Chapter 2

Getting a Handle on Smart Drug Delivery Systems – A Comprehensive View of Therapeutic Targeting Strategies

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Additional information is available at the end of the chapter

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Abstract

Smart drug delivery system (SDDS) is a recently emerging therapeutic approach, now turning into a conventional model to deliver drug to specific sites or target. Drug targeted (DT) delivery systems maintain the concentration of the drugs at desirable doses in the body and avoid the need for repeated doses. The DT delivery system have specific distinguishing features such as self-regulated, pre-programmed, multi-targeted, controlled by timely response, monitoring of the targeted drug delivery, responsive to pH, and spatially targeted. The DT delivery system exploits the biological membrane changes in the physiology of malignant cells to increase absorption or entry of drug-coated nanoparticles into targeted tissues. This system delivers a certain quantity of a therapeutic drug for longevity of its action to a targeted area within the human tissue, which in turn enhances efficacy of the treatment by reducing the side effects of drug administration. A new DT therapy strategy is a health improvement technique used in future generations for treatment of genetic diseases and intelligent drug delivery. The ultimate goal of SDDS is to administrate the drugs at the correct time with an exact dose in the body and with efficiency and specificity to the targeted cells that help the patients better adhere to their therapy regimen. The DT system enhances the maintenance of drug levels in targeted tissues and plasma without any destruction to the healthy tissues. This DT delivery system uses various strategies in targeting cells, drug delivery mechanisms, properties of targeted drug, organ-based targeted sites, disease, and drug-targeted vehicles. This chapter deals with all aspects of drug targeting and provides an overview of approaches in drug targeting, drug delivery vehicles, and strategies involved in successful delivery.

Keywords: Smart Dug Delivery System (SDDS), drug targeting strategies, nanoparticles, nanocarriers, passive and active targeting, folate receptor targeting, antibody targeting, glycoprotein targeting, drug delivery, malignant cells

1. Introduction

Smart drug delivery system (SDDS) is an advanced method of Drug Targeted (DT) delivery. The smart drug delivered by this system must fulfill the following criteria: 1) increase the doses of delivered drug to targeted body part of interest (tissue/cells/organs), 2) not be degraded by any of the body fluids, 3) diminish side effects by improving the efficacy of drug treatment, 4) absorption of the delivered drug must cross a biological membrane, and 5) drug is released in appropriate dosages to the body part of interest. The ultimate goal of a DT delivery system is to localize, maintain drug properties, ensure a specific route taken for the delivery of the drug, target the desired site only, reduce side effects of the drugs, and prolong drug interaction with the diseased tissue. Targeted delivery system maintains the required concentration of the drug in plasma and tissues at the targeted sites, therefore, evading damage to normal tissue/cells induced by the drug. The DT delivery system is highly complex and involves an integration of various disciplines, such as biology, chemistry, and engineering [1–3].

Nanoparticle-based drug delivery systems are framed according to specific properties of target cells, transport carrier/vehicles, nature of markers involving dug binding to specific ligands, and receptor being modulated by physical components. Superlatively, DT delivery systems should be non-immunogenic, non-toxic, chemically and physically stable in in vitro as well as in vivo conditions, have restricted drug distribution to target tissue/cells/organ, have uniform capillary distribution, have predictable and controllable rate of drug release, and have minimal drug leakage during transit [3–5]. Carriers used for targeted drug delivery should be easily bio-degradable or freely eliminated from the body without producing any side effects. The preparation of the targeted delivery system should be stress-free or reproductive, reasonably simple, and cost effective. The disadvantages of conventional drugs make attractive the reasons to concentrate our efforts on targeted delivery. Conventional drugs have less solubility of the given drug doses, poor absorption, shorter half-life, require large volume of distribution, less specificity, and less therapeutic index, all these are significantly overcome in the targeted drug delivery system [1–3].

In this chapter, we address: 1) the types of nanoparticles used internally for targeted drug delivery system based on their size, shape, and materials (metal, biological, polymers, and lipid); 2) specifically illustrate the mechanism and strategies of targeted drug delivery systems; 3) introduce the mechanism of organ-based targeted drug delivery system; 4) explain the therapeutic strategies of drug delivery and targeting action; 5) elucidate the significance and desirable properties of targeted delivery; 6) and finally, we validate a brief outlook of future challenges and trends in drug targeted delivery systems that will be established to progress their therapeutic efficiency and efficacy of drug functionality in future treatment of cancer and genetic disorders.

2. Strategies of Targeted Drug Delivery Systems

Drug-targeted delivery increases the therapeutic efficacy by controlling the toxic effects associated with the drug. Delivery of drugs to malignant tissue is increased and the normal

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tissue remains unaltered. The approaches of targeted drug delivery systems such as passive, active, dual, combination, inverse, double, and physical targeting are being used extensively in therapy.

2.1. Passive Targeting System

Passive targeting refers to the accumulation of a drug-carrier system or drug targeting at a precise site; it may be attributed to chemical, physical, pharmacological, and biological aspects of the disease. The nanoparticle size and surface properties of the drug targeted system must be specially controlled to evade uptake by the reticulo-endothelial system to maximize the targeting capability and increase its circulation. Rapid vascularization assists fast-growing tumor tissue, imparting itself to a defective or leaky architecture enhancing the permeability of toxic chemotherapeutic drugs. Few drugs can be administrated as inactive drugs or prodrugs, hence, its exposure to cancerous tissue can be modified into highly active form. Passive targeting also integrates targeted drug delivery to the malignant bed through various invasive modalities.

2.1.1. Leaky Vasculature

Polymer nanoparticles exhibit the enhanced retention and permeability effects on targeted delivery in tumor cells [6]. Capillary endothelium in tumor tissue is disorganized and enhances the permeability towards macromolecules than normal tissues. This phenomenon allows extravasation within the tumor interstitium to the polymeric nanoparticle circulating for targeted drug delivery. The tumor bed lacks lymphatic drainage and results in drug accumulation, enhancing targeted strategies. A chemotherapeutic drug is linked with a specific nanoparticle or nanocarrier by a linker that has the potential of augmenting the concentration of therapeutic drugs within the malignant cells. These characteristic features (polymer-drug conjugates) modulates the drug concentration in malignant tissue levels 10 to 100 times more than free drug.

2.1.2. Tumor Microenvironment

The targeted drug is conjugated to a cancer-specific molecule and administered in an active state. When it reaches its final target, the cancerous environment modulates the dug to a volatile and active substance, the so-called malignant cell-activated prodrug therapy. Malignant tissue is characterized by vascular disorganization, intermittent basement membrane alteration that stimulates the metastasis of atypical cells to normal cells. Insufficient supply of nutrients and modulation of lymphatic networks does not remove the waste products in the cells accurately. A tumor cell retains increasing concentration of protons and leads to a decrease in the physiological pH of the cells [7]. The components of the extracellular matrix such as macrophages, fibroblasts, and collagen fibers in the cancerous tissues are also elevated. The degradation of tumor bed membranes and the extracellular matrix are enhanced by Matrix metalloproteinase-2. A recent study about a water-soluble maleimide derivative of doxorubicin incorporating a matrix metalloproteinase-2-specific peptide sequence by Mansour et al. [8] demonstrated (proved/showed) that this drug conjugate-polymer complex had a high affinity

to cysteine-34 of circulating bound form of albumin. Doxorubin was efficiently cleaved by the matrix metalloproteinase-2 from the bound form of albumin. The redox potential and modulated pH have been exposed as drug release triggers at the tumor site [9] for targeting.

2.1.3. Direct (Local) Drug Application

Direct application of the drug to the cancer cells permits the drug to react directly with the malignant cells without systematic blood circulation. Various methodologies have been used to improve the anticancer drug for targeted delivery for tumors such as intraperitoneal, intravesical injection, and administration of various chemotherapeutic agents. These methodologies require introducing higher concentrations of anticancer agents that is not always possible. Localized targeted drug delivery by intratumoral direction is a modified and attractive methodology, which has been used and tested [10]. Localized administration of anticancer drug mitomycin surface of the malignant tissue leads to an increased concentration of the drug and decreased toxicity at the targeted tumor site [11]. Onyx-0115 is a type 2/5 chimeric adenovirus improved by attenuation of the E1B-55 kDa gene [12]. Its complex with some other proteins binds and inactivates the p53 gene. This drug has been administered by various methods, most of which permit the drug to be applied directly into the malignant cells. Onyx-0115 is used in clinical trials through intratumoral administration to treat head and neck cancer [13], intratumoral via endoscopic ultrasound for pancreatic cancer [14], via hepatic artery for metastatic colorectal cancer [15], intraperitoneal (IP) administration in ovarian cancer [16], and intratumoral under radiographic guidance for advanced sarcomas [17]. Recently, a polymer, poly (lactic-co-glycolic acid), linked with Tacrolimus (FK506) entrapped in pH-sensitive microspheres [18] was administered rectally or orally to colitis animals. The experimental animals showed the released nanoparticles and drug concentration into the tumor environment was different from its surrounding tissues. The drug permeability level in malignant tissues was 3-fold higher than normal tissue when nanoparticles were used as drug carriers. Direct targeted delivery of antitumor drugs into the malignant tissue inhibited the drug from circulating in the blood. The drawback of direct targeted delivery of drugs into the tumor is highly invasive and localization in some type of tumors is not feasible and can be problematic.

2.2. Active Targeting System

"Active targeting" means specific interactions between drug/drug carrier and the target cells, commonly through specific ligand-receptor interactions [19–23]. The ligand and receptor interactions are possible only when these components are in adjacent proximity (<0.5 nm). Specific ligand-receptor interaction for intracellular localization occurs after extravasations and blood circulation. Active targeting is favored as it controls a drug carrier/drug toward a target site (e.g., cruise missile). PEGylation increased the blood circulation time by altering the surface of the drug carrier with poly (ethylene glycol) and/or improving the enhanced permeability and retention (EPR) effect to augment the drug delivery to the targeted tumor site. Earlier reports show that targeting tumor ligands does not result in augmented accumulation of the nanoparticles in targeted tumor sites. The specific molecules in tumor cells or

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intracellular organelles enhance the active targeting pathways needs to active delivery of the drug into the entire tumor site [24–26]. Targeting a drug to a tumor site/specific area not only enhances the efficacy of therapeutic drugs, it also reduces the toxic effects associated with the drug and allows lower dosage of the drug for therapy. Active targeting is categorized into three approaches, these are: 1) targeting and restricting the circulation of nanoparticles to the capillary bed of a determined tumor targeted cell, site, tissue, or organ (cerebral ventricles, peritoneal cavity, compartmental targeting in lymphatics, plural cavity, joints, and eyes); 2) targeted delivery of the drug to a specific type of malignant cells/tissues and not to the normal healthy cells (specifically delivery of the nanoparticles to kupffer cells in the liver); and 3) targeting of nanoparticle delivery exactly to the intracellular site of targeted tumor cells (receptor-based ligand enters into a cell by endocytosis). The third approach is highly favored and used in guiding nanoparticles for targeted delivery through carbohydrates, receptors, and antigens.

2.2.1. Carbohydrate Targeted

The cell surface of the carbohydrates disturbs the tumor cells' communication with normal healthy cells or with the extracellular matrix through metastatic growth and spread. This communication between the cells can be mediated through tumor cell binding proteins and their carbohydrates known as lectins. Endogenous lectins play an important role in the immunity to identify the "foreign patterns" of the cell surface carbohydrates on cancer cells. It clearly depict that lectins disturb the survival of malignant cells, endothelium adhesion/ extracellular matrix, and tumor tissue vascularization processes that play a key role for metastatic growth and spread [27, 28]. This carbohydrate-ligand bonding communication can be made by improving the nanoparticles enclosing carbohydrate moieties focused on targeting certain lectins (direct lectin targeting Consequently, targeted drug delivery systems have been established based on this unique interaction/communication between lectins and carbohydrates targeted towards whole organs [29] and may be dangerous to normal healthy tissues. This is a major drawback of lectins, it should be rectified for the development of ''smart carrier'' molecules for targeted drug delivery. Lectin possesses a unique affinity for sugar moieties present on the surface of cancer tissues. Thus, unique characteristic features seem to be an attractive tool for further augmentation of nano-drug targeted delivery.

2.2.2. Receptor- and Antigen-directed Targeted

Human cancer cells overexpress the receptors or antigens on their surface that enhances the efficient uptake of nanoparticles through receptor-mediated endocytosis, by which extracellular particles may enter into the intracellular environment. In general, drug-coated nanoparticles can enter into to the targeted tumor cells through ligand-receptor interactions. Once it reaches the localized area of the tumor cell surface, the targeted drug-coated nanoparticles may exert cytosolic action either after internalization or at the plasma membrane. Detachment of the drug from its carrier can occur at the cell surface, extracellular space, or more prominently, in lysosomes by lysosomal enzymes ensuing in the release of the drug alone (without carrier molecule) into the cytosol [30]. After the completion of drug delivery, the antigens or receptors should be reprocessed back to the cell surface. Therefore, this form of targeted drug

delivery contains essential molecules such as a nano-carrier to which targeted drug can be conjugated and to which ligands-antibodies are conjugated, and enhances the high affinity to the tumor cell surface, antigens, or receptors, respectively.

2.3. Dual Targeting System

The targeted drug delivery system is activated by stimuli, such as temperature, pH, redox, etc., some type of malignancies possess two stimuli around the tumor targeted environment at the same time. Alteration by reduction in extracellular pH [31] and slight rise in local temperature [32] would be more favorable for guiding drug delivery carriers that resort to two or more external stimuli concurrently. However, emerging dual or multi-stimuli approachable nanocarriers for tumor targeted therapy remains a great challenge. Nowadays, smart drug targeted delivery system are drawing our attention toward thermo- and pH-sensitive activated drug targeted delivery system. Various hyper-branched polymers that have the ability of amalgamation of dual stimuli [33, 34] have been produced, and may be reasonable applications in various malignancies. Furthermore, drug targeted delivery systems retaining sensitivity for dual stimuli have also been designed. An earlier study by Wu et al. [35] examined the release of 10-hydroxycamptothecin from dual stimuli-sensitive nanoparticles. Intestine-targeted hydrogel coated with vitamin B2 accomplished by both thermo and pH stimuli-sensitive developed by Liu [36] validated that noticeable thermo and pH sensitivity are suitable for drug targeted site-specific nanocarrier in the intestine. Furthermore, thermo-sensitive hydrogels, pH-sensitive polymers [37], enzyme-degradable, redox dual responsive micelles, and high-intensity focused ultrasound (HIFU) [38], have also been designed to sustain the release of drug targeted delivery system. Thus, precise information of the dual sensitive system was not well established, but it provides an alternative for effective targeted drug delivery in biomedical applications.

2.4. Inverse Targeting System

Drug targeting attempts made to evade the passive uptake of the colloidal carrier by reticuloendothelial systems are referred to as inverse targeting. The normal function of reticuloendothelial systems is blocked by pre-injecting macromolecules such as dextran sulphate or blank colloidal carriers. This targeted methodology leads to the saturation of reticuloendothelial systems and the destruction of the defense system is used as an effective approach to delivering targeted tumor drugs to non-reticulondothelial system organs. Colloidal-carrier systems such as vesicle, micellar solutions, and liquid crystal and nanoparticle dispersions comprising of small particles demonstrate the promise of great effects for targeted drug delivery systems. The aim is to optimize the drug coating and releasing properties and longevity of self-life of the drug with less toxic effects. The amalgamated drug with the colloidal system involved in this modulation of microstructural system may impact molecular interactions of the drug, which has mesogenic and/or amphiphilic properties [39].

2.5. Stimuli-Responsive/Triggered Drug Release Targeting System

Targeted tumor drug delivery systems are requisite to be biodegradable and nontoxic to normal healthy tissue/cells and lethal and incisively dangerous to destroy the malignant cells.

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However, fast discharge of the drug from the nanoparticles may lead to premature release, triggering systemic side effects; whereas, slow discharge may diminish the efficacy of the drug at the targeted site of action and may enhance the action of multiple-drug resistance (MDR). Hence, discharge of the drug for targeted systems should be in a well-organized manner at the tumor targeted site. The design of stimuli-responsive drug carriers for targeted drug delivery is highly preferred to augment the efficacy and bioavailability of the drug. Characteristic features of typical stimulus include temperature (thermal), pH, light intensity, magnetic field, redox potential (i.e., enzyme), glucose (ionic strength specific stimuli such as concentration of sugar moiety), and concentrations of electrolytes are used to localize the drug-nanocarrier to the determined targeted site. Responses of nanocarriers include precipitation/dissolution, collapsing/swelling, hydrophobic/hydrophilic transition, degradation, bond cleavage, and so on. Henceforth, we clearly state that external stimuli responding system (magnetic field, light, and ultrasound) are of lesser impact, inexpedient and practically not feasible (i.e., costs, scale-up product) than those of internal stimuli-responding systems (temperature, pH, redox potential, etc.)

3. Organ-based Targeted Drug Delivery

The accumulation of the drug within a target area or tissue refers to targeted drug delivery that is independent of the method for the targeted site and direction of drug administration. A successful drug target delivery involves the following steps: appropriate proposed drug coated nanoparticles must be circulated in the blood in concentration to ensure it reaches the targeted site, the site must retain the nanoparticles, the release of the drug into the cells and allowing enough time for effective mechanism of the drug. Targeted drug delivery to specific sites in the human body requires unique delivery systems depending on the route selected.

4. Nanoparticles Used for Targeted Drug Delivery

Nanoparticles referred to as drug delivery vehicles or vectors are the most significant entity necessary for the efficient delivery of the coated drug. A drug vehicle delivers and retains the therapeutic drug to be transported to the site or in the locality of the targeted tissue or area. These vehicles are capable of accomplishing specific functions that can be attributed to minor modifications in its structure. An ideal vehicle must be selectively and specifically recognized by the target site and should retain the functional specificity of the surface ligand without any modification. It should be capable of crossing the barriers, stable in interstitial fluid and plasma with non-toxic, non-immunogenic and biodegradable materials. Once the target cells recognize the carrier system, it must release the therapeutic drug moiety inside the anticipated targeted site. We further discuss the properties and application of delivery vehicles in Table 1. Targeting principles of metal, polymer, lipid, and biological-based nanoparticles used in therapeutics and promising direction in therapeutic research are discussed.

Types and Description			Properties	Application	Examples
Polymeric nanoparticles: Solid colloidal system with drug in various forms either encapsulated, adsorbed, etc. to form nanocapsules or nanospheres			Highly biocompatible and modifiable to make nanoparticle conjugates, e.g., polymeric magnetic nanoparticles, polymersomes, polyplexes, polymer hybrid system, modifiable surface properties High encapsulation of the drug and drug protection, prolonged drug delivery, and long shelf life	Wide range of targeted organs and cells, N-2(hydroxypropyl) methacrylamide (HPMA) polymer most widely used in theranoustics Polymeric micelles and water soluble polymers for improved drug delivery	Synthetic polymers such as PLGA, LPLA, PCL, and natural polymers such as Chitosan, Gelatin, Albumin, Sodium Alginate
Dendrimers: Hyperbranched marcomolecules, densely packed to the periphery till they reach a "starburst effect"			Reduce viscosity of a solution, densely packed improved rheological properties, outermost dendrimeric surface can be both polar or hydrophobic capable or dissolving in different solvents	Used as contrast agents for MRI Vectors in gene therapy, soluble dendrimers able to solubilize acidic hydrophobic molecules and of fungus and bacteria	PAMAM dendrimer, PPI dendrimer, Techto dendrimer, Micellar dendrimer
Inorganic nanoparticles	Metallic	Gold nanoparticles (GNPs): Three shapes of GNPs are rods, shells, and spheres	These have a unique interaction with light, free electrons undergo oscillations in the presence of oscillating electromagnetic field of light	Biosensors, especially colorimetric biosensors, for detection of oligonucleotides immunosensors and redox enzyme biosensing	GNPs are conjugated with Silica, PEG, Chitosan, platinum tethered, gold-SPION hybrid
		Carbon-based nanotubes: Well-ordered hollow graphitic nanomaterial either single- or multi-walled	Possibility of both covalent and non-covalent bonding Site specific delivery of proteins, peptides, nucleic acids, and other drugs	Used as an imaging agent Applications in malignancies of the brain, blood, colon, breast, liver, lymph nodes, cervical, and prostrate cancer	Multi-walled carbon nanotube (MWCNT) Single-walled carbon nanotube (SWCNT)
		Quantum Dots (QD): Uses the	Exceptional physical features applied in optical imaging,	Unique optical features for in vitro and in vivo imaging especially	Multi-spectral fluorescent Imaging –

Types and Description			Properties	Application	Examples
		bandgap between valency and conduction electron bands, exciton is generated due to the difference in absorption energy and the spectral bandgap of the core semi-conductor	strong absorbance, bright fluorescence	biomedical fluorescent imaging, specifically used in the study of neuron and ganglia, used in photodynamic therapy especially to treat lung and gastrointestinal cancer, accurate recognition of molecular targets	Quantum Dots (MSFI-QDs), Carbon dots, carbongenic-QDs, Silica-QD's, Zinc oxide-QDs,
	Metalloid	Silica based nanoparticles: Silica particles are good materials for nanoparticles because of its porosity and surface adaptability	Modifiable in size, porosity and structure Photophysical stability: does not absorb visible or uv light, biocompatibility, favorable colloidal properties, high porosity and extended surface area, relatively chemically inert, low cost of production, easily prepared and water dispersible	Application in combined therapy as they can transfer both genetic material and molecules of various sizes. Used as an optical contrast agent, can conjugate with antibodies, aptamers and polymers	Solid silica-based nanoparticles (SiNPs), Mesoporous silica nanoparticles (MSNs)
	Magnetic	Iron oxide magnetic cores with changing shells are used	Some forms of iron oxide naturally occur in the body (maghemite, magnetite), thus reducing toxicity, various bindings, and interactions between the MNP and the drug are possible such as covalent, electrostatic, encapsulation, and adsorption	Used both in diagnosis and therapy concomitantly, Liver and spleen readily imbibe the MNP and can also be used in barin malignancies and it is able to cross the blood brain barrier	Iron oxide cores with shells of gold, polymer, dendrimers, and silane
Biological	Lipids	Homolipids, Heterolipids, complex-lipids	Increase in drug solubility, pharmokokinetics properties, reduced toxic effects	Applications in oral drug delivery, parenteral dug delivery, peptide and	Solid lipid nanoparticles (SLN), Nanostructured

Types and Description	Properties	Application	Examples
		protein drug delivery, nasal vaccination, etc.	lipid carriers (NLC), Lipid drug conjugates (LDC), Liposome, transferosomes, niosomes

Table 1. Types of nanoparticles, properties and applications in medicine.

4.1. Lipids-based Nanoparticles

Liposomes are small, artificially designed vesicles entirely surrounded by phospholipid bilayer membranes with various size ranges (20 to 10,000 nm) [40]. Drug molecules are encapsulated or intercalated into the phospholipid bilayers that extend the location of the drug with physico-chemical nature of lipids. Recent study demonstrates that lipid DOX loaded nanoparticles have potential effects on useful therapeutic targeted drug against adriamycin-resistant breast cancer. Entrapped drug (chemical compounds) molecules inside the modified liposomes (transferring [41] or antibody [42, 43]) cause apoptosis of tumor cells [41–43]. Solid lipid nanocarriers can be commonly used for the treatment of chemotherapy resistant tumor [44] to deliver the targeted drug.

Self-assembled, hydrophobic interactions of amphiphilic block copolymers (5–50 nm) form supramolecular core-shell structures in aqueous solutions called micelles are gaining great attention in targeted drug delivery applications. Pluronic, phospholipid, polyester, and poly (L-amino acid) are the most often used micelles. Drug entrapped with block copolymer micelles and transported at high concentrations can exceed their intrinsic water-solubility. Furthermore, hydrophilic blocks form hydrogen bonds within the aqueous solution and form a compact shell that covers the micellar core protecting it against hydrolysis and enzymatic degradation with the help of hydrophobic core. Moreover, the reticuloendothelial system may prevent the recognition of the corona and eliminate the polymeric micelles from the blood circulation. The molecular weight, chemical composition, and block length ratios can be easily changed that control the size and morphology of the micelles. The cross linkable group with block copolymer can enhance the stability of the micelles and increase their temporal control. Polymeric micelles can be linked with various ligands, such as epidermal growth factors, antibody fragments, α-2-glycoprotein, folic acid, and transferrin, delivering the targeted anticancer drug to the tumor tissues/cells by passive and active mechanisms. Most of the anticancer drugs are poorly water soluble in nature, polymeric micelles deliver these anti-cancer drugs to the targeted tumor sites that selectively act only on targeted cells and do not affect the normal healthy cells. However, most of the polymeric micelles have been successfully established in targeted therapeutics and some are still at preclinical trials. Future studies need to pave the way for these therapies into clinical practice to increase the survival rate of cancer patients and enhance anticipation of cancer chemotherapy [45].

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Niosomes are defined as nonionic surfactant vesicles that entrap both lipophilic and hydrophilic drugs in the vesicular membrane/aqueous phase. These are made up of lipid material possessing better stability than liposomes. Niosomes may be established as useful carriers for targeting the drugs to treat tumor, viral, parasitic, and other microbial diseases more effectively. Pharmacosomes are self-assembling components consisting of a pharmocon (active component) and a carrier molecule composed of amphipathic drugs. Drugs covalently linked to lipid molecules may be in colloidal dispersion as micelles or as ultrafine hexagonal aggregates used in targeted therapy. Ufasomes are single-chain fatty acid surfactant vesicles formed from double-chain amphiphiles and micelles. They are composed of lipid bilayer liposomes made of single-chain unsaturated fatty acids used in targeted drug delivery. Ufasome vesicles are colloidal suspensions of closed lipid bilayers consisting of ionized species (soap) and fatty acid molecules composed of more amphiphiles than micelles. These readily available fatty acids give ufasomes an advantage over liposomes. Cubosomes refer to liquid crystalline liposomes formed into cubic nanoparticles that are suitable for injection at the targeted site. Lipid droplets that allow easy penetration through the pores are called transferosomes, which are smaller than a droplet. Transferosomes is a supramolecular entity that can pass via permeability barriers and transport drug from one side to the other and is more elastic than a liposome.

4.2. Biological-based Nanoparticles

In addition to micelles, some groups of nanoparticles forming self-assembling structure are known as cell-penetrating peptides (CPPs). These molecules are applied in recognizing hydrophobic drugs and delivering biomolecules such as nucleic acids (siRNA, pDNA) intracellularly to the targeted cells. Furthermore, CPP drug delivery system is more constructive owing to its low toxicity, biocompatibility, structural stability, and easy preparation [46–49]. Addition to hydrophobic interaction, CPPs improve the nucleic acid delivery system. Both hydrophobic interactions and the electrostatic nature of CPPs contribute to its stable structure that can easily enter into the cells and deliver the siRNA.

Proteins are also important and promising agents for drug delivery that bioconjugate with drugs and deliver to the targeted sites (albumin-conjugated with paclitaxel named as abraxane). Albumin and paclitaxel linkage (abraxane) are prepared by homogenization under high pressure [50]. However abraxane is a more effective and less cytotoxic drug compared to conventional drugs. The drug is released from abraxane through the albumin receptor in blood vessels of the tumor cells [50, 51]. Bioconjugation of albumin-paclitaxel combination has been effectively used against lung cancer [50], breast cancer, [51] and gastric cancer [52].

4.3. Polymeric-based Nanoparticles

Polymers have good biocompatibility, are easily prepared, and morphologically manipulated into a variety of designs and structures. They possess bio-mimetic properties making it a widely used biomaterial. Polymers play an important role in smart drug delivery systems as they can effectively deliver chemotherapeutic drugs directly into the targeted site. The surface of polymeric nanoparticles has been functionalized by the alteration of nanoparticles through emulsification, adsorption, polymerization, functional surfactants, modulation of various

forms of bio-conjugation, and covalently-bound functional molecules. Polymers are widely used in numerous therapeutic applications for targeting cancer, disorders of the central nervous system (CNS), and other bacterial and viral infections. Zhang et al. [53] reported that more than 26 nanoparticles based on their therapeutic action have been approved for clinical trials and a few more are in the pipeline. Polymeric nanoparticles possess characteristic properties that affect its bio-distribution, efficiently enhancing the delivery of targeted drug across the blood brain barrier compared to conventional drug treatments as well as other well-known drug carriers [54].

Microspheres are biocompatible polymers either particle or soluble in nature. Polymeric backbone carriers are *N*-(2-Hydroxypropyl) methacrylamide (HPMA) prepared by ficoll, dextrans, sepharose, or poly-L-lysine as core carrier system for chemotherapeutic drugs. Microspheres (30–200 μm) are larger than nanoparticles (0.2–0.5 μm) but have a smaller area for drug loading than soluble polymers. The drug incorporation of microsphere considerably affects its release rate. Once the drug is administered or systematically transported, it rapidly dispenses into the target site and is subsequently internalized by macrophages of the phagocytic system. Moreover, microspheres and nanoparticles are mostly used for cell-selective applications of drug delivery (oral delivery peptides and peptidomimetics) [55–58].

Dendrimers play a significant role in the delivery of different compounds such as tamsulosin, primaquine phosphate, 5-fluorouracil, doxorubicin, tropicamide, indomethacin, artemether, and pilocarpine as targeted drugs [59]. Bioconjugated dendrimers can deliver the targeted drug transdermally, intravenously, orally, and through the ophthalmic route, which proves the versatility and functionality of dendrimers [60].

4.4. Carbon-based Nanoparticles

The properties [61], application [62–68], and solubility nature [69] of carbon nanotubes are well-established nanocarriers for drug delivery. Jain et al. [70] reported that chemical modification of carbon nanotubes by carbohydrate D-galactose can generate a novel cascade of chemical functionalization of multi-walled carbon nanotubes (MWCNTs). Therefore, galactosylated MWCNTs are used to deliver the active ligands (such as galactose) as a bioactive(s) targeted drug to the tumor site (hepatic tissues) [70].

Carbon nanohorns related to carbon nanotubes belong to a new class of carbon materials. Single-walled carbon nanohorn (SWNH) aggregates consist of thousands of graphitic tubules (2–5 nm in diameter, similar structure to single-walled CNTs) having a spherical structure (50–100 nm in diameter). Based on the morphological features, nanohorns are divided into bud, dahlia, and seed types. SWNHs are non-metallic catalysts produced by laser ablation of a pure graphite target; however, its toxicity must be proactively investigated. Molecules completely composed of carbon are fullerene, spherical fullerenes are known as buckyballs. Fullerenes are similar to graphite structure consisting of stacked graphene sheets of connected hexagonal rings and pentagonal rings. Fullerene C60 is highly biocompatible with reduced toxicity and is used for targeted drug delivery for several diseases such as Parkinson's and HIV.

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Nanoshells have a dielectric core covered with a thin metallic shell of gold-coated silica that is spherical in shape. These are used for early stages of cancer detection and treatment. Injected embedded drugs consist of cancer-targeted hydrogel polymers that are released at the tumor targeted site when exposed to laser (infrared).

4.5. Metal-based Nanoparticles

Metal-based nanoparticles are fascinating because the metal exhibits an important electronic and optical property and acts as an insulator or semiconductor [71–73]. Transition (Al, Co, Cu, Fe, Ni, Ti) and noble (Au and Ag) metal nanoparticles reveal a luminescence emission in the visible wavelength of light. Recent studies show metal linked with carbon nanotubets (Ag/CNT composites) are gaining increased attention due to their potential applications as optical limiters [74], catalyst [75], and advanced materials [76] capable of being used in bio-imaging of the cancer cells for targeted therapy [74].

Targeted drug delivery with gold nanoparticles possess a unique chemical and physical characteristic feature as they have strong binding interaction with proteins, thiols [77], aptamers [78], carboxylic acid [79], and disulfides linkages. These are widely used in tumor targeted delivery system for therapeutics. Gold particles can enter into targeted sites by phagocytosis, fluidphase endocytosis, and receptor-mediated endocytosis [80], depending upon the shape, size, surface charge, synthesis process, functionalized molecules, and surface coating toxicity of gold. Moreover, gold nanoparticles are considered to be non-toxic agents for drug delivery [81]. Gold nanoparticles possess a functional flexibility with prodrug molecules by covalent or non-covalent linkage enhancing the efficient transport of the drug into the targeted tumor sites. Gold nanoparticles can hold high drug concentration and deliver it to the specific targeted site via various routes of drug administration. Conventional drug side effects can be reduced by conjugated gold nanoparticles reducing the tumor survival rate.

5. Therapeutic Strategies for Drug Delivery

5.1. Folate Targeting

Folate receptors (FRs) are overexpressed in various tumors (including leukemia, endometrial, ovarian, and kidney cancer), which binds vitamin folate and folate-drug conjugates with a high affinity [82]. Folate receptors are targets of various therapeutic strategies aimed at efficient delivery of chemotherapeutic drugs. Folate receptors also play a role in the uptake of antifolate drugs that are used for therapeutic intervention in malignant disorders. The salient features of folic acid for therapeutic strategies are: i) reasonable binding affinity to both diagnostic and targeted therapeutic agents; ii) its unique and high affinity for the folate receptor, even after binding to diagnostic and therapeutic cargo; and iii) the folate receptor in normal healthy tissues have limited scattering, despite its overexpression on both type of tumors cells (FR-α and FR-β isoforms) [83]. Earlier investigations [84] show that folate enter the cells through receptor-mediated endocytic process. Hence, folic acid is repeatedly used as a drug targeting

ligand coated with delivery vehicles (polymeric nanoparticles, liposomes, dendrimers, and protein toxins) to selectively deliver targeted drugs into malignant cells.

We were the first to report that curcumin enhances the up-regulation of folate receptor β mRNA and protein levels in KG-1 cells by modulating the uptake and cytotoxicity of methotrexate. Notably, curcumin also augmented folate receptor β function as a transporter for radiolabeled folic acid and methotrexate in KG-1 cells. These reports optimized curcumin dosage and reduced the concentration of methotrexate resulting in the effective destruction of tumor cells. Therefore, amalgamation of non-toxic concentrations of methotrexate and curcumin may be a viable strategy for therapeutic intervention for leukemia using a folate receptor-targeted drug delivery system [85]. Shen et al. [86] reported that folate receptor-targeted drug conjugate had less communication with the cells and easily entered through overexpressed folate receptor of malignant cells by receptor-mediated endocytosis. Later the drug was transferred into lysosomes, wherein the active form of drug poly (amido amine)] dendrimers (PAMAM) was regenerated. The PAMAM left the lysosome and released anti-cancer drug camptothecin (CPT) in the nucleus. This modulation creates PAMAM dendrimers as valuable drug carriers for in vivo tumor cell nuclear drug targeted delivery. Folate receptor-targeted (nanoparticles) delivery systems, despite showing significant promising effects in human pathologies, enhance the tumor selectivity for tumor targeting. This modulatory strategy avoids possible obstacles, and we anticipate that folic acid will act as an essential candidate for receptor-targeted therapeutics in the near future.

5.2. Antibodies Targeting

Specific antigens are exclusively expressed on the surface of the cancer cells. Antibodies, especially monoclonal antibodies (mAb), can be produced to identify and specially bind to the antigens associated with tumor cells. In 1981, Milstein [87] developed an mAb that binds to malignant cells, a few functional classes of antibodies that possessed more binding and destroying activity in the tumor cells. Currently, numerous mAb-based tumor tissues targeting therapeutics has been effectively translated into clinical treatment such as trastuzumab, rituximab, cetuximab, and bevacizumab [88-91]. These mAb could be used as fragments or in their native state, generally having higher affinity toward tumor-associated antigens depicting its targeting efficacy. Moreover, the whole mAb are more beneficial than fragments to develop a higher binding affinity, owing to a synergic effect of having more than one binding site. Furthermore, the full or entire antibody sequences express more EPR effects that are maintained in cancer tissues, while in small fragments express less EPR effects that can easily be eliminated from blood circulation [92].

Recent investigations have attention on multi-functionalization of the nanoparticle surface with specific mAbs and encapsulation of therapeutic drugs into nanoparticles to sustain its targeting efficacy. Recent studies by Nobs et al. [93] shows poly-(lactic acid) (PLA) nanoparticles conjugated rituximab and trastuzumab exhibit six-fold enhances affinity and uptake compared with similar particles without mAb targeting molecules. The investigation of Miyano et al. [94] shows conjugated KG6Etrastuzumab (KG6E-amino acid dendrimer with surface modified by sixth-generation lysine dendrimer with glutamate –KG6Etrastuzumab)

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was expressively internalized and then transferred to lysosome for human epidermal growth factor receptor -2 (HER-2) positive cells (SKBR3), compared to HER2 – negative cells (MCF-7) indicates that KG6E-trastuzumab conjugates act as HER-2 targeting carriers in drug targeted delivery for cancer therapy. However, nanoparticles conjugated with mAbs still encounter numerous tasks and boundaries, owing to a "binding-site barrier" (decreased rate of penetration of nanocarriers due to high binding affinity) in solid tumors [95].

5.3. Glycoprotein Targeting

Serum glycoprotein transferrin (Tf) acts as a transporter to deliver the iron molecule into the cells via blood by binding to the transferrin receptor successfully that is being internalized through receptor-mediated endocytosis [96]. TfR is overexpressed on most of the tumor cells such as colon, pancreatic, lung, and bladder cancer cells due to increased metabolic rates. The TfR expression is 100 times greater in cancerous cells than normal healthy cells, this increase in expression is a result of a higher demand for iron in tumor cells, essential for their survival [97]. Tf has been often used as a drug targeting ligand in TfR-targeted drug delivery system for tumor cells. Direct conjugations of nanocarriers to Tf have enhanced intracellular drug delivery and efficient therapeutic outcome. Ishida et al. [98] demonstrated Tf conjugated with polyethyleneglycol (PEG)-liposomes exposed over prolonged periods in blood circulation but had reduced uptake via reticuloendothelial system (RES) in colon cancer. This proposes that Tf-conjugated nanoparticles were internalized by receptor-mediated endocytosis owing to specific ligand-receptor binding for cytoplasmic targeting to cancer cells. Tf-conjugated paclitaxel coated with poly (lactic-*co*-glycolic acid) (PLGA) nanoparticles showed enhanced suppression in cell growth than free paclitaxel in MCF-7 and MCF-7/Adr cells [99]. Doxorubicin (Dox)-coated, HAIYPRH (T7)-conjugated, PEG-modified polyamidoamine dendrimer (PAMAM-PEG-T7/Dox) nanoparticles was fabricated by Jiang et al. [100]. This modified targeted drug effectively accumulates in malignant cells via intravenous administration and can be internalized into cancer cells with Tf. These studies proved that Tf acts as a ligand for targeted drug delivery system in TfR overexpressed malignancies. However, TfR is also expressed in normal fast growing healthy cells (epithelial, fibroblast, and endothelial cells) that could lead to non-specific targeting and increase the cytotoxic effects reducing the efficacy of the targeted drug [101]. Furthermore, Tf with nanoparticles targeting ligands may improve drug delivery in tumor tissues and distribution in blood circulation similar to normal healthy cells expressing TfR (non-targeted systems) [102].

5.4. Oligonucleotide Targeting

Short, single-stranded RNA or DNA oligonucleotides designed in vitro from a huge number of random sequences around 1014–1015 that can identify the specific target sites are known as aptamers [103]. Aptamers possess high affinity and specificity features enhanced to bind a wide range of intracellular molecules, such as receptors, small molecule drugs, and proteins [104] specified for aptamer-based targeted cancer therapy. Although, aptamers and mAbs have similar and specific affinity against selected molecules, aptamers possess their own unique features: they can be synthesized in vitro without laboratory animals [105] and nanoparticle-

conjugated aptamers very efficiently target the tumor tissue via active targeting pathway. Lupold et al. [106] established nanoparticle-conjugated aptamer (A10 aptamer) that target overexpressed transmembrane protein of prostate specific membrane antigen (PSMA) in various tumor tissues. Aptamers-doxorubicin (Apt-Dox) are conjugates that are also implemented (designed) for targeted delivery to malignant cells [107]. Furthermore, Huang et al. [107] demonstrated that Dox conjugated to DNA apatamer-sgc8c (sgc8c-Dox conjugate) retains its high binding affinity features increasing efficiency of internalization by tumor targeted cells. These characteristic features make targeted delivery of chemotherapeutic drugs more feasible with abundant targeting potencies. Furthermore, these therapeutic strategies give rise to a novel targeted drug delivery and provide promising approaches for future treatment.

5.5. Membrane Protein Targeting/Cell Surface Receptors Targeting

Integrin membrane glycoproteins are heterodimeric in nature composed of non-covalent bonding of α and β subunits; they play a major role in tumor malignancy and angiogenesis [107]. In tumor endothelium $\alpha_v\beta_3$ and $\alpha_v\beta_5$, integrins are overexpressed at the highest levels. Asparagine/glycine/arginine (NGR) and arginine/glycine/aspartic acid (RGD) are the largest number of tumor-homing peptides used to detect the corresponding receptors of integrins $\alpha_v\beta_3$ on tumor endothelial cells. Brooks et al. [109] reported that RGD vascular homing peptides enhanced intracellular targeted drug delivery accomplished via integrin-binding RGD and suppress the tumor growth. Recent studies described Dox-coated nanoparticles with cyclic RGD peptide ligand delivered the drug to targeted integrin $\alpha_v\beta_3$ and caused a decrease in survival rate of the tumor cells [110]. Moreover, investigations on paclitaxel entrapped liposomes with peptide consisting of specific ligand to alpha $_V$ integrins and specific motif to neuropilin-1 showed significant increase in paclitaxel uptake in targeted tumor cells (A549 and HUVEC) depicting the enhanced suppression of cell growth by dual targeted mechanism compared with single-targeted paclitaxel entrapped liposomes and paclitaxel injections (Taxol) alone [111]. Furthermore, investigations show that cyclic RGD peptide (cRGDyK) conjugated in PEG-b-PLGA micelles deliver the targeted hydrophobic drug into intracellular cancer cells and its neovasculature, enhancing the antiproliferative and cytotoxicity efficacy compared with cRGDyK-free non-targeted micelles [112]. However, targeted delivery to integrin glycoprotein meets many challenging tasks for therapeutic strategies. The most common are integrins receptors, which are extracellular and expressed in normal fast growing healthy epithelial cells other than tumor cells. Treatment with RGD also targets the normal functional integrin ($\alpha_5\beta_1$ and $\alpha_4\beta_1$) molecules, thus resulting in targets of nonspecific tumor cells [113].

6. Significant Role and Functional Properties of Targeted Drug Delivery

The application purpose of nanoparticles in nanomedicine is targeted drug delivery system [114]. In the past two decades, scientists have developed and understood the mechanism of drug delivery and drugs have been designed for targeted delivery s [3]. Most of the new and currently available therapeutic drugs (95%) have poor biopharmaceuticals and pharmacoki-

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netics properties [40]. Therapeutic index of efficiently biological targeted drugs must be improved by suitable nanotechnological application for targeted delivery in tumor cells/tissues. Nanotechnological approaches [114] enhance reconsideration of failed clinical trials of chemotherapeutic drugs.

The targeted drug should be safe and effective with sufficient drug concentration in the body to deliver an effective dosage at the targeted tumor site. Chemotherapeutic targeted drugs must possess high toxicity and strong inhibition toward the targeted tumor tissue/cells proliferation. Many researchers have demonstrated that biological toxins, protein macromolecules, hydrophobic, and hydrophilic drugs are delivered through nanocarriers. Nanostructured designs are promising components that enable novel chemotherapeutic drugs for targeted delivery and explain the principles of component-targeted drug delivery systems (Figure 1). Nanomedicine has continuously released drug delivery mechanisms that enter into the cell by intracellular mechanisms and reduces its side effects. Nanoparticles have greater advantage than microparticles. They are appropriate for intravenous targeted delivery, tremendously exploited for well-controlled targeted drug release at site-specific targeting, have prolonged the time of blood circulation facilitating extravasation of drug delivery, and have favorable outcomes in site-specific drug targeting for treating cancer as well as disorders of the CNS and immunodeficiency infection [115]. Moreover, 300 pharmaceutical companies in the United States (US) mainly focus on targeted drug delivery systems. Additionally, drugs can be administrated through oral, pulmonary, ocular, transmucosal, and implantation routes of delivery.

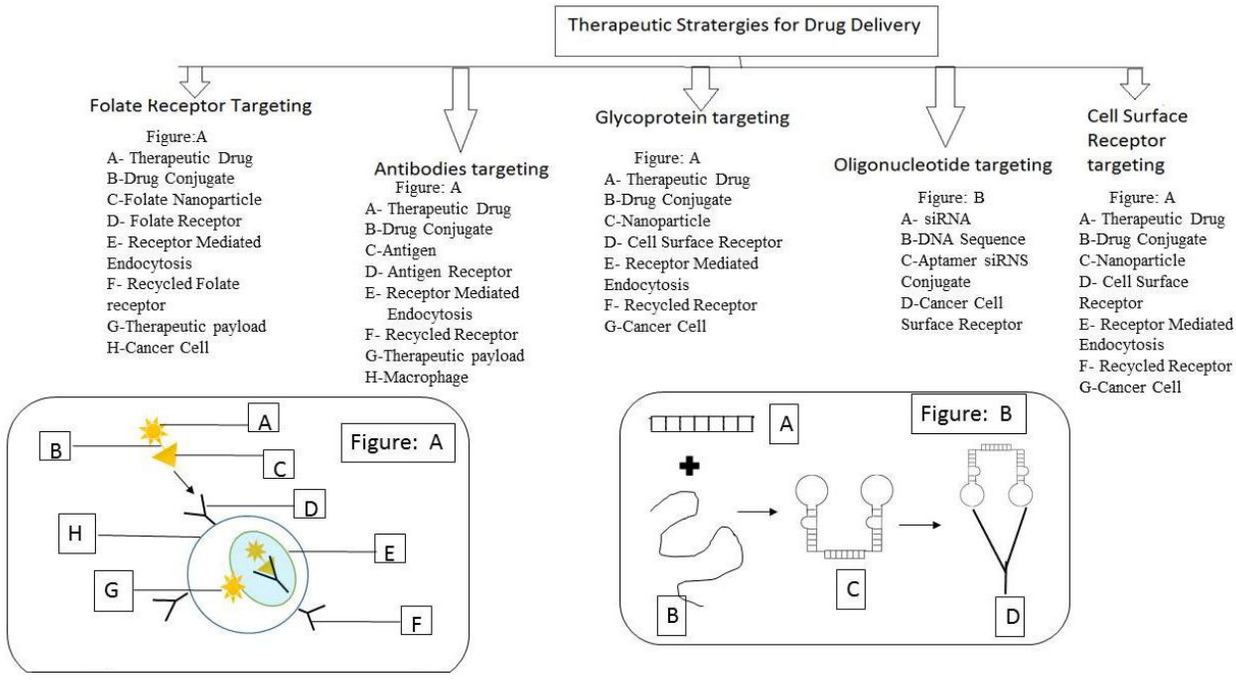

Figure 1. Schematic representation of components of targeted drug delivery

Nanomaterials are used in targeted drug delivery including metal-, biological-, lipid-, silicon-, carbon-, and polymer-based materials [114]. These technology-based medicines (nanomedicine platforms) can be multifunctional, also known as intelligent/smart drug system. We raise awareness of the physiological and functional challenges of therapeutic application and enlighten recent advances in our understanding and mechanism of tumor biology [116]. Nanoscale drug targeted delivery system is capable of enhancing pharmacokinetics and increasing the bio-distribution of therapeutic agents to targeted organs/tissues/cells with improved efficacy of the drug. The volume of drug distribution and toxicity is reduced, owing to drug accumulation at specific targeted sites and reduced concentration in normal healthy cells while using nanoscale carriers. It is designed to target cancer and inflammation sites through permeable vasculature. It is also biocompatible and made of biodegradable materials reported as safe replacement drug carriers than existing vehicles that may cause allergic reaction and peripheral neuropathy [40]. Few drugs have a very short half-life in blood circulation. The efficacy and stability of the drug can be increased by enclosing a drug with a nanocarrier to extend its short-half life. For example, a drug can be enclosed with a nanosized carrier (liposome).

Most of the drugs face difficulties in targeting tumor sites while crossing the blood brain barrier (BBB). Nanoparticle-coated drugs potentially penetrate BBB and are shown to potentially enhance the therapeutic concentration and index of anticancer drugs that have been delivered to the brain tumor. Its most noteworthy advantage is reduced toxicity and enhanced efficacy of the drug by guiding the drug to its target and retaining the drug concentration at the targeted site for a longer duration to increase its therapeutic action. [114]. Figure 2 explains the desirable therapeutic strategies of smart drug targeted delivery systems. Solid tumors possess vascular pores (vascular pore cut-off 380–780 nm) depending on various sizes, type of cancer, microenvironments, and proliferation rate. Thus, drug with the carrier molecules should be smaller than vascular pore cut-off size (diameter) to reach its targeted tumor sites. Normal healthy blood vessels do not permit drug-associated carrier molecules larger than 2–4nm size compared with unassociated drug molecules. Thus, nanomedicine has paved the way to enhance drug accumulation and its concentration in targeted cells/tissues/sites by extravasation and considerably diminishing its toxicity and distribution to normal healthy cells [40]. Ideal nanocarrier materials should be without any chemical modification and must fulfill the demands of biocompatibility, biodegradability, and release dynamics of targeted drugs [117, 118].

Nanocarriers essentially need to prolong exposure time in blood circulation and allow the nanocarriers to reach the targeted site through multiple pathways. Generally, nanoparticles possess a very short half-life, owing to natural immune/defense mechanisms of the human system that eradicate them after opsonisation by phagocytic mechanisms. Thus, the nanocarrier surface must be altered to be invisible to the opsonisation process.

Nanocarriers are naturally made up of macromolecular materials or entrapped lipids, adsorbed onto the surface of the nanoparticles or dissolved within the polymeric matrix. They are categorized into two types: nanospheres (matrix systems used to dispersing drug molecules) and nanocapsules (vesicular systems drugs that are surrounded by a membrane). Nanotechnology-based polymers are designed as top-down and bottom-up processes. The top-down method is initiated by breaking down larger objects into nanostructured molecules

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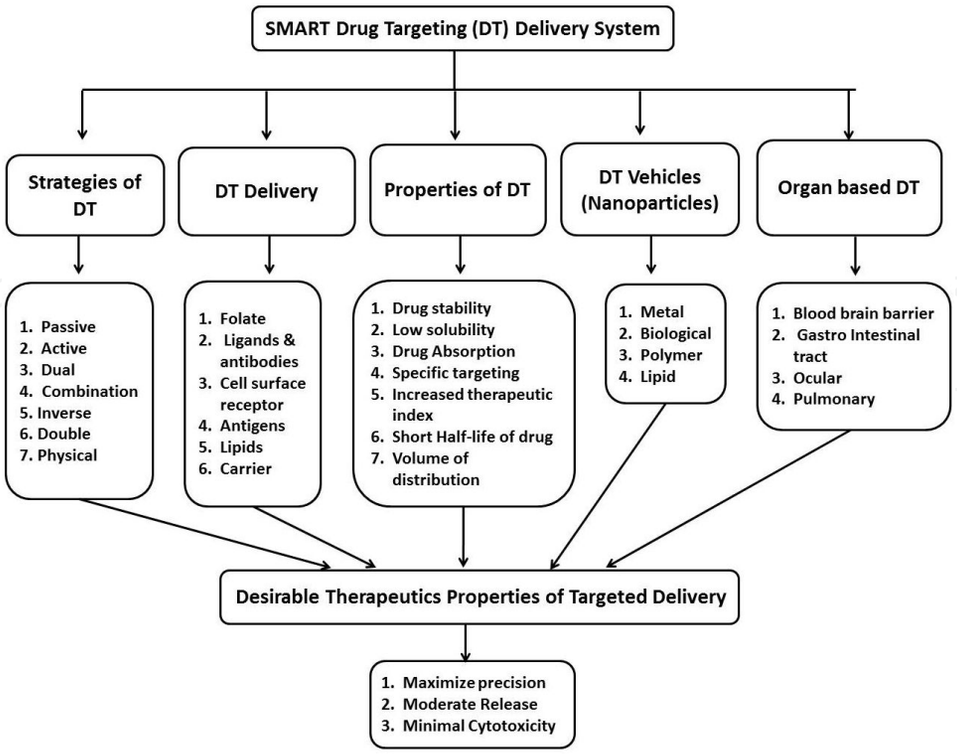

Figure 2. Schematic representation of SMART drug targeted strategies

by over grinding, etching, or ball milling enhanced by laser or the addition of chemicals. However, this technique is time-consuming and repeatedly produces considerably wider particle size of distribution. This type of production is based on atom-by-atom or molecule-by-molecule arrangements in a well-programed manner, organized chemical reaction by both liquid or gas phase, ensuring in nucleation and growth of nanoparticles. The bottom-up process generates heavily clustered masses of particles that do not break up on reconstitution [119]. Particles prepared by complex coacervation, salting-out, solvent emulsification diffusion, high-pressure homogenization, nanoprecipitation, supercritical fluid, co-precipitation, rapid expansion of supercritical solutions, supercritical antisolvent precipitation, and self-assembly methods [119]. The nanoparticles used as carriers are polymeric nanoparticles, magnetic nanoparticles, metal and inorganic nanoparticles, quantum dots, polymeric micelles (PMs), solid lipid nanoparticles, and colloidal nanoliposomes.

7. Targeted Drug Delivery in Anticancer Therapy

A clear understanding of molecular mechanism of tumor proliferation, formation metastasis, invasion, and angiogenesis ensures a new mechanistic basis for targeted tumor drug discovery (targeted anticancer therapy). Exact blocking or altering of the molecular mechanism associated in the pathogenesis of tumor cell proliferation by targeted chemotherapeutic agents modify the natural process of the disease as well as improve therapeutic index with cytotoxic agents. Anticancer drug for targeted delivery system must meet a few requirements: a) the

targeted drug must have minimal activity loss, b) it should destroy the targeted tumor cells, c) must be well-regulated and predicate the active form of drug release [120], and d) leakage of drug during transit must be minimal. Concurrently, therapeutic drugs with less dosage should be used during targeted therapy (minimal dose than the normal chemotherapy) with minimal side effects [120, 121]. Drugs are conjugated with nanocarriers and delivered to the receptor (outside) or inside the targeted tumor cells by a selective targeting mechanism [121]. The previous traditional process of administration of chemotherapy is an aggregation of drugs inside the tumor cells/tissues through EPR [122, 123, 117] as a result of the abnormal structure of blood vessels closer to the tumor tissues. Thus, the drug discharges easily to the tissues near the cancer cells [40, 123]. Furthermore, few drugs are used in conventional treatment such as methotrexate [124], paclitaxel [125], doxorubicin [126], gemcitabine [127] hexamethylmelamine [128], and cisplatin (DDP) or carboplatin (drugs based on platinum) [129]. The drug may be delivered to: a) the capillary bed of the active site, b) specific type of cells, c) intracellular region of tumour cells absent in normal healthy cells, and d) specific organ/tissues by complexion with the nanocarrier that recognizes the target. Conventional anticancer targeted therapy is composed of ligands (receptor, antibodies, and chemotherapeutic drugs) conjugated with nanocarriers, thus, the fabricated drug enables binding affinity with particular receptors of the targeted cancer cells. Overexpression of receptors in cancer cells enhances the binding affinity of the nanocarrier conjugated ligands to the receptor [121, 123, 117]. The targeted delivery system discharges the chemotherapeutic drugs directly to tumor cells and maintains prolonged circulation of the drugs with high concentration inside the tumor cells. However, targeted drugs cannot be released back to the blood stream because of the ligand and receptor binding affinity, the same principle that is used in immunogenicity [122].

8. Challenges and Future Directions

Smart drug targeted delivery system is approaching optimal therapeutic strategies for malignant and other chronic diseases. Targeted drug delivery is a rather complex mechanism that has many aspects that are far-fetched; however, it is an approach that has been successfully used to treat cancer and other chronic diseases. An ideal delivery system of targeted drug molecules to its specific tissue/cells/organs is still beyond our reach in many ways and still poses a challenging task in the complex cellular network system of organisms. An ideal drug targeted delivery system is the one that delivers the drug to the exact targeted tumor site in the right dosage required [130]. The reality, however, is far away from the ideal scenario of bench-to-bedside treatment. The dosage levels of drugs delivered to targets sites is much less than 5% at most.

Our efforts must be motivated toward improving moderate drug dosages delivered to the target sites. As chronic diseases and tumors may not be eradicated by just targeting one site, it may also be necessary to concurrently aim at multiple targets. Consequently, it may be worthwhile to develop a new technology or a “magic shotgun” strategy that distributes the multiple drugs into multiple targets to achieve optimal therapy [130]. It will be a challenging task to modify our current approaches on targeted drug delivery systems through such alterations that will influence not only the strategies selected but also the approaches to identify, modify, and test the success of these methodologies.

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Furthermore, clear validation for identifying new approaches and modifications, do not basically lead to an improved outcomes without theatrical changes in our current protocols on targeted drug delivery research to make significant improvements in the future. Advanced nanomedicine technology-based drug delivery to the target sites will be limited by extravasation and blood circulation. However, selective ligand targets a tumor cell marker or receptor through receptor-ligand binding that occurs only after delivery by extravasation and blood circulation. The receptor-ligand communication will be problematic for tumors as cells "over-express" targeted surface markers. The selective targeted surface marker will also be expressed on the surface of the non-cancer cells due to the gross surplus of the cancer cell burden.

Relatively, over-dependence on nanoparticles alone will be inadequate for significant clinical benefits. Improvement of targeted drug delivery systems will need better understanding of various factors involved in the regulation of distribution in the blood, temporal heterogeneity, tumor markers, energetic aspects of tumor spatial, and complexities of diffusional barriers in solid tumors. In addition, we may not depend on a sole over-expressed tumor marker for specific drug targeting therapeutic managements. Modern drug targeted delivery and its methodologies are scientifically sound rationale with limited success mainly due to the construction of nanomaterials and drugs according to biochemical and engineering principles alone. The currently available nanoparticles can improve the blood circulation time and pave the way into malignant cells by potentially modulating their ability to intermingle with tumor cell receptors. These promising nanoparticles ensure problems such as the forceful modulation of the malignant cells and cancer heterogeneity.

For malignant and other therapies, the ideal smart drug targeted delivery system delivers the drug at a targeted tumor site. In the future, efforts must focus on exploring the delivery of increased concentration of the drug to the targeted site. Malignant cells may not be eliminated by just targeting one site, it may also be important to aim at multiple targets. Furthermore, in the future, merging expertise in drug targeted delivery with technological improvements in molecular medicine will pave the way to elucidate molecular and cellular mechanism underlying diseases. New approaches under investigation should focus on "bench-to-bedside" practices to reduce delay of therapeutic stages.

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References

[1] Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs—a review of drug nanocrystal technology and lipid nanoparticles. Journal of Biotechnology. 2004; 113(1–3):151–170.

[2] Mark SW, Torchilin, Vladimir P. Drug delivery systems. Access Science, McGraw-Hill Companies, 2011.

[3] Vyas SP, Khar RK. Basis of targeted drug delivery. In Targeted and controlled Drug Delivery, CBS Publishers and Distributors Reprint, 2008: 42–46, 74.

[4] Won R. Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen, Patent No 4690825 US: 1987.

[5] Mastrobattista E, Koning GA, Storm G. Immunoliposomes for the targeted delivery of antitumor drugs. Advance Drug Delivery Reviews. 1999;10:40(1-2):103–127.

[6] Maeda H, Matsumura Y. Tumoritropic and lymphotropic principles of macromolecular drugs. Crit Rev Ther Drug Carrier Syst. 1989;6:193–210.

[7] Gref R1, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V, Langer R. Biodegradable long-circulating polymeric nanospheres. Science. 1994;263(5153):1600–1603.

[8] Mansour AM, Drevs J, Esser N, et al. A new approach for the treatment of malignant melanoma: Enhanced antitumor efficacy of an albumin binding doxorubicin prodrug that is cleaved by matrix metalloproteinase 2. Cancer Res. 2003;63:4062–6.

[9] Guo X, Szoka FC, Jr. Chemical approaches to triggerable lipid vesicles for drug and gene delivery. Acc Chem Res. 2003;36:335–41.

[10] Yockman JW, Maheshwari A, Han SO, Kim SW. Tumor regression by repeated intratumoral delivery of water soluble lipopolymers/p2CMVmIL-12 complexes. J Control Release, 2003;87:177–86.

[11] Nomura T, Saikawa A, Morita S, et al. Pharmacokinetic characteristics and therapeutic effects of mitomycin C-dextran conjugates after intratumoural injection. J Control Release. 1998;52:239–52.

[12] Barker DD, Berk AJ. Adenovirus proteins from both E1B reading frames are required for transformation of rodent cells by viral infection and DNA transfection. Virology. 1987;156:107–21.

[13] Khuri FR, Nemunaitis J, Ganly I, et al. A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer. Nat Med. 2000;6:879–85.

[14] Hecht JR, Bedford R, Abbruzzese JL, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. Clin Cancer Res. 2003;9:555–61.

[15] Reid T, Galanis E, Abbruzzese J, et al. Hepatic arterial infusion of a replication-selective oncolytic adenovirus (dl1520): Phase II viral, immunologic, and clinical endpoints. Cancer Res. 2002;62:6070–9.

[16] Vasey PA, Shulman LN, Campos S, et al. Phase I trial of intraperitoneal injection of the E1B-55-kd-gene-deleted adenovirus ONYX-015 (dl1520) given on days 1 through 5 every 3 weeks in patients with recurrent/refractory epithelial ovarian cancer. J Clin Oncol. 2002;20:1562–9.

[17] Galanis E, Okuno SH, Nascimento AG, et al. Phase I-II trial of ONYX-015 in combination with MAP chemotherapy in patients with advanced sarcomas. Gene Ther. 2005;12:437–45.

[18] Lamprecht A, Yamamoto H, Takeuchi H, Kawashima Y. Nanoparticles enhance therapeutic efficiency by selectively increased local drug dose in experimental colitis in rats. J Pharmacol Exp Ther. 2005;315:196–202.

[19] Beduneau A, Saulnier P, Hindre F, Clavreul A, Leroux JC, Benoit JP. Design of targeted lipid nanocapsules by conjugation of whole antibodies and antibody Fab' fragments. Biomaterials. 2007;28:4978–4990.

[20] Deckert PM. Current constructs and targets in clinical development for antibody-based cancer therapy. Current Drug Targets. 2009;10:158–175.

[21] Hong M, Zhu S, Jiang Y, Tang G, Pei Y. Efficient tumor targeting of hydroxycamptothecin loaded PEGylated niosomes modified with transferrin. J Control Release. 2009;133:96–102.

[22] Zensi A, Begley D, Pontikis C, Legros C, Mihoreanu L, Wagner S, Büchel C, Briesen Hv, Kreuter J. Albumin nanoparticles targeted with ApoE enter the CNS by transcytosis and are delivered to neurons. J Control Release. 2009;137:78–86.

[23] Canal F, Vicent MJ, Pasut G, Schiavon O. Relevance of folic acid/polymer ratio in targeted PEGepirubicin conjugates. J Control Release. 2010;146:388–399.

[24] Pirollo KF, Chang EH. Does a targeting ligand influence nanoparticle tumor localization or uptake? Trends Biotechnol. 2008;26:552–558.

[25] Kirpotin DB, Drummond DC, Shao Y, Shalaby MR, Hong K, Nielsen UB, Marks JD, Benz CC, Park JW. Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. Cancer Res. 2006;66:6732–6740.

[26] Mikhail AS, Allen C. Block copolymer micelles for delivery of cancer therapy: transport at the whole body, tissue and cellular levels. J Control Release. 2009;138:214–223.

[27] Raz A, Meromsky L, Lotan R. Differential expression of endogenous lectins on the surface of nontumorigenic, tumorigenic, and metastatic cells. Cancer Res. 1986;46:3667–72.

[28] Gorelik E, Galili U, Raz A. On the role of cell surface carbohydrates and their binding proteins (lectins) in tumor metastasis. Cancer Metastasis Rev. 2001;20:245–77.

[29] Yamazaki N, Kojima S, Bovin NV, et al. Endogenous lectins as targets for drug delivery. Adv Drug Deliv Rev. 2000;43:225–44. 24.

[30] Olsnes S, Sandvig K. How protein toxins enter and kill cells. Cancer Treat Res. 1988;37:39–73.

[31] Stefanadis C, Chrysochoou C, Markou D, Petraki K, Panagiotakos DB, Fasoulakis C, Kyriakidis A, Papadimitriou C, Toutouzas PK. Increased temperature of malignant urinary bladder tumors in vivo: The application of a new method based on a catheter technique. J. Clin. Oncol. 2001;19(3):676–681.

[32] Gerweck LE, Seetharaman K. Cellular pH gradient in tumor versus normal tissue: Potential exploitation for the treatment o cancer. Cancer Res. 1996;56(6):1194–1198.

[33] Gao M, Jia XR, Li Y, Liang DH, Wei Y. Synthesis and thermo-/pH- dual-responsive properties of poly (amidoamine) dendronized poly (2-hydroxyethyl) Methacrylate. Macromolecules. 2010;43:4314–4323.

[34] Pang Y, Zhu Q, Zhou DL, Liu JY, Chen Y, Su Y, Yan DY, Zhu XY, Zhu BS. Synthesis of backbone thermo and pH dual-responsive hyperbranched poly (amine-ether)s through proton-transfer polymerization. J. Polym. Sci. Part A: Polym. Chem. 2011:49:966–975.

[35] Li F, Wu H, Fan L, Zhang HT, Zhang H, Gu CH. Study of dual responsive poly[(maleilated dextran)-graft-(Nisopropylacrylamide)] hydrogel nanoparticles: Preparation, characterization and biological evaluation. Polym. Int. 2009;58:1023–1033.

[36] Ma LW, Liu MZ, Liu HL, Chen J, Gao CM, Cui DP. Dual crosslinked pH- and temperature-sensitive hydrogel beads for intestine-targeted controlled release. Polym. Adv. Technol. 2010;21:348–355.

[37] Kim IS, Oh IJ. Drug release from the enzyme-degradable and pH-sensitive hydrogel composed of glycidyl methacrylate dextran and poly (acrylic acid). Arch. Pharm. Res. 2005:28(8):983–987.

[38] Li YW, Tong R, Xia HS, Zhang HJ, Xuan J. High intensity focused ultrasound and redox dual responsive polymer micelles. Chem. Commun. 2010;46;7739–7741.

[39] Deol P, Khuller GK. Lung specific stealth liposomes: Stability, biodistribution and toxicity of liposomal antitubercular drugs in mice. Biochimica Biophysi Acta. 1997;1334:161–72.

[40] Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: A concise review. Nanomedicine. 2005 Sep;1(3):193–212.

[41] Koren E, Apte A, Jani A, Torchilin VP. Multifunctional PEGylated 2C5-immunoliposomes containing pH-sensitive bonds and TAT peptide for enhanced tumor cell internalization and cytotoxicity. J Control Release. 2012 Jun 10;160(2):264–73. doi: 10.1016/j.jconrel.2011.12.002. Epub 2011 Dec 13.

[42] Koshkaryev A, Piroyan A, Torchilin VP. Increased apoptosis in cancer cells in vitro and in vivo by ceramides in transferrin-modified liposomes. Cancer Biol Ther. 2012 Jan 1;13(1):50–60. doi: 10.4161/cbt.13.1.18871.

[43] Etzerodt A, Maniecki MB, Graversen JH, Møller HJ, Torchilin VP, Moestrup SK. Efficient intracellular drug-targeting of macrophages using stealth liposomes directed to the hemoglobin scavenger receptor CD163. J Control Release. 2012 May 30;160(1):72–80. doi: 10.1016/j.jconrel.2012.01.034. Epub 2012 Jan 27.

[44] Kang KW, Chun MK, Kim O, Subedi RK, Ahn SG, Yoon JH, Choi HK. Doxorubicin-loaded solid lipid nanoparticles to overcome multidrug resistance in cancer therapy. Nanomedicine. 2010 Apr;6(2):210–3. doi: 10.1016/j.nano.2009.12.006. Epub 2010 Jan 6.

[45] Kedar U, Phutane P, Shidhaye S, Kadam V. Advances in polymeric micelles for drug delivery and tumor targeting. Nanomedicine. 2010 Dec;6(6):714–29. doi: 10.1016/j.nano.2010.05.005. Epub 2010 Jun 11.

[46] Arukuusk P, Pärnaste L, Oskolkov N, Copolovici DM, Margus H, Padari K, Möll K, Maslovskaja J, Tegova R, Kivi G, Tover A, Pooga M, Ustav M, Langel U. New generation of efficient peptide-based vectors, NickFects, for the delivery ofnucleic acids. Biochim Biophys Acta. 2013 May;1828(5):1365–73. doi: 10.1016/j.bbamem.2013.01.011. Epub 2013 Jan 26.

[47] Wu Y, Sadatmousavi P, Wang R, Lu S, Yuan YF, Chen P. Self-assembling peptide-based nanoparticles enhance anticancer effect of ellipticine in vitro and in vivo. Int J Nanomedicine. 2012;7:3221–33. doi: 10.2147/IJN.S31858. Epub 2012 Jun 28.

[48] Crombez L, Morris MC, Deshayes S, Heitz F, Divita G. Peptide-based nanoparticle for ex vivo and in vivo drug delivery. Curr Pharm Des. 2008;14(34):3656–65.

[49] Nasrolahi Shirazi A, Tiwari R, Chhikara BS, Mandal D, Parang K. Design and biological evaluation of cell-penetrating peptide-doxorubicin conjugates as prodrugs. Mol Pharm. 2013 Feb 4;10(2):488-99. doi: 10.1021/mp3004034. Epub 2013 Jan 15.

[50] Yuan DM, Lv YL, Yao YW, Miao XH, Wang Q, Xiao XW, Song Y. Efficacy and safety of Abraxane in treatment of progressive and recurrent non-small cell lung cancer patients: A retrospective clinical study. Thoracic Cancer. 2012;3(4):341–347.

[51] Yan Z, Xia L, Qiu H, Chen P, Zhang B. Short-term outcomes of albumin-bound paclitaxel (abraxane)-containing chemotherapy in patients with advanced gastric cancer:

A report of 14 cases. The Chinese-German Journal of Clinical Oncology. 2013;12(1): 30-34.

[52] Paik PK, James LP, Riely GJ, Azzoli CG, Miller VA, Ng KK, Sima CS, Heelan RT, Kris MG, Moore E, Rizvi NA. A phase 2 study of weekly albumin-bound paclitaxel (Abraxane®) given as a two-hour infusion. Cancer Chemother Pharmacol. 2011 Nov; 68(5):1331–7. doi: 10.1007/s00280-011-1621-0. Epub 2011 Apr 3.

[53] Zhang H, Chen C, Hou L, Jin N, Shi J, Wang Z, Liu Y, Feng Q, Zhang Z. Targeting and hyperthermia of doxorubicin by the delivery of single-walled carbon nanotubes to EC-109 cells. Journal of Drug Targeting. 2013;21(3):312–319.

[54] Mody N, Tekade RK, Mehra NK, Chopdey P, Jain NK. Dendrimer, liposomes, carbon nanotubes and PLGA nanoparticles: one platform assessment of drug delivery potential. AAPS PharmSciTech. 2014 Apr;15(2):388–99. doi: 10.1208/s12249-014-0073-3. Epub 2014 Jan 16.

[55] Farah RA, Clinchy B, Herrera L, Vitetta ES. The development of monoclonal antibodies for the therapy of cancer. Crit Rev Eukaryot Gene Expr. 1998;8(3-4):321–56.

[56] Kim GJ, Nie S. Targeted cancer nanotherapy. Materials Today. August 2005;8(8):28–33. ISSN: 1369-7021, http://dx.doi.org/10.1016/S1369-7021(05)71034-8.

[57] Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975 Aug 7;256(5517):495–7.

[58] Storm G, Daan J, Crommelin A. Liposomes: quo vadis? Pharmaceutical Science & Technology Today. 1 April 1998;1(1):19–31. ISSN: 1461-5347, http://dx.doi.org/10.1016/S1461-5347(98)00007-8.

[59] Gupta U, Agashe HB, Asthana A, Jain NK. Dendrimers: Novel polymeric nanoarchitectures for solubility enhancement. Biomacromolecules. 2006 Mar;7(3):649–58.

[60] 42. Wen S, Liu H, Cai H, Shen M, Shi X. Targeted and pH-responsive delivery of doxorubicin to cancer cells using multifunctional dendrimer-modified multi-walled carbon nanotubes. Adv Healthc Mater. 2013 Sep;2(9):1267–76. doi: 10.1002/adhm.201200389. Epub 2013 Feb 28.

[61] Foldvari M, Bagonluri M. Carbon nanotubes as functional excipients for nanomedicines: II. Drug delivery and biocompatibility issues. Nanomedicine. 2008 Sep;4(3): 183–200. doi: 10.1016/j.nano.2008.04.003. Epub 2008 Jun 11.

[62] Liu Z, Chen K, Davis C, Sherlock S, Cao Q, Chen X, Dai H. Drug delivery with carbon nanotubes for in vivo cancer treatment. Cancer Res. 2008 Aug 15;68(16):6652–60. doi: 10.1158/0008-5472.CAN-08-1468.

[63] Liu Z, Fan AC, Rakhra K, Sherlock S, Goodwin A, Chen X, Yang Q, Felsher DW, Dai H. Supramolecular stacking of doxorubicin on carbon nanotubes for in vivo cancer therapy. Angew Chem Int Ed Engl. 2009;48(41):7668–72. doi: 10.1002/anie.200902612.

[64] Wong Shi Kam N, Dai H. Single-walled carbon nanotubes for transport and delivery of biological cargos. 2006.

[65] Kam NW, O'Connell M, Wisdom JA, Dai H. Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction. Proc Natl Acad Sci U S A. 2005 Aug 16;102(33):11600–5. Epub 2005 Aug 8.

[66] Shi Kam NW, Jessop TC, Wender PA, Dai H. Nanotube molecular transporters: Internalization of carbon nanotube-protein conjugates into Mammalian cells. J Am Chem Soc. 2004 Jun 9;126(22):6850–1.

[67] Liu Z, Tabakman S, Welsher K, Dai H. Carbon nanotubes in biology and medicine: In vitro and in vivo detection, imaging and drug delivery. Nano Res. 2009 Feb 1;2(2):85–120.

[68] Liu Z, Tabakman SM, Chen Z, Dai H. Preparation of carbon nanotube bioconjugates for biomedical applications. Nat Protoc. 2009;4(9):1372–82. doi: 10.1038/nprot.2009.146. Epub 2009 Sep 3.

[69] Firme CP 3rd, Bandaru PR. Toxicity issues in the application of carbon nanotubes to biological systems. Nanomedicine. 2010 Apr;6(2):245–56. doi: 10.1016/j.nano.2009.07.003. Epub 2009 Aug 20.

[70] Jain AK, Dubey V, Mehra NK, Lodhi N, Nahar M, Mishra DK, Jain NK. Carbohydrate-conjugated multiwalled carbon nanotubes: development and characterization. Nanomedicine. 2009 Dec;5(4):432–42. doi: 10.1016/j.nano.2009.03.001. Epub 2009 Mar 31.

[71] Sandler J, Shaffer MSP, Prasse T, Bauhofer W, Schulte K, Windle A. Development of a dispersion process for carbon nanotubes in an epoxy matrix and the resulting electrical properties. Polymer. 1999;40(21):5967–5971. http://dx.doi.org/10.1016/S0032-3861(99)00166-4.

[72] Silva LBD, Fagan SB, Mota R. Ab initio study of deformed carbon nanotube sensors for carbon monoxide molecules. Nano Letters. 2004;4(1):65–67. http://dx.doi.org/10.1021/nl034873d.

[73] Guldi DM, Rahman GMA, Prato M, Jux NJ, Qin S, Ford W. Single-wall carbon nanotubes as integrative building blocks for solar energy conversion. General & Introductory Chemistry. 2005;44(13):2015-2018. http://dx.doi.org/10.1002/anie.200462416.

[74] Chin KC, Gohel A, Chen WZ, Elim HI, Ji W, Chong GL, Sow CH, Wee ATS. Gold- and silver-coated carbon nanotubes: An improved broad-band optical limiter. Chemical Physics Letters. 2005;409(1-3):85–88. http://dx.doi.org/10.1016/j.cplett.2005.04.092.

[75] Guo DJ, Li HL. Carbon. 2005;43:1259.

[76] Wu HP, Wu XJ, Ge MY, Zhang GQ, Wang YW, Jiang J. Properties investigation on isotropical conductive adhesives filled with silver coated carbon nanotubes. Compo-

sites Science and Technology. 2007;67(6):1182–1186. http://dx.doi.org/10.1016/j.compscitech.2006.05.010.

[77] Lee K, Lee H, Bae KH, Park TG. Heparin immobilized gold nanoparticles for targeted detection and apoptotic death of metastatic cancer cells. Biomater. 2010;31:6530–6536.

[78] Tarnawski R, Ulbricht M. Amphiphilic gold nanoparticles: Synthesis, characterization and adsorption to PEGylated polymer surfaces. Colloid Surfac A: Physicochem Engineer Aspects. 2011;374:13–21.

[79] Deb S, Patra HK, Lahiri P, Dasgupta AK, Chakrabarti K, Chaudhuri U. Multistability in platelets and their response to gold nanoparticles. Nanomed: Nanotechnol Biol Med. 2011;7376–384.

[80] . Nalawade P, Mukherjee T, Kapoor S. High-yield synthesis of multispiked gold nanoparticles: Characterization and catalytic reactions. Colloid Surfac A: Physicochem Engineer Aspects. 2012;396:336–340.

[81] Benkovicova M, Vegso K, Siffalovic P, Jergel M, Luby S, Majkova E. Preparation of gold nanoparticles for plasmonic applications. Thin Solid Films. 2013;543:138–141.

[82] Leamon CP, Reddy JA. Folate-targeted chemotherapy. Adv Drug Deliv Rev. 2004 Apr 29;56(8):1127–41.

[83] Low PS, Henne WA, Doorneweerd DD. Discovery and development of folic-acid-based receptor targeting for imaging and therapy of cancer and inflammatory diseases. Acc Chem Res. 2008 Jan;41(1):120–9. Epub 2007 Jul 27.

[84] Kamen BA, Capdevila A. Receptor-mediated folate accumulation is regulated by the cellular folate content. Proc Natl Acad Sci U S A. 1986 Aug;83(16):5983–7.

[85] Sugapriya D, Biswal BK, Sumantran VN, Verma RS. Augmented sensitivity to methotrexate by curcumin induced overexpression of folate receptor in KG-1 Cells. Biochimie. 2013;95:1567–1573.

[86] Shen Y, Zhou Z, Sui M, Tang J, Xu P, Van Kirk EA, Murdoch WJ, Fan M, Radosz M. Charge-reversal polyamidoamine dendrimer for cascade nuclear drug delivery. Nanomedicine (Lond). 2010 Oct;5(8):1205–17. doi: 10.2217/nnm.10.86.

[87] Warenius HM, Galfre G, Bleehen NM, Milstein C. Attempted targeting of a monoclonal antibody in a human tumour xenograft system. Eur J Cancer Clin Oncol. 1981 Sep;17(9):1009–15.

[88] James JS, Dubs G. FDA approves new kind of lymphoma treatment. Food and Drug Administration. AIDS Treat News. 1997 Dec 5;(284):2–3.

[89] 160. Albanell J, Baselga J. Trastuzumab, a humanized anti-HER2 monoclonal antibody, for the treatment of breast cancer. Drugs Today (Barc). 1999 Dec;35(12):931–46.

[90] De Roock W, Piessevaux H, De Schutter J, Janssens M, De Hertogh G, Personeni N, Biesmans B, Van Laethem JL, Peeters M, Humblet Y, Van Cutsem E, Tejpar S. KRAS

wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol. 2008 Mar;19(3):508–15.

[91] Ferrara N. VEGF as a therapeutic target in cancer. Oncology. 2005;69 Suppl 3:11–6. Epub 2005 Nov 21.

[92] Matsumura Y, Kataoka K. Preclinical and clinical studies of anticancer agent-incorporating polymer micelles. Cancer Sci. 2009 Apr;100(4):572–9.

[93] Nobs L, Buchegger F, Gurny R, Allémann E. Biodegradable nanoparticles for direct or two-step tumor immunotargeting. Bioconjug Chem. 2006 Jan-Feb;17(1):139–45.

[94] Miyano T, Wijagkanalan W, Kawakami S, Yamashita F, Hashida M. Anionic amino acid dendrimer-trastuzumab conjugates for specific internalization in HER2-positive cancer cells. Mol Pharm. 2010 Aug 2;7(4):1318–27. doi: 10.1021/mp100105c.

[95] Adams GP, Schier R, McCall AM, Simmons HH, Horak EM, Alpaugh RK, Marks JD, Weiner LM. High affinity restricts the localization and tumor penetration of single-chain fv antibody molecules. Cancer Res. 2001 Jun 15;61(12):4750–5.

[96] Qian ZM, Tang PL. Mechanisms of iron uptake by mammalian cells. Biochim. Biophys. Acta. 1995;1269:205–214.

[97] Prost AC, Menegaux F, Langlois P, Vidal JM, Koulibaly M, Jost JL, Duron JJ, Chigot JP, Vayre P, Aurengo A, Legrand JC, Rosselin G, Gespach C. Differential transferrin receptor density in human colorectal cancer: A potential probe for diagnosis and therapy. Int. J. Oncol. 1998;13(4):871–875.

[98] Ishida O, Maruyama K, Tanahashi H, Iwatsuru M, Sasaki K, Eriguchi M, Yanagie H. Liposomes bearing polyethyleneglycol-coupled transferrin with intracellular targeting property to the solid tumors in vivo. Pharm Res. 2001 Jul;18(7):1042–8.

[99] Sahoo SK, Labhasetwar V. Enhanced antiproliferative activity of transferrin-conjugated paclitaxel-loaded nanoparticles is mediated via sustained intracellular drug retention. Mol Pharm. 2005 Sep–Oct;2(5):373–83.

[100] Han L, Huang R, Liu S, Huang S, Jiang C. Peptide-conjugated PAMAM for targeted doxorubicin delivery to transferrin receptor overexpressed tumors. Mol Pharm. 2010 Dec 6;7(6):2156–65. doi: 10.1021/mp100185f. Epub 2010 Oct 14.

[101] Ekblom P, Thesleff I, Lehto VP, Virtanen I. Distribution of the transferrin receptor in normal human fibroblasts and fibrosarcoma cells. Int J Cancer. 1983 Jan 15;31(1):111–7.

[102] Bartlett DW, Su H, Hildebrandt IJ, Weber WA, Davis ME. Impact of tumor-specific targeting on the biodistribution and efficacy of siRNA nanoparticles measured by multimodality in vivo imaging. Proc Natl Acad Sci U S A. 2007 Sep 25;104(39):15549–54. Epub 2007 Sep 17.

[103] Joyce GF. Amplification, mutation and selection of catalytic RNA. Gene. 1989 Oct 15;82(1):83–7.

[104] Jayasena SD. Aptamers: An emerging class of molecules that rival antibodies in diagnostics. Clin Chem. 1999 Sep;45(9):1628–50.

[105] Michel F, Ellington AD, Couture S, Szostak JW. Phylogenetic and genetic evidence for base-triples in the catalytic domain of group I introns. Nature. 1990 Oct 11;347(6293):578–80.

[106] Lupold SE, Hicke BJ, Lin Y, Coffey DS. Identification and characterization of nuclease-stabilized RNA molecules that bind human prostate cancer cells via the prostate-specific membrane antigen. Cancer Res. 2002 Jul 15;62(14):4029–33. Erratum in: Cancer Res. 2012 Aug 1;72(15):3887.

[107] Bagalkot V, Farokhzad OC, Langer R, Jon S. An aptamer-doxorubicin physical conjugate as a novel targeted drug-delivery platform. Angew Chem Int Ed Engl. 2006 Dec 11;45(48):8149–52.

[108] Brooks PC, Montgomery AM, Rosenfeld M, Reisfeld RA, Hu T, Klier G, Cheresh DA. Integrin alpha v beta 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. Cell. 1994 Dec 30;79(7):1157–64.

[109] Erdreich-Epstein A, Shimada H, Groshen S, Liu M, Metelitsa LS, Kim KS, Stins MF, Seeger RC, Durden DL. Integrins alpha(v)beta3 and alpha(v)beta5 are expressed by endothelium of high-risk neuroblastoma and their inhibition is associated with increased endogenous ceramide. Cancer Res. 2000 Feb 1;60(3):712–21.

[110] Yu MK, Park J, Jeong YY, Moon WK, Jon S. Integrin-targeting thermally cross-linked superparamagnetic iron oxide nanoparticles for combined cancer imaging and drug delivery. Nanotechnology. 2010 Oct 15;21(41):415102. doi: 10.1088/0957-4484/21/41/415102. Epub 2010 Sep 17.

[111] Meng S, Su B, Li W, Ding Y, Tang L, Zhou W, Song Y, Li H, Zhou C. Enhanced antitumor effect of novel dual-targeted paclitaxel liposomes. Nanotechnology. 2010 Oct 15;21(41):415103. doi: 10.1088/0957-4484/21/41/415103. Epub 2010 Sep 17.

[112] Yin J, Li Z, Yang T, Wang J, Zhang X, Zhang Q. Cyclic RGDyK conjugation facilitates intracellular drug delivery of polymeric micelles to integrin-overexpressing tumor cells and neovasculature. J Drug Target. 2011 Jan;19(1):25–36. doi: 10.3109/10611861003663531. Epub 2010 Mar 16.

[113] Bibby DC, Talmadge JE, Dalal MK, Kurz SG, Chytil KM, Barry SE, Shand DG, Steiert M. Pharmacokinetics and biodistribution of RGD-targeted doxorubicin-loaded nanoparticles in tumor-bearing mice. Int J Pharm. 2005 Apr 11;293(1–2):281–90.

[114] Cirillo G, Hampel S, Spizzirri UG, Parisi OI, Picci N, Iemma F. Carbon nanotubes hybrid hydrogels in drug delivery: A perspective review. Biomed Res Int. 2014;2014:825017. doi: 10.1155/2014/825017. Epub 2014 Jan 21.

[115] Sahoo SK, Parveen S, Panda JJ. The present and future of nanotechnology in human health care. Nanomedicine. 2007 Mar;3(1):20–31.

[116] Kim KY. Nanotechnology platforms and physiological challenges for cancertherapeutics. Nanomedicine. 2007 Jun;3(2):103–10. Epub 2007 Apr 17.

[117] Parveen S, Misra R, Sahoo SK. Nanoparticles: A boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine. 2012 Feb;8(2):147–66. doi:10.1016/j.nano.2011.05.016. Epub 2011 Jun 7.

[118] Chouhan R, Bajpai AK. Release dynamics of ciprofloxacin from swellable nanocarriers of poly(2-hydroxyethyl methacrylate): An in vitro study. Nanomedicine. 2010 Jun;6(3):453–62. doi: 10.1016/j.nano.2009.11.006. Epub 2010 Jan 4.

[119] Mishra B, Patel BB, Tiwari S. Colloidal nanocarriers: A review on formulation technology, types and applications toward targeted drug delivery. Nanomedicine. 2010 Feb;6(1):9–24. doi: 10.1016/j.nano.2009.04.008. Epub 2009 May 15.

[120] Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev. 2014 Feb;66:2–25. doi: 10.1016/j.addr.2013.11.009. Epub 2013 Nov 22.

[121] Liu Y, Miyoshi H, Nakamura M. Nanomedicine for drug delivery and imaging: A promising avenue for cancer therapy and diagnosis using targeted functional nanoparticles. Int J Cancer. 2007 Jun 15;120(12):2527–37.

[122] Mehra NK, Mishra V, Jain NK. A review of ligand tethered surface engineered carbon nanotubes. Biomaterials. 2014 Jan;35(4):1267–83. doi: 10.1016/j.biomaterials.2013.10.032. Epub 2013 Nov 7.

[123] Torchilin VP. Multifunctional nanocarriers. Adv Drug Deliv Rev. 2006 Dec 1;58(14):1532–55. Epub 2006 Sep 28.

[124] Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: Molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004 Jun;56(2):185–229.

[125] Verweij J, Clavel M, Chevalier B. Paclitaxel (Taxol) and docetaxel (Taxotere): Not simply two of a kind. Ann Oncol. 1994 Jul;5(6):495–505.

[126] Samorì C, Ali-Boucetta H, Sainz R, Guo C, Toma FM, Fabbro C, da Ros T, Prato M, Kostarelos K, Bianco A. Enhanced anticancer activity of multi-walled carbon nanotube-methotrexate conjugates using cleavable linkers. Chem Commun (Camb). 2010 Mar 7;46(9):1494–6. doi: 10.1039/b923560d. Epub 2009 Dec 23.

[127] Ren Y, Pastorin G. Incorporation of hexamethylmelamine inside capped carbon nanotubes. Advanced Materials. 2008;20(11):2031–2036.

[128] Aryal S, Hu CM, Zhang L. Combinatorial drug conjugation enables nanoparticle dual-drug delivery. Small. 2010 Jul 5;6(13):1442–8. doi: 10.1002/smll.201000631.

[129] Oberoi HS, Nukolova NV, Kabanov AV, Bronich TK. Nanocarriers for delivery of platinum anticancer drugs. Adv Drug Deliv Rev. 2013 Nov;65(13–14):1667–85. doi: 10.1016/j.addr.2013.09.014. Epub 2013 Oct 8.

[130] Agnihotri J, Saraf S, Khale A. Targeting: New potential carriers for targeted drug delivery system. International Journal of Pharmaceutical Sciences Review and Research. 2011;8(2):117–123.

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