mechanisms of tumorigenesis, has led to the discovery and development of highly specific agents that are capable of exerting their effects on individual proteins or pathways, which are over expressed or aberrant in tumor cells. For example, human epidermal growth factor receptor 2 (HER2) was found to be over expressed in one-fourth of breast tumors, which led to the development of trastuzumab (Herceptin), a recombinant monoclonal antibody that binds to the extracellular domain of HER2 [1]. Though the novel chemotherapeutic agents led to improved survival, there is a number of biological barriers that limits the effective drug delivery, leading to only a small fraction of drugs reaching the tumor. Most of these novel preparations are sequestered by the reticulo-endothelial system (RES) [2]. This results in the accumulation of drugs in healthy organs, and leading to inherent toxicity associated with the drug as seen with doxorubicin, a DNA intercalator that results in cardio toxicity [3]. Additionally, abnormal blood flow in and around tumors, interstitial pressure gradients, and cellular/nuclear membrane traversals are some of the factors that hinder the curative potential of anticancer drugs. Taking into account all these factors, there is need for further discovery and development of more effective ways to deliver drugs to tumor cells.

Nanomedicine represents an innovative field with immense potential for the improvement of cancer treatment. Nanomedicine is defined as the design and development of therapeutics and/or agents in the nanoscale range (with diameters ranging from1nm to1000nm), with the possibility, by moving within biological systems, to transport and deliver a variety of biomedical entities for the treatment, prevention, and diagnosis of many diseases [4-6]. Unique properties of nanoparticles like large surface area, structural properties and long circulation time in blood compared to small molecules have made them to emerge as attractive candidates for optimized therapy through personalized medicine [7].

The major advantages of engineered therapeutic nanoparticles includes their ability to improve the unfavorable physiochemical properties of active drugs to more desirable pharmacologic profiles; enhance the delivery of therapeutics across biological barriers and compartments; control release of bioactive agents; improve therapeutic efficacy by selective delivery of drugs to biological targets; and develop multifunctional nanoplatforms by performing the agnostic functions through combining multimodal imaging and simultaneous diagnosis and imaging [8-13].

Many tools have been developed in the past decades from various components of metals, proteins, carbons, silicaoxides, metaloxides, lipids, polymers, nanocrystals, dendrimers and quantumdots [14-18]. Recently, many carbon nanomaterials with a carbon cage (eg: fullerenes, nanodiamonds) and grapheme structures (eg: carbon nanotubes, nanohorns) have been explored as carriers for the drug delivery and other biomedical applications. This is due to their high carrier capacity, chemical stability, high variability, presence of high tailorable surface chemistry, and the feasibility of incorporating a variety of molecules as therapeutic agents for cancer. [19-20]. Newer perspectives in nanomaterials for cancer was offered by gold nanoparticles, with the ability to imaging and therapy, and also implementing multiple receptor targeting [21].

The most important nanoparticle platforms with regard to drug delivery are liposome's, polymer conjugates, polymeric micelles, dendrimers, nanoshells, and protein and nucleic acid-based nanoparticles [4-6]. Among these, liposome's and polymeric based nanoformulations are the main nanoparticle therapeutics in the clinical use. [10,22,23]. Although most of the nanomaterials can demonstrate a high degree of biocompatibility, their utilization in various pathological states requires controlled interactions with bio-macromolecules. The success of translation of various nanomedicine formulations depends on their ability to achieve favorable blood half-life and physiologic behavior with minimal off-target effects, effective clearance from humans, and minimal or no toxicity to healthy tissues in the living organisms [24]. To be more specific, the hydrodynamic diameter, surface charge, and hydrophobic/hydrophilic balance are most important physiochemical properties that can affect the in-vivo biodistribution and clearance of administered nanoparticles [25]. For example, in an effort to reduce opsonisation and uptake processes in the reticulo-endothelial system, and optical nanoparticle surfaces are modified by using biocompatible and biodegradable polymers, such as polyethylene glycol (PEG), which also facilitates efficient clearance of nanoparticle and/or their metabolites from the body [26-27]. Therefore, much effort has to be laid on optimizing the physiochemical properties of nanoparticles to achieve a favorable blood half-life and biodistribution with minimal recognition and elimination by the reticulo-endothelial system.

Another aspect pertaining to the limitation of effectiveness of chemotherapeutic agents is multidrug resistance (MDR) that is observed in some cancers. MDR is a pathophysiological phenomenon that is primarily based on the over-expression of drug efflux pumps in the cell membrane. Several nanomedical strategies have been evaluated to overcome MDR, including the use of carrier materials with intrinsic anti-MDR properties, use of nanomedicines to modify the mode of cellular uptake, co-formulation of anticancer drugs to gather with low-and high-molecular-weight, MDR inhibitors within a single drug delivery system, and recently the use of nanohybrids [28].

These reviews high light the advances in technologies for the development of nanomedical formulations to treat cancers in a more effective way. The potential impact of nanotechnology in medicine is addressed briefly taking into account the various strategies; like passive targeting, active targeting of site-directed and endothelial cell directed nanoparticles, triggered drug delivery, multi stage drug delivery, and nanohybrids.

Clinically approved nanomedicines

Doxil, obtained by encapsulating doxorubicin within liposome's, was the first nanomedicine to be approved by the FDA for the treatment of Kaposi's sarcoma in 1995 [29,30]. This lead to the improvement of pharmacokinetic parameters of doxorubicin, thereby resulting in prolongation of circulating half-life and increased drug accumulation in tumor tissue. Inspite of advances in liposome technology, these nano-vehicles fails to render a favorable pharmacokinetic profile and drug localization at the target tumor tissue. Non- PEGylated liposomal doxorubicin (Mycomet) was approved for breast cancer, and the non-PEGylated liposomal daunorubcin (DaunoXome) for Kaposi sarcoma [31-32]. Non-PEGylated Liposomal nanocarrier loaded with cytarabine (DepoCyt), which was approved for local intrathecal treatment of lymphoma to us-meningitisin1999. In addition, it is also now evaluated for leukemia in phase III trials and for glioblastoma in phase I/II clinical trials [31].

Polymeric nanocarrier, Genexol-PM, a paclitaxel-loaded poly (lactic acid)-block- poly (ethylene glycol) micelle formulation was developed to avoid the need for the use of Cremophor EL and was approved in 2007 in Korea [33]. This enhance the potency of paclitaxel in the treatment of breast and lung cancer. As of now, Genexol-PM is being evaluated in phase II clinical trials.

Abraxane (albumin-bound paclitaxel) was approved by FDA in 2005 [32]. Results of the phase III trial comparing Abraxane with Cremophor-formulated version of paclitaxel demonstrated significantly greater tumor response rates and longer times to tumor progression in patients with metastatic breast cancer. [34]. However, the use of this technology was limited to improve the therapeutic index of therapeutic agents with poorly tolerated vehicles. Oncaspar, a combination of PEG-L- asparagines was recently approved for treatment of leukemia [31].

Novel nanoformulations in clinical development

The main limitations of the liposome-based nanocarriers includes the difficulty in modulation of drug release in-vivo, only limited amount of drug can be loaded, phospholipids which are the main constituents of liposome's can be easily oxidized, and problems with the maintenance of stable shelf life. Conversely, polymer-based nanocarriers were found to demonstrate similar to superior stability in-vivo compared to liposome's, have a high drug- loading capacity, and these are also suitable for both controlled and triggered release of drugs. In view of all these advantages, polymer-based nanocarriers have potential to overcome many limitations in nanomedicines [35-39].

Langer and Folkman in 1976 demonstrated the controlled release of macromolecules from biodegradable polymers in a temporal manner, which lead to clinical translation of controlled release polymeric nanoparticles [40]. Work published by Grefetal in 1994, further evidenced that biocompatible polymers with PEG can increase the controlled release and circulation half-life of polymeric nanoparticles [41]. Biocompatibility, biodegradability, and chemical and technologic flexibility of many polymeric materials like PLA, poly (D,L-lactide-co-glycolide) (PLGA), poly (caprolactone) (PCL), poly (glutamic acid), N-(2-hydroxypropyl)-methacrylate copolymers, and poly (aminoacids); make them more suitable materials to be used for controlled drug release [37].

"Drug –targeting" strategies in nanomedicines for improved tumor treatment

Paul Ehrlich proposed the concept of "magic bullet" that suggests, "a drug that selectively attaches to diseased cells but is not toxic to healthy cells" [42]. Since then a lot of research was channeled in this direction to explore innovative ways to treat cancer [43]. Novel strategies that are extensively exploited in order to make the drug reach the biological target include passive drug targeting, active drug targeting, active drug targeting to endothelial cells, triggered drug delivery, multi stage drug delivery, and hybrid nanaoparticles [35,44,48].

Passive drug targeting

Accumulation of drug at particular sites seen with many of the nanosystems is due to the balance between vascular hemodynamic forces and diffusion mechanisms. Passive targeting is much exploited in cancer chemotherapy since nanoparticles in the blood stream can be localized to neoplastic tissues through enhanced permeation and retention effects [49,50]. Anatomical changes in the tumor micro vasculature leading to large gaps between endothelial cells facilitate the extravasations and selective accumulation of nanoparticles from surrounding vessels into the tumor interstitium via a passive targeting mechanism (Figure1) [51,53]. Enhanced permeation and retention effect is a very heterogeneous phenomenon that varies from tumor to tumor and from patient to patient. [54] Even, in a single tumor, there might be many differences with regard to vascular permeability, where particles with a diameter>200-300 nm is able to extravasate, whereas in another part of the same tumor, molecules of size of few nanometers may find difficulty in entering the interstitium.

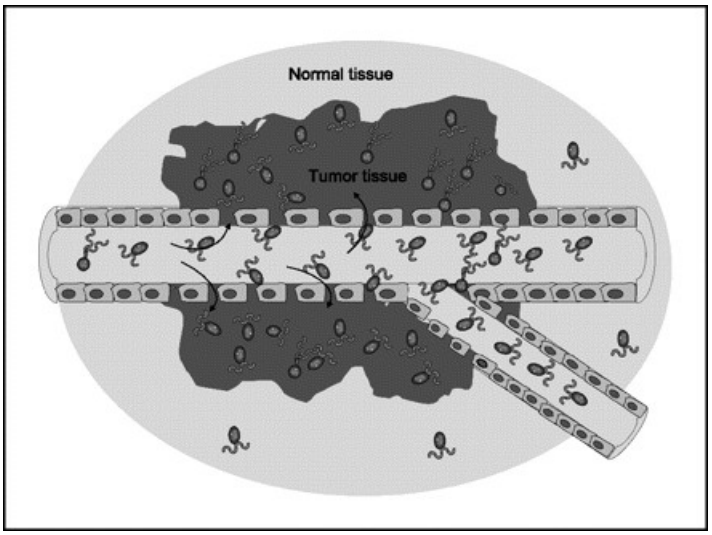

Figure 1. Tumortargeting of nanoparticles passivelybyenhanced permeabilityand retention. Long-circulating therapeuticnanoparticlesaccumulatepassivelyin solid tumortissue bythe enhanced permeabilityand retention effect. Angiogenictumor vessels aredisorganized and leaky. Hyperpermeableangiogenictumorvasculature allows preferential extravasation of circulating nanoparticles.

Many of the passive targeting systems have surfaces coated with PEG for biocompatibility and "stealth" purposes [50,55,56]. Increased hydrophilicity on the nanoparticle surface is one of the hindering factors to uptake of nanoparticles by the cancer cells, thereby causing in efficient drug delivery to tumors by passive targeting nanoparticles [25,57]. However, PEG-based polymers have resulted in clinical translation of numerous passive targeting polymeric nanoparticles.

NK911, a micellar nanoparticle that is constituted by PEG, doxorubicin, and poly (aspartic acid) and it is presently in Phase II clinical development for various types of cancer [58]. SP1049C, is a pluronic polymeric micelle nanoparticle carrying doxorubicin that is presently undergoing Phase II trials in metastatic cancer of esophagus refractory to standard chemotherapeutic regimens [59]. Opaxio, a paclitaxel/poly (L-glutamic acid) nanoconstruct which demonstrated effective results in ovarian tumors [60,61]. CRXL101, a camp in-cyclodextrin polymer which demonstrated enhanced pharmacokinetic efficacy in both preclinical and clinical studies [62]. Paclical, a micellar formulation of paclitaxel recently received orphan drug status by FDA and is presently in Phase III trials for ovarian cancer [63]. Intensive efforts are being made to get passive targeting lipid nanocarriers into clinical practice. A thermosensitive liposomal doxorubicin formulation, Thermodex, releases the active drug at temperatures around 39°C, and is presently being tested in Phase III trials combined with radiofrequency ablation in hepatocellular carcinoma [64]. SPI-77, a PEGylated liposomal formulation of cisplatin which is presently in Phase II trials for patients with recurrent epithelial ovarian cancer. [65]. CPT-11, a nanoliposomal formulation of irinotecan is in Phase I trial for glioma [66].

Active drug targeting for developing site-directed nanoparticles

Though "passive targeting" of nanoparticles resulted in increased accumulation in tumor cells, there is also some significant non-specific uptake in healthy cells. Thus, presently a lot of work is being undertaken to investigate active targeting nanoformulations that maximizes their accumulation at sites of interest [45-47]. Modifications in the composition and functionalization of polymeric nanoparticles can facilitate the targeting ability of nanoparticles in biological systems [35,37-39,67]. Active drug targeting uses a variety of affinity ligands that direct the binding of nanoparticles to many biological targets like antigens that are over expressed differently in plasma membrane and diseased tissues [35-68]. This can be effectively used for controlled drug release strategies, where the drug is released either into the extracellular or intracellular compartment. When the drug is released into intracellular compartment, internalization of nanoparticles by receptor-mediated endocytosis can occur through several pathways that lead to endosome formation and generation of lysosomes (Figure 2) [37,69]. As the primary role of targeting ligand is to enhance the uptake of nanoparticles into target cells, and it is postulated that active targeting nanoparticles improve the therapeutic efficacy as compared to non-targeted nanoparticles [37-39].

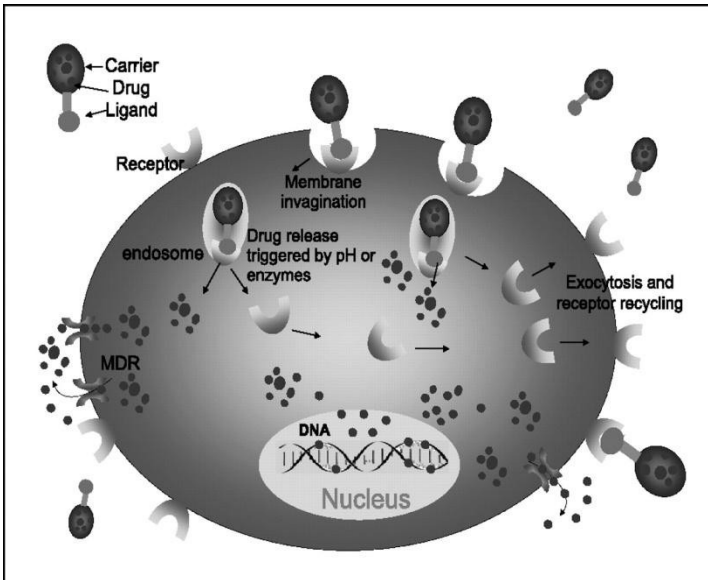

Figure 2. Internalization ofnanoparticles via receptor-mediated endocytosisin activedrug targeting. Tumor-specificligands or antibodies on the nanoparticles bind tocell-surface receptors, which triggerinternalization ofthe nanoparticles into the cellthrough endosome. As apH value in the interiorof the endosomebecomes acidic, the drug is releasedfrom the nanoparticlesand goes into thecytoplasm. Drug-loaded nanoparticles bypass theP- glycoprotein efflux pumpnot being recognized when the drug enters cells, leading to high intracellular concentration.

Actg targeting to endothelial cells

Though active drug targeting has more potential in controlled and targeted drug delivery, there is failure of translation of targeted nanomedicines from trials to clinical use. This failure is most likely attributed to the inability of the targeted nanoparticles to overcome membrane layers which mainly function as biological barriers. These barriers may be pericyte-based, smooth cell-based and fibroblast-based cell layers hindering the movement of nanoparticles from the blood to cancer cells. Additionally, complex cellular processes and tumor issues like the high cellular density and high interstitial fluid pressure within solid tumors are notably important obstacles for nanoparticles to reach the target tumor interstitium [44,46,47,70].

In an effort to overcome this, many vascular-targeted nanoformulations have been designed and evaluated [37,46,47,71]. The example of ligands targeting tumor endothelium are linear and cyclic derivatives of an oligopeptide containing the Arg-Gly-Asp (RGD) sequence binding to the target endothelium through integrin receptors [72,73].

Triggered drug delivery

This strategy generates nanoformulations in such a manner that the nanosystem can be triggered to release its contents on exposure to external stimuli like heat, ultrasound, and magnetic fields that maximize drug release at the pathological site [47]. Thermodex, a temperature-sensitive doxorubicin-PEGylated liposome, is an example of stimuli-responsive nanomedicine [64]. In-spite of this, there are several important limitations that includes manufacturing difficulties and problems with managing the way in which they respond to stimuli-responsive drug release. There is lot of research underway to improve the stimuli- responsiveness of these formulations and there is a development of more effective nanoparticles for triggered drug delivery in the near future [74-75].

Multistage drug delivery

Multistage drug delivery is a novel strategy, that is not only capable of circumnavigating several biological barriers encountered by nanoparticles enroute to the tumor cells, but also maximizes site specific localization and release of therapeutics [76-77]. The rationale for this strategy lies in the application of "oncophysics" to develop formulations to overcome bio-barriers [78]. This involves encapsulating drug containing nanoconstructs within mesoporous silicon particles (MSP) that protect and deliver these nanoparticles to tumor vasculature. So, this strategy of drug delivery involves partitioning of individual tasks from the time of injection to the arrival at the tumor site for enhanced therapeutic effect. The components of this strategy are: (i) mesoporous silicon particles (also known as first stage); (ii) nanoparticles (also known as the second stage) loaded with; (iii) anticancer therapeutics (also known as third stage). Biocompatible porous silicon was chosen as the housing material of the first stage as it is highly biodegradable under physiological conditions and has received FDA approval [79].

The proposed mechanism of action of multistage drug delivery strategy involves successful margination and attachment to tumor endothelium, accumulation at the tumor site, and release of drug containing second-stage nanoparticles. MSP were rationally designed with specific geometries and sizes in order to attain maximum localization within the tumor vasculature while minimizing reticulo endothelial system uptake [80]. Advantages of this strategy of drug delivery lies in its multi-function and its ability to severely alter the pharmacokinetics of injectables. Fine-tuning of porosity of MSP can alter the kinetics of the formulation as release of nanoparticles from MSP is largely dependent on biodegradation of porous multistage particles [77]. Highly porous multistage particles degraded within hours compared to particles with low porosity, which takes days to degrade, enabling sustained, and long- term release of the payload. In addition, degradation was also found to be dependent on surface functionalization of MSP.

Multistage drug delivery can also be effectively used in achieving a theranostic nanoplatformthat incorporates both therapeutic and imaging moieties within the same construct. As part of this, MRI contrast agents were encapsulated within MSP and the magnetic properties were examined. Gadolinium-loaded MSP demonstrated an enhanced longitudinal proton relaxivity that directly correlates with improved image contrast. Few cases demonstrated relaxivity values of 4-50 times greater than commercially available formulations. These enhanced relaxivity values were likely due to direct result of nano confinement and clustering of gadolinium within the MSP [82]. These findings highlight the potential of multistage delivery in treating and diagnosing cancer more efficaciously.

Hybrid nanoparticles

Hybrid nanoparticles are drug formulations where two different and independently active compounds are combined into one compound that shows synergistic effect. This hybrid technology is being used to deliver multiple therapeutic agents to tumor cells at a time. Nanocells" is one of the nanoscale delivery systems that are able to first release anti- angiogenic agent combretastatin and subsequently release the chemotherapeutic agent doxorubicin [83].

Various advances in nanohybrids particles are underway and are being explored for increased effectiveness of the chemotherapeutic agents. Kim et al successfully hybridized methotrexate (MTX) with layered double hydroxide (LDH) through

coprecipitation route to produce MTX-LDH nanohybrids (MTX-LDH). The anticancer efficacy of MTX-LDH was examined in human breast adenocarcinoma MCF-7cells. The cellular uptake of MTX was considerably higher in MTX-LDH-treated cells than in free MTX-treated cells, giving a lower IC50 value for the former than the latter. All the results demonstrated that the MTX- LDH nanohybrid allows the efficient drug delivery in cells, and thus enhances drug efficacy [84].

Lipid-polymer hybrid nanoparticles (LPNs) are core-shell nanoparticle structures comprising polymer cores and lipid/lipid-PEG shells, which exhibit complementary characteristics of both polymeric nanoparticles and liposome's, particularly in terms of their physical stability and biocompatibility. Significantly, the LPNs have recently been demonstrated to exhibit superior in vivo cellular delivery efficacy compared to that obtained from polymeric nanoparticles and liposomes. Zhang et al engineered the novel lipid-polymer hybrid nanoparticle and it was prepared by self-assembly through a single-step nano-precipitation method, which demonstrated high drug encapsulation yield, tunable and sustained drug release profile, excellent serum stability, and has the potential for differential targeting of cells or tissues. The novel lipid-polymer hybrid nanoparticles comprised three distinct functional components: (i) a hydrophobic polymeric core where poorly water-soluble drugs can been capsulated; (ii) a hydrophilic polymeric shell with anti-biofouling properties to enhance hybrid nanoparticle stability and systemic circulation half-life; and (iii) a lipid monolayer at the interface of the core and the shell that acts as a molecular fence to promote drug retention inside the polymeric core, thereby enhancing drug encapsulation efficiency, increasing drug loading yield, and controlling the drug release [85]. The scope of LPNs' applications has also been extended beyond single drug delivery for anticancer therapy, to include combinatorial and active targeted drug deliveries, and deliveries of genetic materials, vaccines, and diagnostic imaging agents [86].

Limitation of poor aqueous solubility of drugs, leading to the low absorption profile and bioavailability can be overcome with the help of nanohybrids. In a study by Choi et al, there was a dramatic increase in delivery of the poorly soluble drug, ursodeoxy cholic acid (UDCA), when it was intercalated into inorganic nanovehicle, layered double hydroxides (LDHs), to enhance its solubility in biological fluid and coated with an anionic polymer, Eudragit S100, to increase the dissolution rate of UDCA. In vitro studies demonstrated that LDHs nanovehicle coated with an anionic polymer is a promising delivery system for improving aqueous solubility of poorly soluble drugs [87]. Paclitaxel loaded cerasomes exhibited sophisticated controlled release behavior and remarkably high stability towards surfactant solubilization, long-term storage, acidic treatment, and all factors which were susceptible to destabilize conventional liposome's, demonstrating that liposomal nanohybrid cerasomes can be a new promising drug delivery system [88]. Recently, a super-stable and free standing hybrid liposomal cerasome (partially ceramic or silica-coated liposome) has drawn much attention as a novel drug delivery system because its atomic layer of poly organosiloxane surface imparts higher morphological stability than conventional liposome's and its liposomal bilayer structure reduces the overall rigidity and density greatly compared to silica nanoparticles. Cerasomes are more biocompatible than silica nanoparticles due to the incorporation of the liposomal architecture into cerasomes. Cerasomes combine the advantages of both liposome's and silica nanoparticles but overcome their disadvantages, so cerasomes are ideal drug delivery systems [89].

A nanohybrid vesicle was developed from cholesteryl succinyl silane (CSS). These CSS vesicles alone exhibited selective antiproliferative effects on leukemia cells without destroying normal blood cells. In addition, they are able to encapsulate not only hydrophilic guest species inside the inner water compartment but also hydrophobic molecules in the cholesteryl succinyl bilayer membrane. When CSS vesicles loaded with doxorubicin then it demonstrated enhanced antitumor effects and minimized the use of inactive materials and lowered the exposure of normal cells to toxic side effects [90]. A novel Pluronic F127/grapheme nano sheet (PF127/GN) hybrid exhibited high water dispersibility and stability in physiological environment and was found to be capable of effectively encapsulating doxorubicin (DOX) with ultra-high drug-loading efficiency (DLE; 289%, w/w), that exhibited a pH responsive drug release behavior suggesting the potential application of this novel nanocarrier in biomedicine [91]. In a other study, Li C et al demonstrated that silica-coated flexible liposome's loaded with curcumin had significantly higher stability against artificial gastric fluid and showed more sustained drug release in artificial intestinal fluid compared to curcumin-loaded flexible liposome's without silica-coatings in vitro release assays, suggesting that this nanohybrid system may be employed as a potential carrier to deliver drugs with poor water solubility via the oral route with improved bioavailability [92]. Nanohybrids were also evaluated for transdermal drug delivery. Kim MH et al prepared a drug-inorganic nanohybrid (FB-LDH) by intercalating a transdermal model drug, flurbiprofen (FB), into the layered double hydroxides (LDHs) via coprecipitation reaction. The in vitro drug revealed that the EudragitS-100 in release media could facilitate the drug out- diffusion by effectively replacing the intercalated drug and also enlarging the lattice spacing of the FB-LDH. In this work, a hydrophobic gel suspension of the FB-LDH was suggested as a transdermal controlled delivery formulation, where the suspensions were mixed with varying amounts of EudragitS-100 aqueous solution, concluding that the gel formulation of the FB-LDH have a potential for transdermal controlled drug delivery [93]. Recent studies have also shown that Au-Fe3O4 hybrid nanoparticles are viable additives for formulating sustained drug delivery systems based on glycolic acid grafted chitosan [94].

Nanoparticles have the great potential to achieve dual functions such as diagnostic and therapeutic, if more than one type

of nanostructure can be incorporated in the nanohybrid. Such nanohybrids are designed based on two strategies (barge vs. tanker), in which liposomal, micellar, porous silica, polymeric, viral, noble metal, and nanotube systems are incorporated either within (barge) or at the surface of (tanker) a nanoparticle. These strategies are effective in designing nanodevices for cancer detection and treatment [95]. Nanohybrid drug delivery systems have presented lots of characteristic advantages as an efficient strategy to facilitate oral drug delivery, but still it faces great challenges owing to the multiple biobarriers ranging from poorly physicochemical properties of drugs, to complex gastro intestinal disposition and to pre-systemic metabolism. Many nanoparticulate drug delivery strategies have been developed to overcome the above obstacles, including metabolic enzyme inhibition, enteric-coated nanocarriers, bioadhesive, and mucus-penetrating strategies, P-gp inhibition and active targeting. The research has further advanced from the present low-efficiency drug delivery of any single approach, such as mixed polymeric micelles and nanocomposite particulate systems to the trend of integrated hybrid nanosystems, which facilitates the intravenous-to-oral switch in cancer chemotherapy [96].

Nanohybrids to overcome multidrug resistance:

Multidrug resistance (MDR) is a pathophysiological phenomenon employed by cancer cells which limits the prolonged and effective use of chemotherapeutic agents. MDR is primarily due to over-expression of drug efflux pumps in the cellular membrane. Its significance can be illustrated by the fact that almost all non-small cell lung cancer patients treated with chemotherapy eventually develop resistance against the anticancer agents used [97].

Mechanisms responsible for chemo-resistance are too complex and include: inhibition of apoptosis, alterations of drug target structure, induction of DNA repair mechanisms, elevated expression of drug efflux pumps, and modifications in cell membrane composition leading to reduced drug uptake [28]. Among many different strategies employed to overcome MDR, the use of low-molecular-weight inhibitors had great expectations, but most of these attempts were unsuccessful due to low selectivity, inherent toxicity, and pharmacokinetic interactions with anticancer drugs [98]. Nanomedicine formulations have the potential for improving the treatment of multidrug-resistant malignancies.

Nanomedicines, with their prolonged circulation properties and ability to accumulate in tumors via Enhanced Permeability and Retention (EPR) and these are able to deliver high concentrations of chemotherapeutic drugs and/or MDR inhibitors to tumors [99-102]. Chemotherapeutics or other small molecules are passively diffused across the cell membrane resulting in high intracellular concentrations. Cellular retention depends on the balance between drug uptake and drug efflux. In resistant cells, most of the rapidly internalized small molecules are rapidly sensed by MDR proteins and are effluxes out of the cells [103]. Compared to low-molecular-weight drugs which generally are <1nm, nanomedicines are1-2 orders of magnitude larger (preventing them from internalization via passive diffusion) and are endocytosed via endo-lysosomal trafficking and carried relatively deep into the cells. Asa consequence of endocytosis, nanomedicines bypass drug efflux pumps, and are not negatively influenced by the over expression of MDR proteins [28]. Nanomedical solutions to overcome MDR include nanocarriers like pluronics, which possess intrinsic anti-MDR properties. Further, combination of nanomedicineswith low-molecular-weight MDR inhibitors either via co-administration to resistant cells and tumors, or via co-formulation (i.e. incorporation of both MDR inhibitors and chemotherapeutic drugs within a single nanomedicine system) have also been used. These combinational concepts have been further extended to nucleic acid-based therapeutics, where carrier materials are developed to hold both the standard chemotherapeutic drugs and anti-MDR siRNA.

Pluronic nanomedicines to overcome MDR

Pluronics is also called as poloxamers, these are block copolymers of hydrophilic ethylene oxide and hydrophobic propylene oxide. Pluronics have potent drug encapsulating properties with intrinsic ability to modify biological responses. Multiple phenomena are responsible for the ability of the pluronics to overcome MDR [104]. It has been reported that, pluronics are incorporated into the cell membrane and bring about changes in micro-viscosity. They also have a role in reducing the ATP levels in cells, thereby resulting in significant reduction in the activity of drug efflux pumps. Additionally, pluronics have the ability to induce the release of cytochrome C and ROS, mitigate anti-apoptotic defensive mechanisms, inhibit glutathione/glutathione-s-transferase detoxification systems, and the propensity to de-promote the sequestration of drugs within the cytoplasmic vesicles for clearance. Based on these anti-MDR effects, several studies have been performed in
which pluronics have been used to overcome multi drug resistance [104-106]. Chen and colleagues, evaluated the anti-tumor efficacy of methotrexate-conjugated mixed pluronic micelles, in mice bearing multidrug-resistant epidermoid KBv tumors, and found that the treatment with pluronic based mixed micelles in which methotrexate was physically entrapped and were found to be significantly more effective than treatment with the free methotrexate [107].

Nanohybrids using MDR modulators

Another strategy that was developed for the use of nanomedicines in combination with MDR- and in particular ABCD1-modulators. This strategy can either use free or nanomed-

icine-incorporated MDR inhibitors in combination with a nano-encapsulated chemotherapeutic drug, or a nanomedicine formulation containing both MDR modulators and chemotherapeutic drugs within a single drug delivery system. Wang et al combined liposome's containing verapamil with liposome's containing doxorubicin, and these formulations were tested in multi drug resistant Dunning Mat-Ly Lu- B2 rat prostate carcinoma and MESSA/Dx5 uterus sarcoma. It was found that free verapamil plus liposomal doxorubicin was notable to reverse/overcome MDR in these two resistant tumor models but combining verapamil-liposome's with doxorubicin-liposome's, drastically improved cytotoxicity and therapeutic efficacy [108]. Patel et al studied the effect of tariquidar and paclitaxel loaded- liposomal formulations in resistant and non-resistant variants of ovarian carcinoma (SKOV-3TR and SKOV-3, respectively), which demonstrated that co- delivery of this liposome's potently reduced MDR in ovarian carcinoma cells [109]. Wong and colleagues developed polymer lipid hybrid nanoparticles that are capable of co-delivering doxorubicin and a BRCP inhibitor, GG918 (Elacridar). This strategy was further evaluated in multidrug resistant breast cancer cell line MDA435/LCC6/MDR1 by determining the clonogenic survival, the results indicated that the nanoparticles loaded with doxorubicin and BCRP inhibitor exhibited highest degree of anticancer activity [110].

SiRNA-based nanohybrids

Presently, a large number of recent anti-MDR studies involve the use of siRNA. Newer strategies include the co-encapsulation of siRNA and chemotherapeutics within (mostly cationic) polymer-and lipid-based drug delivery systems. Xiao-Bing and colleagues used micelles based on degradable poly (ethylene oxide)-block- poly (ε-capro lactone) (PEO-b-PCL) block copolymers carrying doxorubicin and anti-ABCB1 siRNA, the efficacy of which was tested in mice bearing Pgp-over-expression MDA-MB-435 tumors. This multifunctional nanomedicine formulation has demonstrated highest level of cellular internalization and inhibited cell growth by more than 70% in in-vitro studies [111]. In an another study, Saad and colleagues prepared liposome's carrying doxorubicin as a chemotherapeutic agent and two different siRNAs that target different proteins responsible for drug efflux and for anti-apoptotic responses. This study tried to target multidrug resistance at two levels i.e. at the pump and non-pump related resistance mechanisms. They incorporated siRNA against ABCC1 (pump-resistance) and BCL2 (non-pumpresistance). BCL2 is a potent anti-apoptotic protein that is over-expressed in many cancers. In vitro study of this nanoformulation was studied by incubating in multidrug resistant H69AR lung cancer cells. It was observed that liposomes efficiently entered the cells and siRNA and doxorubicin were efficiently delivered to the cytoplasm and the nucleus. Further, it was observed that the liposome's containing only siRNA targeting ABCC1, siRNA targeting BCL2 and/or doxorubicin were much less efficient in inducing programmed cell death than the liposome's containing all the three drugs within a single formulation. This states that simultaneous suppression of pump and non-pump based resistance resulted in more efficient cell killing [112]. These findings convincingly confirm that nanomedicines containing chemotherapeutics, siRNA and targeting ligands hold significant potential for overcoming multidrug resistance.

Novel nanohybrids to overcome MDR

Novel nanohybrid systems are further being evaluated to overcome multidrug resistance. Ji X et al prepared nanohybrid systems of non- ionic surfactant inserting liposome's loading paclitaxel (PTX) (NLPs) to overcome multidrug resistance (MDR) in PTX-resistance human lung cancer cell line. In vitro studies with this formulation suggested that this could overcome MDR by combination of drug delivery, P-gp inhibition and ATP depletion, and showed potential for treatment of MDR [113]. Jin R et al designed a nanohybrid based on nanoscale graphene oxide (NGO) and dextran loaded with doxorubicin, which demonstrated more efficient killing of drug-resistant MCF-7/ADR cells than the free doxorubicin because the nanohybrid caused a higher amount of doxorubicin accumulation in the tumor cells [114].

Discussion

Nanotechnology have brought about many innovative strategies for the use of nanomedicines as effective drug delivery systems in oncology to improve drug performance by overcoming many of the limitations of the classical chemotherapeutic agents like unfavorable biodistribution upon intravenous administration, rapid clearance from the circulation, and only a small fraction of the drug reaching the tumor site. The most striking feature of nanomedicines is their ability to target a drug to the tumor site, thereby enhancing tumor drug levels. Further, they also can direct a drug away from those body sites that are particularly sensitive to the toxic effects of the drugs, thereby providing convincing evidence for their role as potential candidates in treatment of various cancers.

This article has highlighted the importance of nanotechnology in cancer therapeutics. It provides a brief overview of the nanomaterials used for drug development, much emphasis was given to innovative strategies that are being designed and developed using nanotechnology. Additionally, their effective role in combating multidrug resistance was also addressed. Various strategies like passive drug targeting, active drug targeting for developing site-directed nanoparticles, active drug targeting the endothelial cells, triggered drug delivery, multistage drug delivery and nanohybrids were discussed with appropriate examples.

In-spite of many advances in strategies for development of various formulations of nanomedicines, several issues need to be addressed before translation from preclinical to clinical development. Most important is the physicochemical characteristics of nanoparticles that dictate the in vivo efficacy. Due to this, though many preparations are found to be efficacious in in-vitro studies, they are unable to make an impact in in-vivo studies. Better understanding of the biological and pathophysiological principles of drug targeting with nanoparticles is needed to overcome these obstacles and development of rationally designed nanomedicines.

Conclusion

Though certain challenges still need to be overcome before many of the innovations can be applied in the clinic, the insights obtained, and the progress made strongly suggest that nanomedicine formulations developed by various technologies hold significant potential in improvement of cancer therapeutics.

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