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ADVANCED TARGETED DRUG DELIVERY SYSTEMS FOR CANCER THERAPY: FROM CONVENTIONAL APPROACHES TO PRECISION MEDICINE

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ABSTRACT

Cancer remains one of the major causes of morbidity and mortality worldwide, despite substantial advances in surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy. Conventional antineoplastic chemotherapy remains an important component of cancer treatment; however, its clinical utility is frequently limited by nonspecific distribution, systemic toxicity, poor pharmacokinetics, inadequate tumor accumulation, multidrug resistance, and tumor heterogeneity. Targeted drug delivery systems have emerged as an important strategy for improving the therapeutic index of anticancer agents by modifying drug distribution and facilitating preferential delivery to tumors or specific cellular and molecular targets. Early nanomedicine approaches primarily relied on passive tumor accumulation associated with the enhanced permeability and retention effect, whereas contemporary systems increasingly incorporate active ligand-mediated targeting, stimuli-responsive release, biomimetic carriers, and molecularly guided therapeutic strategies. Major platforms include liposomes, polymeric nanoparticles, polymeric micelles, lipid-based nanoparticles, dendrimers, antibody–drug conjugates, and biomimetic or extracellular-vesicle-based systems. These systems can improve drug solubility, stability, circulation time, cellular uptake, and controlled release while potentially reducing exposure of healthy tissues. Nevertheless, clinical translation remains challenging because of tumor heterogeneity, biological barriers, variable tumor accumulation, protein-corona formation, manufacturing complexity, scalability, toxicity, and regulatory requirements. Precision medicine provides an emerging framework in which molecular profiling, biomarkers, and patient-specific tumor characteristics can guide the selection and design of targeted delivery systems. This review discusses the evolution, principles, major platforms, targeting strategies, stimuli-responsive systems, clinical translation, limitations, and future prospects of targeted drug delivery for antineoplastic therapy, with particular emphasis on the transition from conventional chemotherapy toward precision nanomedicine.

KEYWORDS: Antineoplastic therapy, targeted drug delivery, cancer nanomedicine, nanoparticles, active targeting.

1. INTRODUCTION

Cancer is a heterogeneous group of diseases characterized by uncontrolled cellular proliferation, invasion of surrounding tissues, and, in many cases, metastatic dissemination. The biological diversity of tumors creates major challenges for effective treatment because tumors can differ considerably in their molecular characteristics, vascular architecture, immune environment, drug sensitivity, and mechanisms of resistance. Current cancer treatment commonly involves combinations of surgery, radiotherapy, chemotherapy, molecularly targeted therapy, hormonal therapy, and immunotherapy.

Chemotherapy remains an important component of treatment for numerous malignancies. However, most conventional cytotoxic drugs do not distinguish adequately between malignant and rapidly dividing normal cells. Consequently, treatment may produce adverse effects such as myelosuppression, gastrointestinal toxicity, alopecia, cardiotoxicity, nephrotoxicity, and neurotoxicity, depending on the therapeutic agent. Poor aqueous solubility, rapid metabolism, nonspecific biodistribution, inadequate tumor penetration, and development of drug resistance further restrict therapeutic effectiveness. These limitations have stimulated the development of drug-delivery approaches capable of improving drug localization and controlling drug release.

Nanomedicine has become an important component of this development. Nanocarriers can modify the physicochemical and pharmacokinetic characteristics of therapeutic molecules and can be engineered with specific sizes, surface properties, targeting ligands, and release mechanisms. Cancer nanomedicine has progressed from relatively simple formulations designed to alter drug pharmacokinetics toward increasingly sophisticated systems capable of responding to tumor-associated biological signals.[1]

An important conceptual transition has also occurred in the understanding of tumor targeting. Early approaches emphasized the enhanced permeability and retention (EPR) effect as the major mechanism for passive tumor accumulation. Current evidence indicates that tumor accumulation is highly heterogeneous and that active transport, vascular characteristics, stromal interactions, and tumor microenvironmental factors also influence nanoparticle delivery.[2]

The integration of targeted delivery with molecular profiling and precision oncology therefore represents an important future direction. Instead of assuming that one nanocarrier will work equally well in all patients, precision nanomedicine seeks to match carrier properties and therapeutic payloads with tumor-specific biological characteristics.

2. Limitations of Conventional Antineoplastic Therapy

2.1 Nonspecific drug distribution

Conventional chemotherapeutic agents are generally distributed throughout the body following systemic administration. Although tumor cells may be particularly susceptible because of their rapid proliferation, healthy tissues with high proliferative activity can also be affected. This limits the maximum dose that can be administered safely.

Targeted delivery attempts to modify this distribution by increasing drug exposure at the tumor site or by facilitating interaction with tumor-associated molecular targets.

2.2 Pharmacokinetic limitations

Many anticancer drugs have unfavorable pharmacokinetic characteristics, including short circulation half-life, rapid metabolism, poor aqueous solubility, or extensive nonspecific distribution. Formulation within a suitable delivery system can improve solubility, protect drugs from degradation, modify circulation time, and provide controlled release.

2.3 Tumor heterogeneity

Tumors are not biologically uniform. Different cells within the same tumor may express different receptors and biomarkers. Furthermore, expression patterns can change during disease progression or following treatment. This creates a major challenge for highly specific targeting strategies because a carrier directed against a single receptor may not reach all malignant cells.

2.4 Multidrug resistance

Resistance to chemotherapy may develop through multiple mechanisms, including increased drug efflux, altered drug metabolism, changes in apoptotic signaling, DNA repair, and modification of drug targets. Nanocarriers can potentially address some resistance mechanisms by improving intracellular drug delivery, facilitating co-delivery of multiple agents, or incorporating nucleic-acid therapeutics.

2.5 Tumor penetration

Reaching a tumor is not equivalent to reaching every malignant cell. Dense extracellular matrix, abnormal blood vessels, high interstitial pressure, hypoxia, and stromal components may restrict nanoparticle penetration. Therefore, modern targeted delivery requires consideration of tissue penetration in addition to tumor accumulation.

3. Evolution of Targeted Drug Delivery in Cancer Therapy

The development of targeted cancer delivery can broadly be viewed as a progression through several stages.

Conventional chemotherapy → passive targeting → active molecular targeting → stimuli-responsive delivery → biomimetic systems → precision nanomedicine.

The first major advance was the development of formulations capable of modifying the pharmacokinetics and toxicity of established drugs. Liposomal formulations provided an important example of this concept. Doxil, a PEGylated liposomal formulation of doxorubicin, became an important milestone in cancer nanomedicine following its approval in 1995.[3]

Passive targeting subsequently became strongly associated with the EPR effect, in which abnormal tumor vasculature and impaired lymphatic drainage can promote accumulation of appropriately sized nanoparticles. However, the magnitude and clinical relevance of the EPR effect vary substantially among tumors and patients. Recent work emphasizes that nanoparticle transport into and through tumors is more complex than a simple passive accumulation model.[4]

Active targeting introduced ligands such as antibodies, peptides, aptamers, or small molecules onto nanocarrier surfaces. These ligands can recognize receptors or antigens that are enriched on cancer cells. However, active targeting generally cannot compensate for inadequate delivery of the carrier to the tumor. Thus, successful active targeting requires both tumor access and appropriate molecular recognition.

The latest generation includes intelligent systems capable of responding to tumor-associated stimuli, such as acidic pH, enzymes, reactive oxygen species, redox conditions, hypoxia, temperature, or externally applied physical stimuli.[5]

4. Major Targeted Drug Delivery Systems

4.1 Liposomes

Liposomes are phospholipid-based spherical vesicular nanocarriers consisting of an aqueous core. Their amphiphilic architecture allows hydrophilic drugs to get incorporated within the aqueous compartment and hydrophobic agents into the lipid bilayer. By adjusting the lipid composition, particle size, surface characteristics and circulation properties, liposomes can change the pharmacokinetic profile and tissue distribution of conventional antineoplastic agents. Surface modification with polyethylene glycol (PEG) can also further prolong circulation, whereas incorporation of specific ligands enables tumour-cell recognition and receptor-mediated uptake.[6]

One major advantage of liposomal delivery is their ability to modify the therapeutic index of cytotoxic drugs by reducing nonspecific exposure as well as controlling drug distribution. Liposomes can accommodate chemically diverse therapeutic molecules and those surfaces can be engineered for ligand-mediated or stimuli-responsive delivery.[7]

Encapsulation can also improve drug stability and distribution while limiting the exposure of healthy tissues to the free drug. Various studies demonstrated considerable clinical translation, with formulations such as liposomal daunorubicin, pegylated liposomal doxorubicin, and liposomal daunorubicin/cytarabine providing clinically established examples of liposome-based cancer therapy. Despite of these advantages, liposomal systems have some limitations. Tumour accumulation is non-uniform and remains strongly influenced by heterogeneous vascular permeability. The tumour microenvironment even after prolonged circulation, does not necessarily ensure deep tumour penetration or efficient intracellular delivery. Active targeting can improve cellular specificity but introduces additional challenges related to receptor heterogeneity, ligand accessibility, long-term stability and manufacturing complexity.[8]

4.2 Polymeric nanoparticles

Polymeric nanoparticles are sub-micron carriers which are prepared from biodegradable polymers like poly-lactic-co-glycolic acid (PLGA), polylactic acid (PLA) and poly(ε-caprolactone) (PCL). Encapsulation of the drug can be done within the polymeric matrix or associated with its surface, followed by controlled release through polymer diffusion and degradation. Their size, composition and surface chemistry can be tailored to influence circulation, tumour accumulation and cellular uptake. Their main advantage is the ability to give sustained and gradual drug release while protecting the payload from premature degradation. Biodegradability, flexibility, high formulation and modifiable surface properties allow polymeric nanoparticles to accommodate conventional chemotherapeutics and other therapeutic molecules.[9]

Their performance solely depends on particle size, surface characteristics, polymer composition and drug-loading efficiency. Rapid clearance, limited penetration into solid tumours and variability in nanoparticle tumour interactions can restrict their therapeutic delivery. In addition to this, reproducible large-scale manufacturing and translation from promising preclinical results to clinical use remain important challenges. PLGA- and other polyester-based nanoparticles have been investigated for delivering doxorubicin, paclitaxel, cisplatin, 5-fluorouracil etc; other anticancer agents, with applications extending to combination treatment and gene therapy. Recent studies also show

explored surface-functionalized polymeric nanoparticles for receptor-directed delivery and improved tumour selectivity, supporting their potential role in precision antineoplastic therapy.[10]

4.3 Polymeric Micelles

Polymeric micelles are self-assembled structures which are formed from the amphiphilic block copolymers, surrounded by a hydrophilic shell with a hydrophobic core. The core gives a suitable environment for incorporating the poorly water-soluble anticancer drugs, while the hydrophilic shell helps to maintain the dispersion in the aqueous environment. Drug release occurs through diffusion, micelle destabilization or via degradation of the polymeric components.[11]

The main advantage of polymer micelles, is the ability to improve the apparent solubility and delivery of hydrophobic chemotherapeutic agents. Their tunable composition, small size and relatively simple surface modification permits the incorporation of controlled drug-release, stimuli-responsive or targeting features. Several polymeric micellar formulations have progressed to clinical evaluation by demonstrating their translational potential. The stability of micelles can decrease after dilution into the bloodstream, leading to premature/disassembly drug release.[12] Limited drug-loading capacity for some drug polymer combinations, variable tumour accumulation and difficulties in maintaining formulation stability during large-scale manufacture remain important barriers in clinical translation.[13]

Polymeric micelles have been explored extensively for anticancer drugs with poor aqueous solubility, mainly docetaxel, paclitaxel, camptothecin, its derivatives, and doxorubicin. Their hydrophobic core can improve drug solubilization and helps in maintaining the drug in a dispersed form, while the polymeric shell can be modified to regulate circulation and drug release. Paclitaxel-loaded micellar systems have progressed furthest toward clinical application,[14] with various formulations such as Genexol-PM in conventional chemotherapy. Beyond single-drug delivery, recent studies have explored polymeric micelles for co-delivery of chemotherapeutics and nucleic acids, aiming to address multidrug resistance and achieve complementary therapeutic effects. Micellar encapsulation is being used in camptothecin-based micelles to overcome the drug's poor aqueous solubility and improve its stability and tumour exposure. More recent formulations are targeting ligands or stimuli-responsive components to couple improved drug solubilization with selective release at the tumour site.[15] These developments position polymeric micelles as a bridge between conventional cytotoxic chemotherapy and more precisely engineered antineoplastic delivery systems.[16]

4.4 Lipid Nanoparticles

Lipid nanoparticles (LNPs) are nanoscale delivery systems made up from combinations of lipids that organize into structures that are capable of carrying therapeutic molecules. Depending on their composition, LNPs can encapsulate various hydrophobic drugs, hydrophilic molecules, proteins, small interfering RNA (siRNA), messenger RNA (mRNA), and other nucleic-acid-based therapeutics. After administration, the nanoparticles can circulate throughout the body, accumulate in the tumour tissue, and interact with cancer cells. Cellular uptake is followed by intracellular release of the therapeutic cargo, permitting the drug or genetic material to act at its intended site. Ionizable lipids are particularly important in modern LNP formulations because they can remain relatively neutral under any physiological conditions but become positively charged in acidic intracellular compartments, helping the nanoparticles to escape from the endosomes and release their cargo into the cytoplasm.[17]

Unlike conventional drug formulations, which are mainly designed to transport small-molecule chemotherapeutic agents, LNPs can be modified to carry much broader range of therapeutic payloads. This makes them particularly

relevant to precision oncology, where treatment may involve chemotherapy together along with gene silencing, gene replacement, immunomodulation, or even cancer vaccines. Their lipid composition can also be modified to influence stability, particle size, cellular uptake, circulation, biodistribution, and drug release. LNPs may therefore improve the therapeutic index of anticancer agents by increasing delivery to tumour tissue while reducing unnecessary exposure of healthy tissues. They are also biocompatibility and biodegradability. Even after this, their distribution after systemic administration is strongly influenced by its interactions in the bloodstream, and the physiological characteristics of individual patients. Tumour heterogeneity can also reduce the effectiveness of a single targeting strategy because of receptor expression, vascular permeability, and immune-cell composition may differ between tumours and regions of the same tumour. Other challenges include premature cargo leakage, limited penetration into dense tumour tissue, endosomal entrapment, inflammatory or immune responses, and difficulties in maintaining consistent formulation properties during large-scale manufacturing.[18]

LNPs have been studied for delivery of siRNA to silence genes involved in tumour growth or drug resistance, mRNA encoding tumour antigens or immune-stimulating proteins, and combinations of therapeutic agents designed to attack cancer through complementary mechanisms. By adjusting lipid composition, surface ligands, cargo type, release properties, and administration route, researchers can design LNPs for particular biological targets or therapeutic objectives. This approach fits closely with the transition from conventional chemotherapy toward precision medicine, in which treatment is increasingly selected according to tumour molecular characteristics and the specific vulnerabilities of cancer cells. But, achieving truly personalized LNP therapy will require better understanding of patient-to-patient differences in tumour biology, nanoparticle distribution, and treatment response, together with more reproducible manufacturing and clinically validated targeting strategies.[19] Advanced LNPs incorporate targeting ligands such as antibodies, peptides, aptamers, or other receptor-binding molecules on their surface can promote interaction with receptors that are overexpressed on particular cancer cells or tumour-associated cells, thereby increasing cellular uptake. LNP composition, surface chemistry, administration route, and biological barriers are increasingly being considered together to achieve more selective tissue and cellular drug deliver.[20]

4.5 Dendrimers

Dendrimers possess highly branched, three-dimensional macromolecules-nanoscale architecture composed of a central core, internal cavities and multiple surface functional groups. Their internal cavities can entrap anticancer drugs, physically within and accommodate therapeutic molecules, while the numerous surface groups permit drug conjugation and attachment of targeting ligands. Drug release can be controlled through cleavable linkers or stimuli-responsive interactions, allowing the carrier to be adapted for tumour-directed delivery or imaging moieties, providing a platform for multifunctional delivery.[21]

Their architectural design and multivalent surface provide considerable flexibility in drug loading and functionalization and also distinguish dendrimers from many other nanocarriers. Dendrimers can improve the aqueous solubility of poorly soluble drugs and facilitate co-delivery of different therapeutic agents. Thus, making them attractive for combination chemotherapy, imaging or gene-based therapy. The biological performance and toxicity of dendrimers is strongly depended on their generation, size and surface chemistry with cationic dendrimers being particularly at higher surface charge densities, may cause membrane-associated toxicity and nonspecific interactions. Complex synthesis, purification, characterization and limited clinical validation continue to restrict their translation despite extensive preclinical investigation.[22]

Dendrimer systems have been investigated as carriers for the delivery of doxorubicin, paclitaxel, methotrexate, cisplatin and other anticancer agents across breast, ovarian, lung, colorectal, pancreatic and brain cancers. Their multivalency has been exploited for co-delivery of various chemotherapeutic agents with siRNA or other genetic cargos, particularly where cytotoxicity and suppression of resistance-associated pathways are desirable. Recent studies have also explored dendrimers as platforms for photodynamic and photothermal therapy, imaging-guided treatment and combination chemo-gene therapy. PAMAM dendrimers have also been explored for tumour imaging and theragnostic applications, including systems combining chemotherapy with photodynamic or photothermal treatment.[23]

4.6 Exosomes and Biomimetic Systems

Exosomes are naturally occurring extracellular vesicles that transport proteins, lipids and nucleic acids between cells. Their biological membrane preserves therapeutic cargo and facilitates cellular interaction and uptake. Biomimetic systems reproduce these properties using cell membranes, exosome-derived components or synthetic structures, combining biological targeting characteristics with greater control over composition and drug loading.

Unlike conventional synthetic carriers, exosomes offer high biocompatibility, relatively low immunogenicity and intrinsic cellular communication properties. Their ability to carry diverse cargos, including chemotherapeutic drugs, nucleic acids, small-molecule drugs, siRNA, miRNA and proteins, makes them particularly attractive for multifunctional cancer therapy. Biomimetic and exosome-mimetic systems may additionally overcome some limitations of natural vesicles by providing better control over cargo loading, surface engineering, reproducibility and scalability. Their major obstacle is that natural exosomes composition varies with source-cell variability, heterogeneous composition, purification and characterization, inefficient or inconsistent cargo loading, complicate reproducible production. Their biological activity may also vary according to the cell source, and large-scale manufacturing with consistent quality also remains unresolved. Exosome-mimetic systems improve some of these limitations but require further validation of their safety, biodistribution and long-term biological effects.[24]

Exosomes have been explored as carriers for doxorubicin, paclitaxel and other chemotherapeutic drugs, as well as siRNA, miRNA and other nucleic-acid cargos designed to modify tumour-associated pathways and immune responses. Recent studies have explored engineered exosomes with modified surfaces or specific cargo-loading strategies to enhance tumour targeting and overcome multidrug resistance. In parallel, exosome-mimetic nanocarriers are being developed to combine biological functions such as immune evasion and tumour recognition with the manufacturing flexibility of synthetic nanoparticles. These systems hence represent an emerging link between biomimetic delivery and precision antineoplastic therapy, although clinical translation remains limited.[25]

Table 1: Targeted Applications of Major Nanocarrier Systems in Cancer Therapy.

Nanocarrier	Common targeting strategy	Therapeutic application	Key advantage in cancer therapy
Liposomes	Antibodies, peptides, folate or PEGylation	Targeted delivery of doxorubicin and other cytotoxic drugs	Reduces systemic toxicity and improves drug accumulation
Polymeric nanoparticles	Ligand-mediated or passive tumour targeting	Delivery of paclitaxel, docetaxel and nucleic acids	Controlled and sustained drug release
Polymeric micelles	Receptor-targeting ligands and tumour-responsive release	Delivery of poorly soluble anticancer drugs	Improves drug solubility and bioavailability

Lipid nanoparticles	Ionizable lipids and surface ligands	mRNA, siRNA and gene-based cancer therapies	Efficient intracellular nucleic-acid delivery
Dendrimers	Folate, antibodies, peptides or aptamers	Co-delivery of drugs and genetic material	High drug-loading capacity and multivalent targeting
Exosomes/biomimetic systems	Natural membrane proteins or engineered surface ligands	Delivery of drugs, miRNA, siRNA and proteins	High biocompatibility and potential tumour tropism

FIG 1: MAJOR TARGETED DRUG DELIVERY SYSTEMS IN ANTINEOPLASTIC THERAPY

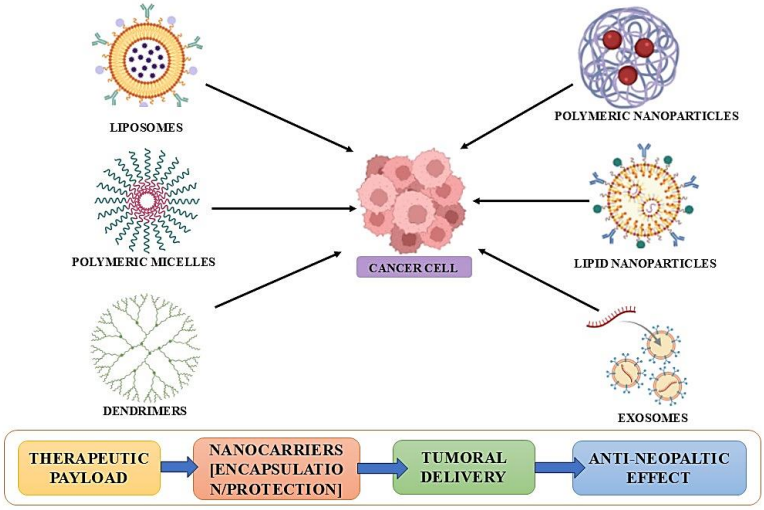


Table 2: Targeting strategies and precision medicine.

Barrier	Effect on drug delivery	Possible solution
Protein corona	Can hide targeting molecules	Surface modification
Immune clearance	Removes nanoparticles from blood	Improve nanoparticle stability
Poor tumour blood flow	Limits drug reaching the tumor	Optimize particle size
Dense tumour tissue	Reduces drug penetration	Use smaller or responsive nanoparticles
Tumour heterogeneity	Different cells have different targets	Use multiple targeting ligands
Endosomal trapping	Prevents drug from reaching its site of action	Add endosomal escape mechanisms
Tumour microenvironment	Can reduce drug release or activity	Use pH-, enzyme-, or redox-responsive systems
Drug resistance	Reduces treatment effectiveness	Co-deliver drugs or resistance-modulating agents

5. Targeting Strategies

5.1 Passive Targeting and the EPR Effect

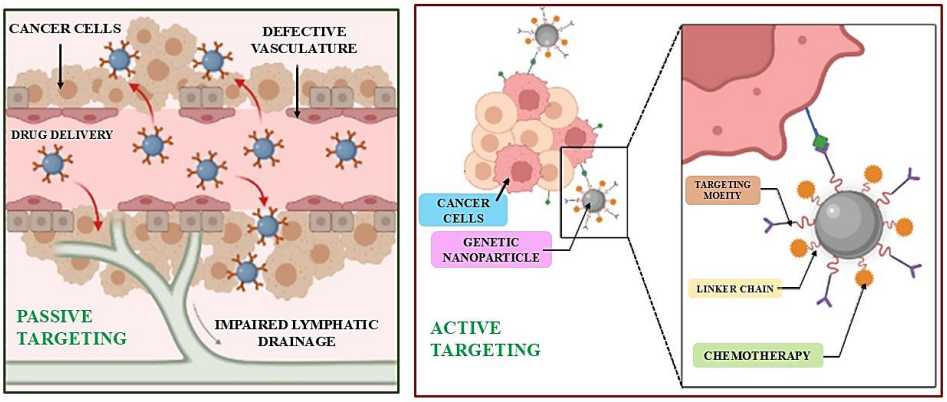
Passive targeting relies on the enhanced permeability and retention (EPR) effect, whereby nanoparticles preferentially accumulate in the solid tumours because of abnormal, permeable vasculature and inadequate lymphatic drainage system. This phenomenon gives an important basis for the development of nanocarrier-based chemotherapy, permitting drug-loaded systems to accumulate within the tumour tissue without requiring a specific molecular ligand. However, EPR is highly variable between tumour types and even in between individual lesions. Dense extracellular matrix, poor perfusion, elevated interstitial fluid pressure, and differences in vascular architecture can restrict nanoparticle penetration and retention time. Further evidences hence suggest that EPR alone is insufficient for consistent tumour targeting in patients. Its limitations have driven the development of active and biologically responsive targeting strategies aimed at achieving greater cellular specificity and more predictable drug delivery.[26]

5.2 Active Targeting

Active targeting involves decorating or manipulating the surface of a nanocarrier with a ligand that recognizes a receptor or antigen expressed preferentially on cancer cells or other components of the tumour microenvironment (target cells). Unlike passive accumulation, the purpose is not only simply to increase the amount of drug reaching to the tumour, but rather to promote selective cellular recognition and receptor-mediated uptake after the carrier reaches the tumour cells. Antibodies, peptides, aptamers and small molecules such as folate can serve as targeting ligands. Targets including HER2, EGFR, folate receptor and CD44 have therefore been explored for directing nanocarriers toward specific tumour populations.[27]

The approach can improve intracellular drug delivery and reduce reliance on the heterogeneous EPR effect, but its success depends on ligand accessibility, receptor expression, binding affinity and the biological fate of the carrier after binding. Tumour heterogeneity and receptor expression in some normal tissues can also limit specificity. Therefore, active targeting should be viewed as a strategy for enhancing the cellular selectivity rather than guaranteeing tumour-specific delivery.

FIG 2: TYPES OF TARGETING OF DIFFERENT DRUG DELIVERY SYSTEMS



5.3 Antibody Targeting

Monoclonal antibodies or antibody fragments used to target antigens that are overexpressed on cancer cells. After the carrier containing the required antibody binds its target, the complex can undergo receptor-mediated internalization, improving intracellular delivery of the therapeutic. An established example of binary targeting is HER2, where trastuzumab is used as a therapeutic antibody, and also as a targeting ligand for drug-loaded nanoparticles and other delivery systems. Recent research has also examined smaller antibody-derived formats, including nanobodies, to enhance tumour penetration while maintaining specificity for the target.[28]

The main strength of antibody targeting is its molecular specificity although size of antibodies, heterogeneous antigen expression and possible binding to normal tissues expressing the antigen may limit penetration and selectivity. Antibody-mediated delivery is especially relevant, when a well-characterized antigen linked to cells is available.

5.4 Peptide targeting

Peptides are attractive targeting ligands because of their small size, structural flexibility and ease of modification permit efficient functionalization of nanocarriers. EGFR and HER2 are important targets for peptide-functionalized nanocarriers because their overexpression in several tumour types can enhance selective nanoparticle binding and

receptor-mediated cellular uptake, providing more selective delivery of anticancer drugs or nucleic acids. Peptides specifically bind to EGFR GE11 and HER2 were being investigated for targeted delivery. The EGFR-binding peptide GE11 has been incorporated into nanocarriers for targeted delivery of anticancer drugs and nucleic acids, while HER2-binding peptides have similarly been explored to improve nanoparticle accumulation and internalization in HER2-positive cancer cells. While the CD44-binding A6 peptide has recently shown potential for improving tumour delivery of RNA therapeutics. But peptides are also susceptible to proteolysis, and binding affinities and receptor heterogeneity can preclude significance in therapeutics.[29]

5.5 Aptamer targeting

Aptamers are short single-stranded DNA or RNA molecules that fold into structures capable of recognizing specific tumour-associated targets with high affinity. Compared to antibodies, aptamers have the advantage of being more versatile and less immunogenic, making them better candidates for active targeting of drugs. Aptamers can be directly coupled to drugs or incorporated into nanocarriers to promote selective cellular uptake and intracellular delivery. EGFR-targeting aptamers can selectively recognize EGFR overexpressed on many cancer cells and promote receptor-mediated uptake of therapeutic cargo. They have been incorporated into aptamer-drug conjugates, nanoparticles, and nucleic-acid delivery systems to enhance tumour selectivity and reduce nonspecific toxicity. Similarly, HER2-directed aptamers can recognize the extracellular domain of HER2 and facilitate targeted delivery to HER2-positive cancer cells; recent work has identified short DNA aptamers with particularly strong HER2 binding. These approaches offer promising precision-delivery strategies, although stability, off-target effects, and translation from preclinical studies to clinical applications remain important challenges. Despite their potential, susceptibility to nuclease degradation, limited in vivo stability and off-target interactions remain important barriers to clinical translation.[30]

5.6 Receptor-mediated targeting

Receptor-mediated targeting shows receptors that are overexpressed on tumour cells to promote selective binding, internalization and intracellular drug release. HER2, EGFR, folate receptor and CD44 are among the most investigated targets, with ligands such as antibodies, peptides or folic acid incorporated into drug carriers to enhance receptor-specific uptake. The therapeutic benefit not only depends on receptor expression but also on internalization kinetics, receptor density and intracellular trafficking. Consequently, tumour heterogeneity and variable receptor expression can limit the effectiveness of this approach, highlighting the need for patient and tumour-specific target selection.[31]

Table 3: Targeting strategies in antineoplastic drug delivery.

Targeting Strategy	Core principle	Key strength	Principal constraint
Passive	Tumour accumulation via abnormal vasculature/EPR	Simple, carrier-driven accumulation	Highly heterogeneous EPR
Active	Ligand–target recognition	Improves cellular selectivity	Requires accessible target
Antibody	Antigen-specific binding	High affinity and specificity	Size, cost and immunogenicity
Peptide	Receptor/marker recognition	Small and readily engineered	Proteolytic instability
Aptamer	Structured nucleic-acid recognition	Programmable and versatile	Limited in vivo stability
Receptor-mediated	Binding followed by receptor internalization	Facilitates intracellular delivery	Variable receptor expression/trafficking

FIG 3: PRINCIPLE OF MOLECULAR TARGETED DRUG DELIVERY

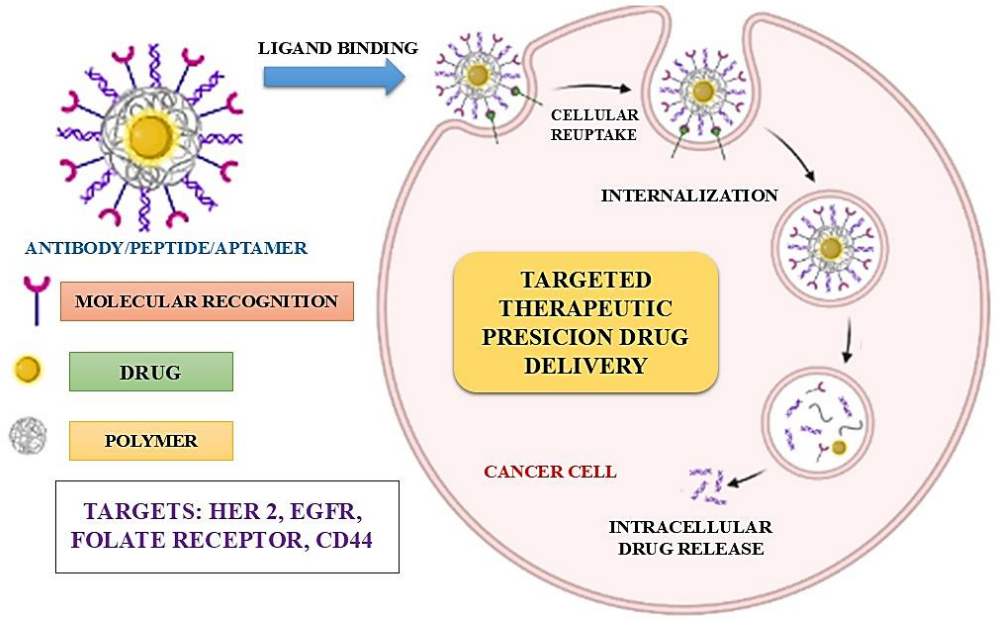


Table 4: Key molecular targets for precision antineoplastic delivery.

Target	Targeting rationale	Representative ligands
HER2	Overexpression in defined tumour subsets	Antibodies, peptides, aptamers
EGFR	Dysregulated signalling and surface expression	Antibodies, peptides, aptamers
Folate receptor	Preferential expression in several malignancies	Folic acid/folate ligands
CD44	Tumour progression and stem-cell-associated phenotypes	Hyaluronic acid, peptides

6. Stimuli-Responsive Systems

6.1 pH-Responsive Systems: Site-Specific Drug Release

pH-responsive drug delivery mechanisms are engineered to utilize of pH differences between normal tissues, diseased tissues and intracellular compartments for controlled drug release. Therapeutic agents can be loaded into nanoparticles, polymeric micelles, liposomes, hydrogels, dendrimers, mesoporous nanoparticles or metal-organic frameworks containing pH-sensitive polymers or acid-labile linkages such as hydrazone, acetal, ketal and imine bonds. The carrier is relatively stable at about pH 7.4 during systemic circulation, and thus, the premature drug leakage is minimal. Surface-charge conversion, polymer swelling, carrier disassembly or cleavage of acid-sensitive bonds can destabilise the system and trigger drug release when the carrier encounters an acidic target environment such as the extracellular tumour microenvironment protonation/deprotonation. Thus, the difference between physiological and pathological pH acts as an endogenous trigger for selective drug release at the target site.

After accumulation at the target tissue, pH-responsive nanocarriers can be internalised into the cells by endocytosis, from early endosomes to late endosomes and lysosomes, where the pH is progressively more acidic (around pH 4.5-6.5). This provides an additional trigger for destabilising the carrier, cleavage of acid-labile bonds and release of the drug. This approach can improve the local drug availability and potentially reduce the systemic toxicity; however, tumour pH heterogeneity, the relatively small pH difference between normal and tumour tissues, premature activation and biological barriers are still important challenges. The site specificity can be improved by combining pH responsiveness with active targeting ligands or other stimuli.[32]

6.2 Enzyme-Responsive Stimuli Systems

Enzyme-responsive delivery systems for drugs are intelligent drug carriers that release their payload upon encountering specific enzymes which are overexpressed at the diseased site. The carrier is equipped with enzyme-cleavable linkers, peptides, polymers or protective groups that are stable in the systemic circulation but degraded or cleaved by the target enzyme. For example, in tumours the activity of enzymes such as matrix metalloproteinases (MMPs), cathepsins, legumain, hyaluronidase, and phospholipases is often increased. These enzymes cleave the responsive component when the carrier reaches the target tissue, causing the carrier to degrade, the structure to destabilise, the surface to modify, or the drug–carrier bond to cleave, thus triggering drug release.

This mechanism allows for site-specific and controlled drug delivery, as enzyme activity is different in diseased versus healthy tissues. For example, cleavage of MMP-sensitive nanocarriers can occur in the tumour microenvironment while the drug release from cathepsin-sensitive systems can happen after the cellular internalisation into lysosomes. Thus, enzyme-responsive systems can enhance drug accumulation at the target site, avoid premature drug release and systemic toxicity, and improve therapeutic efficacy. The basic sequence is drug loaded carrier, circulation, accumulation at diseased tissue, recognition by overexpressed enzyme, cleavage/degradation of responsive component, drug release at target site.

6.3 Redox/ROS-Responsive Stimuli Systems

Redox/ROS-responsive drug delivery systems rely on the discrepancy in the redox state between healthy and diseased tissue or between extracellular and intracellular milieu for the purpose of specific drug release. Diseased cells, especially cancer cells, exhibit an increased production of ROS, including H_2O_2, superoxide and hydroxyl radicals. The intracellular environment is enriched with reducing agents, like GSH. Accordingly, the drug carriers are provided with redox/ROS-sensitive functional groups including disulfide, Di selenide, thioketal, thioether, and aryl boronated moieties. These groups are rather stable until the arrival at the target site where oxidation or reduction occurs leading to degradation of the carrier, structure dissociation, or cleavage of the drug-carrier conjugate.[33]

Therefore, once the drug reaches the target tissue or the target cell, the oxidative stress and reducing environment become the biological stimulus, resulting in the disruption of the responsive linkage and conversion of the carrier to hydrophilic from hydrophobic, thus triggering drug release. This ensures targeted drug delivery, prevents premature release of the drug, and increases its concentration at the target location.[34]

6.4 Hypoxia-Responsive Stimuli Systems

Drug delivery systems based on hypoxia respond to the low oxygen (hypoxia) condition found in many solid cancers for the purpose of releasing drugs specifically at the desired site. As rapidly dividing cancer cells have defective vasculature and high oxygen demands, their oxygen levels are relatively low when compared with healthy cells. The drug delivery system is constructed using hypoxia-sensitive molecules like nitroimidazole, nitrobenzene, quinone, N-oxide, and azobenzene linkers. These molecules are relatively stable in normal oxygen conditions but react in hypoxic conditions to cause breakage of chemical bonds or structural alteration in the drug carrier.

Once the carrier is loaded into the tumour and exposed to a low oxygen environment, hypoxia-inducing reduction leads to activation of the carrier/prodrug, leading to its structural dissociation and cleavage of the drug-carrier bond and

finally release of the drug. Similarly, hypoxia-activated prodrugs can remain in an inactive state while in the bloodstream but become cytotoxic once they undergo enzymatic reduction due to low oxygen.

6.5 Light/Temperature-Responsive Stimuli Systems

In light and temperature responsive drug delivery systems, external physical stimulus is applied to trigger drug release. Light responsive systems employ drug carriers containing photosensitive molecules or photothermal components that are triggered by ultraviolet, visible, and preferably near infrared light. Light leads to photo cleavage, photoisomerization or destruction of the carrier causing drug release. Near infrared light is preferred due to high tissue penetration and local activation. Photothermal systems include photothermal components such as gold nanoparticles, whose function is to transform light energy into heat energy, thus leading to destabilization of the nanocarrier or phase change of the carrier and hence releasing the drug.

Temperature-dependent systems operate in such a way that they are stable at body temperature, but undergo certain physical changes at high temperatures, usually around 40-42°C, in heated tumour tissues. Temperature-sensitive polymers like PNIPAM and thermally sensitive liposomes are able to undergo a solubility change, swelling, phase transition, or membrane permeability alteration, resulting in drug delivery. Hence, the complete process involves a drug-loaded carrier, which targets tumour tissue, is then exposed to light or heat, causing the physical change to take place and enabling drug delivery.[35]

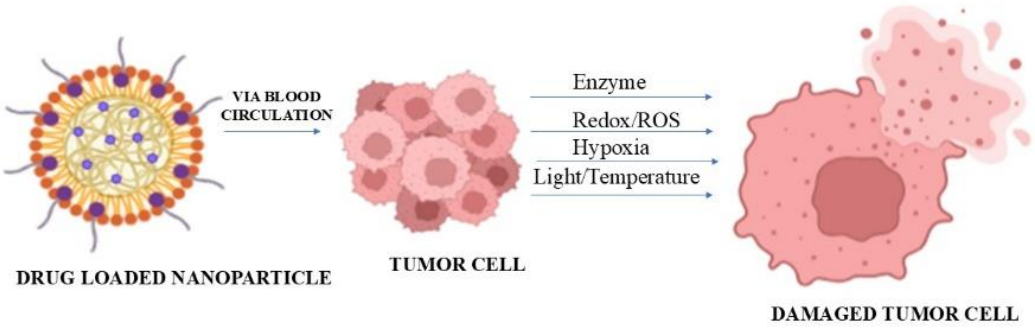


Fig. 4: Stimuli-Responsive Drug Delivery - Site-Specific Drug Release.

7 Multidrug Resistance

7.1 P-glycoprotein

Multi-drug resistance (MDR) is one of the main reasons for chemotherapy failure in cancer, where tumour cells become resistant to more than one structurally unrelated anticancer drugs. One of the common mechanisms is the upregulation of P-glycoprotein, or MDR1/ABCB1, which is an ATP-binding cassette (ABC) transporter localized in the cell membrane. It uses energy derived from the ATP hydrolysis to expel different anticancer drugs from cancer cells, thus decreasing the number of drugs inside the cells and hence their cytotoxic effects.[36]

The efflux activity mediated by P-gap can cause resistance to different drugs, such as anthracyclines, taxanes, and vinca alkaloids, where cancer cells can survive even under drug treatment. The ways to overcome the P-gap-mediated MDR include inhibitors of P-group, ABCB1 expression inhibition, RNA interference, and the nanocarrier-mediated drug delivery system that allows to circumvent the efflux pathways. Despite the good results of many P-group inhibitors in experiments, their use in the clinic is limited due to toxicity and pharmacokinetic interactions.

7.2 Multidrug Resistance - Drug Efflux

One of the most critical methods involved in causing MDR in cancerous cells is drug efflux. Here, ABC transporters embedded in the membrane act by actively extruding anticancer drugs from inside the cells, thereby decreasing their intracellular level and cytotoxicity. Prominent efflux transporters are P-glycoprotein multidrug resistance-associated proteins and breast cancer resistance protein. All these transporters utilize ATP hydrolysis in the active removal of diverse types of drugs from cancer cells.

In case there is an up-regulation of any of these efflux transporters, the intracellular level of the drugs decreases, leading to treatment failure. Anthracyclines, taxanes, vinca alkaloids and many other anticancer drugs are affected. Some of the approaches used to overcome MDR caused by the efflux pump method include efflux pump inhibitors, nanocarrier based delivery of drugs, RNA interference and drugs that are not recognized by the transporters. However, clinical application of the efflux inhibitors is difficult due to toxicities and drug interactions.[37]

7.3 Multidrug Resistance - Tumour Heterogeneity

Tumour heterogeneity is defined as the existence of genetically, epigenetically, and phenotypically diverse populations of cancer cells within one tumour. The cancer subpopulations may vary in their sensitivity to anticancer drugs. Spatial heterogeneity happens when different subpopulations of cancer cells exist in different parts of one tumour, while temporal heterogeneity arises due to the evolution of tumour cells during the course of the disease. Tumour heterogeneity complicates the ability of an anticancer drug to remove all tumour cells.

The mechanism of multidrug resistance in cancer patients can be explained by the fact that chemotherapy kills sensitive cancer cells but allows pre-existing resistant clones to continue living and dividing. In addition, genetic alterations, epigenetic changes, cancer stem-cell characteristics, and tumour microenvironment features such as hypoxia and lack of nutrients also contribute to drug resistance. As a result, surviving resistant subpopulations of cells can lead to tumour relapse.[38]

7.4 Multidrug Resistance - Co-delivery of Anticancer Drugs

Co-delivery of anticancer drugs is an effective approach to MDR that consists of simultaneous delivery of two or several drugs into cancer cells. Nanocarriers like liposomes, polymeric nanoparticles, micelles and dendrimers allow co-loading of two or several drugs and the delivery of drugs in a defined ratio. Combination therapy that uses drugs with different mechanisms of action can help to obtain synergy and target several mechanisms of resistance; this makes it less likely that there will be resistant cells left after the treatment.

The other possibility is a combination of an anticancer drug with a resistance modifier such as the inhibitor of P-glycoprotein or siRNA against the resistance-related genes. Such a combination can result in decreasing drug efflux, increasing intracellular concentration of the drug, and restoring sensitivity of resistant tumour cells to chemotherapy.[39]

7.5 Multidrug Resistance - Co-delivery of Drug + siRNA/miRNA

Delivery of both an anticancer drug and an siRNA/miRNA into a tumour cell is an effective strategy of nanomedicine that can be used for overcoming MDR. An anticancer drug generates the cytotoxic action, whereas the siRNA/miRNA acts on the expression of genes associated with the drug resistance, like ABCB1/P-gap, MRP1 or BCL-2. Various

nanocarriers like liposomes, polymeric nanoparticles, micelles and dendrimers deliver both compounds to a tumour cell.

The approach may help to restore the sensitivity of a tumour to chemotherapy by inhibiting drug efflux pumps or apoptosis inhibitors as well as delivering the drug to the tumour cell. For instance, the co-delivery of doxorubicin with siRNA directed against MRP1 and BCL-2 enhances the intracellular drug concentration and inhibits resistance in MDR cancer cells. Similar results may be obtained using miRNA co-delivery.[40]

8. Precision Medicine -Cancer Biomarkers

Biomarkers of cancer refer to measurable biological markers that indicate the biological features of a patient's tumour, such as gene mutations, protein biomarkers, patterns of gene expression, and ctDNA. They assist in defining the molecular profile of cancer to aid in the personalization of therapy in precision medicine. For instance, biomarkers, like EGFR mutations, HER2 amplification, BRAF mutations, ALK rearrangements, and PD-L1 expression, can be used to determine if the cancer patient can benefit from certain targeted and immunotherapies. Biomarkers may also be used for diagnosis, prognosis, therapy evaluation, and monitoring the emergence of drug resistance.

8.1 Precision Medicine - Genomic/Molecular Profiling

The genomics or molecular profiling test is one of the major parts of precision medicine that involves the use of advanced technology like NGS, gene expression analysis, and multi-omics profiling for the study of genetic and molecular features of a patient's tumour. Molecular alterations such as mutations, gene fusions, copy number alteration, and other molecular abnormalities are discovered that can help in determining a specific therapy or immunotherapy for the patient based on his/her tumour. The treatment can be selected depending on the molecular profile of a particular tumour, instead of the tumour type or histology.[41]

8.2 Precision Medicine - Patient Stratification

Stratification of patients is an essential aspect of precision medicine, whereby patients are categorized into different clinically-relevant sub-groups on the basis of certain genetic, molecular, biomarker, or clinical features. Stratification in oncology is useful in determining the patients who are most likely to respond to a specific targeted or immune-based therapy and to avoid therapies that will not be effective. Thus, stratification through molecular characterization and biomarkers may assist in personalized therapy and predicting the outcomes of treatment.[42]

8.3 Precision Medicine - Target Selection

Target identification is another key process in precision medicine, whereby certain targets that facilitate tumour growth, survival, and drug resistance are identified and selected for treatment through an appropriate therapeutic agent. Biomarker-driven therapies have been used to detect certain actionable changes such as mutations in the EGFR gene, HER2 gene amplification, rearrangements in the ALK gene, and mutations in the BRAF gene, thereby facilitating the selection of treatments that would affect the pathway involved.[43]

8.4 Precision Medicine - Personalized Drug Delivery

Personalized drug delivery can be considered as a new concept in precision medicine where the drug itself, its dosage, mode of delivery, and drug carrier systems are formulated based on the characteristics of the tumour of the individual patient. New drug delivery carriers like targeted nanoparticles, liposomes, and responsive nanocarriers can increase

drug concentration in the tumour tissue, have controlled release, and minimize exposure to normal tissue. The combination of genomic information of the patient with the drug delivery can make this system personalized.[44]

CONCLUSION

Targeted drug delivery has transformed the conceptual framework of antineoplastic therapy from nonspecific systemic exposure toward more controlled and selective therapeutic delivery. Conventional chemotherapy remains clinically important but is limited by systemic toxicity, unfavorable pharmacokinetics, tumor heterogeneity, inadequate tumor penetration, and drug resistance. Nanocarriers such as liposomes, polymeric nanoparticles, micelles, lipid nanoparticles, dendrimers, and biomimetic systems can modify drug distribution and provide opportunities for controlled and targeted delivery.

The field has progressed from passive tumor accumulation toward active molecular targeting and stimuli-responsive systems. Nevertheless, targeting remains biologically complex, and the variable nature of tumor accumulation means that successful laboratory results cannot automatically be translated into clinical benefit. Clinically established liposomal formulations demonstrate the feasibility of nanomedicine, while newer platforms continue to address more sophisticated therapeutic objectives.

The future of targeted antineoplastic delivery is likely to depend on the integration of nanotechnology with molecular profiling, biomarkers, tumor-microenvironment characterization, immunotherapy, nucleic-acid therapeutics, theranostics, and artificial intelligence. Precision medicine may ultimately enable the selection or design of delivery systems according to the biological characteristics of individual tumors. Such an approach could move cancer nanomedicine beyond the concept of a universal nanocarrier toward patient-specific, biomarker-guided and biologically responsive therapy.

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