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Recent Progress in Targeted Drug Delivery Systems for Cancer Treatment

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ABSTRACT

Traditional cancer therapies are often limited by nonspecific distribution, leading to systemic toxicity and poor therapeutic outcomes. Targeted drug delivery systems aim to overcome these limitations by directing therapeutic agents specifically to tumor tissues, minimizing off-target effects. Recent advances have introduced sophisticated platforms, including nanoparticles, liposomes, dendrimers, micelles, and antibody-drug conjugates (ADCs). This review explores the design principles of these delivery systems, their mechanisms of targeting (passive via the enhanced permeability and retention effect and active via ligand-receptor interactions), and their clinical applications. Challenges such as drug resistance, immunogenicity, and tumor heterogeneity are also discussed. Future directions include stimuli-responsive systems, personalized nanomedicine, and combination therapies integrating immunotherapy and targeted delivery.

Keywords: Drug delivery systems, nanoparticles, targeted therapy, cancer treatment, pharmacology.

1. Introduction

Cancer is a group of diseases characterized by unintended cellular proliferation and spread, leading to invasion of normal tissues and affecting the normal functioning of the affected organs. There is an urgent need for improving current treatment strategies [1].

Currently, surgery, radiation therapy (RT), and chemotherapy are the principal treatment strategies against cancer. Surgery is usually recommended for patients at an early stage of the disease, and it is most effective when all cancer cells can be excised. When surgery is no longer an option and/or to improve the outcome of surgery, systemic therapies such as chemotherapy, hormone therapy, and immunotherapy are used. Of these, chemotherapy and RT are the most widely used interventions for the treatment of cancer. Chemotherapy is the use of cytotoxic anticancer drugs which predominantly act by killing the cells which are actively metabolically targeting rapid cell division and growth (i.e., metabolically active cells). Chemotherapy improves the patient's quality of life or prolongs that of the suffering patient but is

frequently associated with severe side effects related to systemic toxicity [2].

Mucositis would be a common adverse effect of RT and chemotherapy chemotherapeutic agents being systemically delivered. This side effect is characterized by increased inflammatory cytokine production, leading to damage of rapidly dividing epithelial cells in normal oral mucosa and/or the digestive tract. Severe mucositis can lead to ulceration, digestive problems, and infection and ultimately treatment avoidance or discontinuation. Moreover, one of the leading causes of treatment failure in cancer therapy is the phenomenon of multidrug resistance syndrome (MDRS) [3]. MDRS is characterized by the ability of the cancer cells to efflux drugs, thereby reducing their therapeutic effect. In the last decade, a diverse range of new drug delivery systems (DDS) has been developed to improve cancer therapies [4]. There are two main types: targeted (or active) DDS and non-targeted (or passive) drug delivery systems endowed with nanometer scale to enable efficient transport in blood vessels and to reach pathological cells.

2. Overview of Cancer Treatment

The American Cancer Society projects that over 1 700 000 new cancer cases and over 160 000 cancer-related deaths will occur in the U. S. in 2019 [3]. Fortunately, the understanding of what cancer is and how it grows has significantly improved over the last fifty years; nevertheless, it is a poorly understood disease that has complicated these events. Tumors originally arise from a single cell, and cancer cells, unlike normal cells, acquire mutations in growth factors, transcription factors, and drug-resistance genes, allowing them to grow uncontrollably. These transformed cells can evade the mechanisms that maintain homeostasis and that prevent normal cells from becoming immortal. Ultimately, all tumors contain a genetically heterogeneous population of cells, including cancer stem cells (CSCs) with the ability to self-renew (stem-like), generate differentiated progeny, and spread to distant organs - metastatic potential. Currently, the strategies used to treat cancer are based on surgery, radiation therapy, and chemotherapy [4].

Surgery is the most effective treatment option when tumors are solid and accessible. Debulking surgery is generally performed following adjuvant chemotherapy, RT, or both to improve quality of life in later-stage cancer. Localized delivery of the chemotherapeutic through bioresorbable implants is being investigated to overcome systemic side effects. RT alone or combined with other treatments is used in 50-70% of tumors. It generates genomic instability through free radicals that produce a chain reaction affecting not only the surrounding tissue but also normal cells. Hybrid nanomaterials entrapping or conjugating drugs, radiosensitizers, and imaging agents are also researched to achieve synergetic effects, reducing the administered dose and minimizing collateral effects.

Chemotherapy, using small-molecule drugs which target DNA, DNA-associated proteins, or soluble factors, is widely used to treat cancer; however, it frequently fails to totally eradicate the disease. One principal cause of treatment failure is the existence of MDRS, a mechanism by which the efficacy of chemotherapy is significantly reduced. Generally, cancer cells obtain drug resistance mainly using ATP-dependent pumps that lower intracellular drug levels, disabling its cytotoxic effect. In the past decades, a wide range of DDSs have been designed to improve tumor therapies. Non-targeted systems consist of drugs that are conjugated to or encapsulated in systems ranging from small polymers to inorganic nanoparticles. The system accumulation at pathological sites can be achieved through the EPR effect, where pores are poorly affected by the high interstitial fluid pressure, high circulating blood volume, and low rate of lymphatic drainage. A Fitzhugh-Nagumo model was developed to predict the spatiotemporal profiles of drug concentration in a tumor and is being further extended to investigate the changes in microenvironment that arise from the treatment. More sophisticated systems were designed to simultaneously release large drug varieties at the optimum dose [5].

2.1. Traditional Methods of Treatment

Cancer is one of the deadliest diseases threatening human lives. It is a group of diseases characterized by uncontrolled cell growth. The tumor originated from one cell in which the internal regulatory mechanism was lost, resulting in continual reproduction. The rapid proliferation of tumor cells requires more nutrients and energy than normal cells, resulting in fast blood vessel formation or tumor angiogenesis, which are necessary for tumor growth. The vascular system forms an entry point for metastases to disseminate to different tissues. At present, surgery, radiation therapy (RT) and chemotherapy are the principal treatment strategies against cancer [3].

Surgery is usually recommended at an early stage of the disease and is most effective when all the cancer cells can be excised. Chemotherapy and RT are the most widely used interventions for the treatment of cancer. Chemotherapy primarily kills metabolically active cells. Normal cells do not divide as often as cancer cells and thus are proportionately less affected by these cytotoxic drugs. The bone marrow, hair follicles, and lining of the gastrointestinal tract are the usual collateral effects of chemotherapy. Chemotherapy and RT are employed to improve the patient's quality of life or to prolong it, but they are frequently associated with severe side-effects. Such side effects, among others, will limit the dosage and preclude the administration of high doses of more potent chemotherapeutic agents (6).

Clinically relevant damage from chemotherapy is dependent on the type of drugs and generally affects highly proliferative tissues. Rapidly dividing cells, such as bone marrow myeloid cells and gut crypts, are severely affected. Bones would stop producing white blood cells, resulting in an increased risk of infection. Chemo or radiotherapy may result in alopecia because both the hair follicle stem cells and their transit amplifying progenitors are highly proliferative. Mucositis may limit the patient's ability to tolerate chemotherapy or RT. On the other hand, RT. Similar to chemotherapy, RT also damages healthy cells, organs, and tissues. Mucositis may limit the patient's ability to tolerate chemotherapy or RT. One of the leading causes of treatment failure in cancer therapy is the phenomenon of multidrug resistance syndrome (MDRS), typically acquired during prolonged exposure to chemotherapy. MDRS is characterized by the ability of cancer cells to efflux drugs, which results in reducing the therapeutic effect. Recent studies have shown that the expression of ATP-binding cassette transporters, coupled with ATP hydrolysis, was responsible for the phenomenon of MDRS. The efflux of drugs from cells reduces the intracellular concentration of therapeutic drugs below their efficacy thresholds after prolonged treatment, thus conferring MDRS.

2.2. Emerging Therapies

Chemotherapy, which involves the use of cytotoxic agents, is a common therapeutic approach employed in cancer treatment. Conventional chemotherapy is characterized by the use of clinically available low molecular weight drugs, whose basic premise is to kill metabolically active and highly proliferating pathological cells such as many types of cancer. However, the clinical efficacy of chemotherapy is often hampered by the emergence of adverse side effects and multidrug resistance (MDR) [4]. On account of that, the discovery and development of novel therapeutic alternatives with non-cross resistance to existing agents have become an important avenue for cancer research.

The concerns over systemic toxicity and poor anticancer efficacy of treatment have spawned tremendous interest in the development of targeted therapeutic strategies. Such approaches take advantage of the distinctive physicochemical properties as well as biological characteristics of abnormal tissues such as tumor cells, allowing for selective targeting of these sites while minimizing side effects on normal tissues 1. Multifaceted pharmaceutical agents have been explored as targeted antineoplastic drugs, ranging from small-molecule compounds to biopharmaceutical macromolecules, siRNA, and gene drugs. While chemical agents are still the workhorse for chemotherapy, the recent breakthroughs in the mechanistic understanding of tumorigenesis processes and cellular signaling pathways offer new

therapeutic opportunities for the development of targeted agents. Among these, protein therapeutics (antibodies, enzymes, etc.), gene drugs (RNA, DNA), and small interfering RNA (siRNA) have the most striking advances. These biological agents can effectively inhibit tumor growth since they selectively target cancer-related molecules.

Nevertheless, translating potential targeted agents into effective clinical medicines has posed significant challenges due, in no small part, to their poor bioavailability upon systemic administration. Firstly, such macromolecular agents are subjected to unfavorable pharmacokinetic profiles in biological circulation, characterized by a rapid clearance and a low level of bioavailability.

3. Principles of Targeted Drug Delivery

Active targeting refers to the use of drug carriers modified with certain ligands, antibodies, or peptides, which can specifically bind to certain moieties or receptors at the target site. Active targeting can significantly improve the accumulation of drugs at the tumor site(4). There are two approaches for active targeting: chemical conjugation modification and physical encapsulation modification. Chemical modification involves covalently modifying ligands onto the surface of drug carriers or drug loading systems. The modification can have a hierarchical structure with the targeting fraction on the outermost layer and the drug encapsulation fraction inside.

Owing to this hierarchical structure, the chemical properties and targeting ability of the drug carrier or drug loading system can be optimized, while toxic or potent agents can be encapsulated in situ. Physical encapsulation involves wrapping the target ligands onto the surface of nanocarriers via electrostatic, hydrogen, hydrophobic, or van der Waals interactions.

Targeted drug delivery can be regarded as a promising therapeutic strategy for personalized therapy due to its low drug dosage, high efficacy, and few side effects. Targeted drug delivery can achieve desired therapeutic effects by increasing drug accumulation. Drug delivery, which is to transport drugs to specific target sites, can be composed of a drug carrier and a targeting moiety.

The targeting moiety is used to actively target a diseased site by specifically binding with receptors, moieties, or proteins over-expressed or uniquely expressed at the target site, of which the over-targeted molecules or proteins can be regarded as “targeting fractions,” while downstream conditioning on drug carriers or other molecules containing a targeting fraction are called “targeting drug delivery systems.” Targeting drug delivery systems can be composed of passively or actively targeting drug carriers. Passive targeting refers to the mechanism that drug delivery systems accumulate in target tissues due to their size or solubility.

The surface modification of drug carriers can increase drug pro/anti-cancer potency via altering the pharmacokinetics and tissue distribution of the carriers, or can enhance the intracellular uptake of drugs after a release from the carriers. Lesions, such as tumors, are generally characterized by abnormal vasculature and a low lymphatic clearance. The enhanced permeability and retention effect is due to the intrinsic irregularities of tumor blood vessels, through which nano-scaled drug carriers can extravasate into up-follicular tissues. Furthermore, with the fast growth of tumors, high vessel permeability without supporting lymphatic vessels may be formed, which can lead to a faster accumulation of drug carriers in tumors. Targeting drug delivery can significantly improve the drugs' therapeutic effects and reduce their side effects by selectively delivering drugs to tumor sites.

3.1. Mechanisms of Action

Targeted drug delivery systems can enhance the accumulation of drugs in tumor tissues, thereby reducing drugs' distribution in normal tissues. The targeting mechanism of these delivery systems depends on their design, modifications, and several biological factors associated with the target site. Three

different targeting mechanisms aim to deliver drugs to the desired sites and release them there: passive targeting, active targeting, and triggered drug release [4]. Passive targeting mechanisms mainly utilize the EPR effect for the accumulation of nanocarriers in solid tumors.

Active targeting mechanisms are based on the specific recognition between modified nanocarriers and target biomolecules. Triggered drug release mechanisms can enhance the release of drugs from the delivery vehicles at the targeted site in response to external stimulation, such as temperature, pH, and light.

Targeted drug delivery systems can realize personalized therapy because of their low drug dosage, high efficacy, and few side effects. Targeted drug delivery can selectively deliver chemotherapeutics to tumor lesions, leading to significantly improved drug efficacy and reduced side effects. In targeted therapy, small molecules or antibodies can be employed to block the activity of specific proteins controlling the growth, migration, and recurrence of tumors, thereby inhibiting malignant phenotypes. Targeted nanocarriers can effectively improve the bioavailability and efficacy of drugs via various targeting mechanisms. For example, nanocarriers can change the pharmacokinetics and tissue distribution of drugs and enhance the intracellular uptake of drugs.

Nanocarrier-based targeted drug delivery can enhance drug accumulation in tumor tissue and reduce drug distribution in normal tissue. Targeted drug delivery systems can accomplish selective drug delivery combined with drug release mechanisms, which means that at the targeted site, the 'active fraction' can realize drug release from the carrier and that the 'targeting fraction' can bind with certain moieties or receptors at the target site. Nanocarrier-based targeted drug delivery can realize selective delivery of drugs to the target sites. It can also enhance drug efficacy and selectivity. The cancerous state selectively activates an auxiliary mechanism of toxicant action on cancer cells in the presence of the targeting agent delivery vehicle. Systemic delivery of the targeting drug can significantly improve the therapeutic effects of the drug.

3.2. Advantages Over Conventional Methods

Conventional drug treatment has shown therapeutic effects in the clinical treatment of cancer patients. However, cancer treatment with chemotherapeutics often suffers from low drug bioavailability and inevitable side effects. Moreover, most of the traditional anticancer drugs are hydrophilic, foamy, and unstable, and conventional oral formulations exhibit poor drug solubility and low and variable bioavailability.

Furthermore, most anticancer drugs are nonspecific and have intense side effects on normal cells, such as loss of appetite, nausea, vomiting, myelosuppression, etc. So the on-going promise of drug delivery in cancer treatment should focus on selective delivery of the drug to tumor sites. Based on specificities of chemical properties or biological targets of the target cells, it is feasible to selectively deliver a cytotoxic to tumor sites and thereby improve tumor control efficacy.

Targeted drug delivery systems are typically classified into two categories, which are based on subtle differences in the chemical moieties of the targeting fraction. The first and mostly used approach is passive drug targeting, which is based on the abnormal pathological characteristics of the tumor, such as the enhanced permeability and retention (EPR) effect.

Based on the EPR effect, polymeric nanoparticles, liposomes, dendrimers and micelles have been developed to enhance the bioavailability of hydrophobic anticancer agents. The second approach is active drug targeting, which is based on the specific biological features of tumor cells and their microenvironment, such as over-expression of specific receptors. Targeting ligands, e.g. monoclonal antibodies, peptides, small organic molecules and aptamers, which can specifically bind with certain moieties or receptors at the target site, are linked with drug carriers to enhance targeting efficacy. In the

past decade, thanks to burgeoning teaching strategies and drug delivery vehicles, target drug delivery (TDD) approaches have been explored to improve the therapeutic performance of chemotherapeutics. By selectively delivering drugs to cancer cells, these delivery systems, compared with conventional therapeutic methods, can to a great extent enhance the efficacy, reduce side effects, switch drug resistance, and implement personalized therapy and comboradiotherapy [4].

4. Types of Targeted Drug Delivery Systems

The normal tissues and cancer tissues differ in biological conditions such as pH, temperature, and tissue structures, providing the basis of drug delivery strategies. Drug delivery strategy can be classified into passive targeting and active targeting. Passive targeting is the earliest and most broadly used targeted drug delivery strategy.

This targeting strategy mainly relies **on the leaky structure of tumor vasculature and the dysregulated lymphatic drainage,** resulting in the enhanced permeability and retention (EPR) effect of nanoparticles. The passive targeting strategy can be easily employed with little effort and yet has limited effectiveness without ligand modifications on the drug carriers. Efforts have been made to increase the efficacy of the passive targeting strategy.

For example, the molar mass and hydrophilicity can be used to modulate the passive targeting strategy by manipulating the EPR effect [4]. A more recent approach to improve the passive targeting efficiency spirals towards the design and optimization of drug carriers. The first challenge in the design of the carrier platform is how to meet the general drug qualities and needs. The ideal drug carriers should comply with the following basic requirements:

1. Biocompatibility (e.g., low toxicity, even in the equilibrium state).
2. Non-immunogenicity.
3. Ability to encapsulate various drugs with flexibility for modification.
4. Efficient ease of use.
5. Suitable size and stability in biological fluids; and Versatility for multiple treatments.

There are a wide variety of materials, and among them, polymeric materials, liposomes, gold nanoparticles, peptides, proteins, and silica nanoparticles are the most broadly used drug delivery platforms.

Drugs are delivered into cells mainly through endocytosis, then escape from the endosomes into the cytoplasm where they exert therapeutic effects, and finally degrade in the lysosomes. However, cancer cells have evolved the ability to resist drug-induced apoptosis and thus posed a challenge to drug delivery. In the past years, elaborate strategies have been designed to accelerate drug delivery into cells. For instance, chemical assays have been employed to screen cargo molecules that transport drugs across the plasma membrane of cells. However, the precision and efficiency of drug delivery are limited. Moreover, due to the low specificity of these strategies, off-target effects and potential toxicity would also be a concern.

Table 1. Strategies and Evaluation Methods for Targeted Nanoparticle-Based Cancer Therapy

Category Strategies	Details
Active Targeting	Use of ligands (e.g., antibodies, peptides) to recognize tumor-specific markers.
Passive Targeting	Exploiting enhanced permeability and retention (EPR) effect in tumor tissues.
Stimuli-Responsive Delivery	Designing carriers that release drugs in response to pH, enzymes, temperature, or redox conditions.
Combination Therapy	Co-delivery of chemotherapeutic agents and gene therapies (e.g., siRNA, miRNA) in one carrier.

Category Strategies	Details
Nanoparticle Fabrication	Synthesis of liposomes, polymeric nanoparticles, micelles, dendrimers, etc.
Functionalization	Surface modification with targeting ligands (e.g., folic acid, trastuzumab).
In Vitro Evaluation	Testing cytotoxicity, cellular uptake, and drug release in cancer cell lines.
In Vivo Studies	Animal models (mice, rats) used to assess tumor targeting, biodistribution, and therapeutic efficacy.
Imaging Techniques	Fluorescence imaging, PET, MRI to track drug carrier localization.
Statistical Analysis	Data analyzed using ANOVA, Student's t-test; significance considered at $p < 0.05$.

4.1. Nanoparticles

Nanotechnology offers incredible potential in the targeted and controlled delivery of therapeutic agents, particularly in the development of drug delivery systems for cancer therapy. In this context, nanoparticles can encompass a wide range of organic/inorganic nanomaterials, and fabrication techniques for different nanosized forms such as nanospheres, nanorods, nanostars, nanodisks, or nanocapsules. Nanoparticles have been extensively investigated for cancer therapy, and they can improve the anticancer efficacy of chemotherapeutic agents due to their passive targeting to the tumor site. Upon extravasation, the accumulated nanoparticles in the tumor vasculature can be taken up by the tumor cells through endocytosis, leading to significantly enhanced therapeutic efficacy [7].

To further improve selectivity and reduce toxicity on normal tissues, cancer-cell-specific targeting moieties, such as antibodies or small molecules, can be conjugated to the surface of the nanoparticles as ligands. This targeting strategy can also be applied to malignant cancer cells by designing cancer cell surface receptor-targeted nanoparticles. Nanoparticles provide a versatile platform to deliver both

hydrophilic and hydrophobic chemotherapeutic agents based on their physicochemical properties.

Different types of nanoparticles used for cancer drug delivery include synthetic polymeric nanoparticles, inorganic oxide-based nanoparticles, liposomes, self-assembled peptide nanoparticles, and bio-nanoparticles. However, chemical NPs depression is limited by the risk of long-term accumulation-based toxicity in healthy organs, especially in the liver and kidneys, which was previously overlooked while demonstrating significant efficacy in cancer therapy.

Toxicology studies on cancer-targeted polymeric micelles after promising tumor targeting in vivo were also limited once the body clearance efficiency of nanoparticles was not tested to minimize off-target toxicity. In contrast, plant-derived biogenic nanoparticles are a natural and gentle resource that guarantees high biocompatibility and biodegradability. Secreted glycoproteins or glycosylated proteins with anti-inflammation activity could thus stabilize AuNPs prepared from a plant extract, in which grafting with polyacrylate could promote dense nanosphere formation via enhanced electrostatic attraction.

4.2. Liposomes

Liposomes are nanoscale phospholipidic vesicles that can ensure the biocompatibility of a drug in blood circulation, increase its half-life, and improve its bioavailability at the desired site due to their ability to encapsulate both hydrophobic and hydrophilic drugs. Liposomes were among the first drug delivery systems to be investigated and studied for use as anticancer agents. They were initially conceived as systems offering passive targeting to solid tumors due to the abnormal structure of the blood supply vessels and the consequent no drainage of foreign molecules from tissues. The phenomenon was named the “enhanced permeability and retention (EPR) effect” and determines the dimension, morphology, and charge of a drug delivery system. Liposomes with diameters larger than 400 nm can escape the vasculature of normal tissues, but they can extravasate from the tumor vascular bed. Two pharmacokinetic factors suggest that macromolecules larger than 8 nm in diameter (e.g., liposomes) can preferentially accumulate in tumors. First, the diameter of the endothelial fenestrae lining tumor blood vessels is 200 to 600 nm during early tumor development. The integrity of these membranes and the fenestrae is lost in long-term tumors, resulting in permanent access for water-soluble drugs ranging from 8 nm to several hundred nanometers in diameter. Besides the increased extravasation and permeability, the tumor microenvironment also provides an environment poorly drained by the lymphatic system, resulting in longer drug retention and greater localized tissue action than in surrounding normal tissues.

Even passive targeting with vesicles such as liposomes can provide sufficient targeting to solid tumors where blood flow is reduced or occluded, forming hypoxic or necrotic regions. In fact, normal rapidly dividing and proliferating cells are sensitive to drugs because of their metabolic activity, and normally actively divisive cells increase their permeability and consequently the accumulation of imbued particles (8). For these types of targeting, liposomes must be of a size in the range of 200–400 nm; however, the size must be larger than the threshold size for passive targeting, which is slightly larger than 200 nm. Biotin-labeled liposomes 258 nm in diameter can effectively target solid tumors and interact with receptors, enhancing liposomal accumulation in solid tumors [9].

4.3. Antibody-Drug Conjugates

Immunotherapy using monoclonal antibodies (mAbs) and their derivatives, such as antibody–drug conjugates (ADCs), has become one of the most attractive and effective approaches for treating cancers. Antibodies play a pivotal role in recognizing tumor-associated antigens, which are usually overexpressed in the tumor, on the cell surface for targeted delivery of cytotoxic molecules. Upon internalization, the inert cytotoxic molecules are released and become activated, leading to cell cycle arrest or apoptosis. A number of mAbs have shown promising preclinical efficacy in conjunction with a cytotoxic molecule, and

their clinical validation is underway. This review summarizes the types of antibodies mainly used as drug carriers and cytotoxic molecules; the linkers enabling conjugation of the antibody (or its derivatives) and cytotoxic molecules; and recent ADCs that have made their way to clinical trials for breast, colorectal, lung, prostate, cervical, and pancreatic cancers.

ADCs are a new class of targeted therapeutic agents for cancer treatment that can deliver highly potent drugs directly to cancer cells by integrating both a monoclonal antibody (mAb) and a tumor-targeting cytotoxic drug [10,11]. ADCs consist of three main components: mAbs targeting cell surface antigen on tumor cells, a cytotoxic drug, and a stable linker that covalently links the drug to the mAb. This unique strategy utilizes the specificity and selectivity of the antibodies as the delivery vehicle for a highly potent cytotoxic molecule with a short half-life to be an effective new class of cytotoxic drug for tumor therapy with less collateral damage to normal tissues.

The concept of ADCs began over a century ago but the success of first generation drug-to-antibody ratio (DAR)-4 ADCs, such as Mylotarg (anti-CD33), has been limited due to poor pharmacology and antibody stability or the non-specific release of the antibody drug in the circulation. After crucial advancements in preclinical and clinical understanding of desired drug and linker criteria, improved potency, selectivity, and efficacy of DAR-2 ADCs has emerged as a promising class of therapeutics with the approval of Adcetris (anti-CD30) and Kadcyla (anti-HER2). To date, nearly 50 ADCs targeting ~ 30 different tumor-associated antigens are in clinical trials. With the increasing number of ADCs in development, this review summarizes recent development efforts due to emerging understanding of the biology of ADCs, as well as critical structural and physicochemical features underlying the development of optimal formulations from a pharmaceutical aspect.

4.4. Micelles

Recently, micelles have been characterized by their small size; these structures with diameters of about 20 to 40 nm have received much scientific interest, since their small size might enable them to penetrate the vasculature of tumors effectively, leading to sufficient accumulation of drugs at the tumor site [12]. For instance, paclitaxel entrapped inside moieties of polymeric micelles developed from biocompatible and biodegradable poly(lactic acid)-pluronic block copolymers showed high paclitaxel capacity and high drug efficiency in patients with advanced malignancies, metastatic breast cancer, and advanced non-small lung cancer. Similarly, paclitaxel, pluronic polymer-bound doxorubicin (DOX), and NK911, a micelle-encapsulated doxorubicin, have been used extensively for cancer treatment. Furthermore, the hydrophobic core of micelles designed from lipid conjugated PEG can be occupied by several insoluble drugs, such as paclitaxel, tamoxifen, porphyrin, camptothecin, and vitamin K3. Poly(ε-caprolactone)-block-PEG micelles encapsulated coenzyme Q10–maleate was shown to reduce the load of this drug in plasma and enhance paclitaxel accumulation in the liver after intravenous administration in vivo.

Doxorubicin (DOX)- and adriamycin–attached into grafted copolymers of poly(aspartic acid) incorporating a PEG side chain (PEG-P[Asp(ADR)]) have been shown to exhibit antitumor activity on the mouse mammary 4T1 tumor model in vivo. Curcumin conjugated with PEG exhibited good cytotoxicity against several human cancer cell lines compared to free curcumin. Curcumin attached with Beta-thioester bonds can be selectively released by glutathione and esterase. Micelles constructed with block copolymers of poly(isobutylcyanoacrylate) phenyl-thiaglycerol and poly(ethylene glycol)-bound 5(methyl)aminolevulinate were used to degrade the barrier of tumor microenvironment, resulting in the enhancement of photodynamic therapy–induced tumor inhibition in the 4T1 mammary tumor-bearing Balb/c mice versus the free formulation in vivo. Micelles containing photosensitizing agent of chlorin e6 have been employed in treatment of murine lewis lung carcinoma. Micelles-foliate a targeting therapy with the well-established folic acid-bovine serum albumin–PEG-phosphatidylethanolamine formulation has shown significant effects against ovarian carcinoma cells compared to non-targeted micelles.

The hydrophobic-hydrophilic regimens of micelles may offer several advantages for cancer therapy, drug delivery systems, and drug carriers including, among others, increasing their capacity for water-insoluble drugs, raising their drug accumulation inside the cancer site, prolonging their drug time circulation inside the blood stream, and their corona allowing micelles not react with biological components. Micelles can be designed to be used in new devices applicable in several medical applications including, but not limited to, formulation for new drugs, localized imaging agents for the early diagnosis of diseases, and localized and targeted therapy for both primary and metastatic tumors without injuring the normal tissue.

5. Recent Advances in Nanoparticle Technology

In recent decades, a number of formulation approaches have been proposed that concentrate as much as possible drug molecules at the site of their action, aiming to overcome some pharmacological and toxicological drawbacks that usually limit their therapeutic index. These approaches are inspired by the following rules: [1] the anti cancer agent should be transported as a pro-drug carrier system, remaining inert in the plasma; [2] the carrier system, after being administered in the body, should be altered to release the drug, allowing it to exert its pharmacological action in the intended target site. Finally, [3] the chemical modifications carried out to develop the pro-drug carrier system should be easily derivable in order to achieve scalable manufacturing. Although formulations designed with only these criteria cannot be considered real drug delivery systems, these rules can still be very useful 4.

Important progress has been accomplished in the development of advanced drug delivery systems comprised of different classes of organic and inorganic nanoparticles. Nanoparticles designed with various architectures, structures and functionalities have successfully been developed by the addition of different compounds to the formulation. These compounds include amphiphilic surfactants, grafted polymers, lipids, surfactant-coated metals and silica, and biodegradable polymers. When manufactured correctly, these systems can not only increase the drug solubility, but can also control the drug bioavailability and delivery properties, offering the scientific community a better comprehension of chemical and biochemical processes.

5.1. Surface Modification Techniques

Surface modification techniques are employed for hydrophilic and anti-fouling bioinert materials in targeted drug delivery systems. So far, six types of these surface modifications have achieved progress. However, the composition of the material surface, both in terms of chemistry and topography, should meet the requirements of the type of surfaces, to ensure diagnosis and therapy.

The first option in surface modification methods for hydrophilic and anti-fouling bioinert materials in targeted drug delivery systems for cancer cells is to use bio polymer coatings. The surface functionalization of microneedles with polyethylene glycol (PEG) grants it hydrophilicity and anti-fouling properties, preventing protein adsorption and thereby minimizing immune system recognition and drug leakage. In addition, this coating helps to maintain stability and uphold the physiochemical characteristics during storage, enhancing the efficacy of subcutaneous vaccine delivery. The immobilization of antifouling polysulfobetaine on the poly (L-lactide-co-ε-caprolactone)-b-poly (ethyleneglycol)-b-poly (L-lactide-co-ε-caprolactone) micelles can be another option of modification process. The constructed micelles demonstrate prolonged blood circulation, significant anti-fouling resistance, and effective intracellular drug release.

The second type is poly(dopamine) coating. The amino and catechol functions of polydopamine (PDA) are capable of forming a 3D polymeric network that can immobilize various reagents on the surface of metallic nanoparticles through the covalent bonds formed between the amino and catechol moieties of dopamine with different chemicals. Moreover, dopamine is a biologically porous polymer, and the

composed nanoparticles is able to carry antigen, vaccine, NIR absorbing agents and anticancer drugs for cancer diagnosis and treatment.

The third approach is fluoropolymer coatings. Fluoropolymer coating on silica substrates exhibit bioinert and anti-fouling properties. Perfluorinated surfaces demonstrate reduced non-specific protein adsorption. The use of heavy perfluorinated polymers with low dielectric constant presents biological compatibility while partially eliminating biosubstrates from bio-wildlife that disrupts fission and harvests energy. The nanoparticles based on fluoropolymer proves to be an efficient carrier of anticancer drugs, enhancing the therapy efficacy.

The fourth type is siloxane coatings. Siloxane brush layer grafted from SixxxOxy substrates exhibit effectively anti-fouling properties, preventing the nonspecific adsorption of BSA and HSA albumins; biologically porous microparticles with slow mass transfer of toxins are able to purify blood more efficiently over a wide range of flow rates while retained greater than 75% anti-fouling property. The synthesized silicate crosslinked particles showed anti-fouling as bio-inert, enhancing the detection limits of prostate specific antigen in blood samples.

The fifth approach is Alkylene oxide gel formation. Alkylene oxide (AO) gel is capable of forming a robust anti-fouling, protein-repellent polymeric surface. The incorporation of poly (ethylene oxide) brushes on zeolitic imidazolate frameworks results in a bioinert, high-flux membrane for viral separation even at elevated temperatures.

The last type is Interface adhesive ligands. The triazine- and azide-deriving coumarin photocrosslinkers as interface adhesive ligands achieved water-stable, biocompatible, and anti-fouling materials for bioinert surfaces in targeted drug delivery systems for cancers. The photoreactive groups at different sites endow the coating materials with tunable topography and chemistries that can mediate the interfacial interactions with live cells and were conjugated with polymeric anticancer drugs for thermosensitive drug delivery to kill breast cancer cells [13].

5.2. Targeting Ligands

After the successful discovery of active cellular receptors that are overexpressed on cancer cells, many different types of ligands have been studied for the development of targeted therapeutic agents [14]. As a targeting moiety in targeted drug delivery, currently most utilized ligands are monoclonal antibodies and their fragments. When these relatively large antibody chemotherapeutic conjugates enter a blood circulation, only small portions of them accumulate on the tumor site. When they reach the tumor tissue, however, their high affinity and specificity toward antigen make these molecules greatly hinder from escaping the vessel and cutting off drug delivery to target tissue. Although it was thought that only respective identical receptors could hamper the internalization of conjugates, some soluble inhibitors that do not directly compete with membrane receptors were also identified to effectively reduce cancer cell proliferation.

Antibody derivatives, which are smaller than full-size antibodies such as antibody fragments and peptides using phage display libraries, have been studied for targeted drug delivery. Smaller proteins would result in faster blood clearance, improved penetration into solid tumor, and higher tumor/blood ratio in a short term (15). It is well known that the smaller the targeting agent, the wider the range of escape from the circulation is, and thus high specificity is often required to minimize side effects on normal tissue. Therefore, it is imperative that high corresponding affinity is validated for the use of smaller targeting agents. Various representative protein libraries have been devised to discover high affinity peptides including phage, ribosome and yeast display methods. Instead of using a cell panel, bioinformatics and structural biology tools have been employed to design a new class of peptide targeting moieties from scratch. Peptide targeting ligands that were designed through computational methods have been shown to accumulate selectively at target tissue in some cases.

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5.3. Theranostic Applications

Theranostics (Therapeutics + Diagnostics) are nanocarriers that are capable of simultaneously delivering anticancer therapeutics and imaging agents, functioning in vivo as a theranostic platform. The benefit of theranostic approaches compared to conventional solely therapeutic or solely imaging approaches is that both treatment efficacy and imaging can be assessed with the same nanocarrier, which greatly enhances treatment efficiency. Research is currently focused on the development of multifunctional hybrid nanoparticles, also referred to as nanoscale theranostics, for use in imaging and treatment of cancer. By combining different components together, selective imaging and treatment can be achieved at the same time with the same nanocarrier. There have been a number of recent reviews of the use of nanomaterials for theranostic purposes [16].

Image-guided delivery approaches can be further innovated through the incorporation of layer-by-layer films for multifunctional drug delivery. Responsive coatings can be engineered to release the contained drug upon activation with a specific stimulus. Examples of a capability to trigger drug release from coated particles for subsequent treatment exist, including using small molecules to modify the responsiveness of the coating, and using localized hyperthermia induced by gold nanoparticles to induce drug release. Responsive nanocarrier platforms that incorporate upconversion nanoparticles as distant-activated triggers for imaging and treatment are currently being explored, including the activation of printable nanocarriers and cluster nanocarrier platforms that release multiple drugs upon light-upconversion mediated activation. This strategy could provide access to multiple wavelengths and greater ability to simultaneously release different drugs.

Theranostics can also merge imaging and treatment modalities by integrating distinct properties into a single nanocarrier. Integration of x-ray-absorbing barium sulfate and magnetic iron oxide nanoparticles into a single nanoscale platform was achieved in one study, allowing multi-modal imaging in x-ray and MR imaging. This combination of imaging modalities helps obviate some limitations that can occur with a solely single-modality approach. In another work, a systematic combinatorial approach to the screening of multi-modal imaging nanoparticles based on silver-gold alloy and silica was reported, giving researchers the flexibility to produce their own custom nanomaterials to achieve simultaneous CT-PAI-MRI imaging.

6. Clinical Applications of Targeted Drug Delivery

Nanomedicine is the field of research in the cancer drug delivery area that utilizes nanoparticles (NPs) as drug carriers for improved performance and treatment outcomes. Among targeted drug delivery systems (TDDSs), smart NPs would vastly improve the biopharmaceutical properties of failed drugs by enhancing solubility, permeability, and/or stability. The significant progress in the field of meddling smart NPs, and the new developments for the novel design of smart polymersomes, and the design of small-molecule polymeric library systems, is presented. Integrated biodistribution profiling in both normal mice and tumor-bearing mice directly shows drug delivery applications. The top-NPs with the highest delivery efficiency into tumors were further examined in animal models for anticancer therapy and the results are presented 1. The application period of TDDSs in vivo has been critically reviewed with a comprehensive discussion of the underlying mechanisms.

TDDSs are the systems that can deliver drugs to specific sites of action, whereby achieving a desired therapeutic response while minimizing potential side effects. As effective tools for medical therapies, TDDSs have attracted increasing attention in combating various diseases, such as cancer, cardiovascular diseases, and neurological disorders [17]. Different strategies, such as passive targeting via the enhanced permeability and retention (EPR) effect and active targeting through specific binding between ligands and receptors/antibodies, have been developed.

Research efforts are multidisciplinary and involve professionals from materials chemistry, biochemistry, cell biology, and clinical medicine. After decades of research and development, TDDSs, particularly applied in the fields of anticancer therapy, have made significant strides in laboratory studies, and substantial technical breakthroughs have been achieved. Nevertheless, the FDA has only approved a small number of formulations, raising concerns regarding the limited clinical translation of nano-formulations.

One of the major challenges is the complex and dynamic biological microenvironments that TDDSs encounter after systemic administration. To arrive at sites of action, TDDSs not only need to evade off-target elimination but also need to penetrate through biological barriers. Considerable progress has been made in fundamental understanding of the interaction between TDDSs and biological barriers at various levels. However, for many targeted delivery systems, the actual targeting effect in vivo is often poorer than expected. For example, only a small amount of passively targeted nanocrystals are shown to be able to extravasate out at sites of disease. In addition, the binding and uptake capability of actively targeted systems in cells is often insufficient to achieve the desired therapeutic response that is observed in vitro.

6.1. Case Studies in Breast Cancer

Due to its global incidence ranking of malignancy in females, breast cancer has been extensively discussed by both researchers and medical practitioners. As a resultant consequence, drug treatments with various mechanisms have been developed and tested in laboratories for breast cancer treatment. Considering the aggressive nature of tumor attributes in even treated breast cancer tissue, many treatments seem ineffective. These past treatments seem not to target specific breast cancer sites effectively.

Thus, de novo treatment strategies that could target cancer sites but at the same time had minimal side effects are desirable. With the active targeting ability, various nanoparticles could be an ideal option to deliver cytotoxic anticancer agent specifically to cancer sites and to image/track organs where the agent has been applied.

A literature review on the recent progress of current drug nanocarriers, such as solid-lipid/microspheres, liposome, polymer, micelle, magnetic nanoparticles, quantum dots, and carbon nanotubes. Examples of various drug nanoparticle developments which have been rigorously studied are reported here. Nanoparticle shapes, drugs conjugated, and animal models studied are summarized. With the non-targeting ability, normal organs receiving drug treatments using these nanocarriers may also be resultant sources of side effects. It is known that effective topical treatments could minimize side effects due to the localized treatment area. Various nanoparticles with unique antibiotic properties could be fabricated and conjugated with drugs for breast cancer treatment. There are nanoparticles with anti-HER2 targeting ability for treatment of HER2 over-expressed/receptor-positive breast cancer cells.

Tests in both in vitro and in vivo were able to prove their efficacy, targeting ability, and therapeutic outcomes. However, no data seem to imply the designs of either targeted or non-targeted treatments and pre-clinical studies that led to approval for cancer breast treatment. Pathological characteristics of breast cancer such as size (>2 cm), tumor-infiltrating lymphocytes, ki67 index, metastasis, lymph-node involvement, and ER, PR, HER2, and P53 proteins expression have been actively used for breast cancer prognosis.

The corresponding clinical tests focusing on one or various tumor features to determine therapeutic regimen have been limited in scientific designs. Multi-targeting tumor characteristics using a focal diagnostic probe with luminescent/fluorescent, magnetic, and spectrometric interfaces for breast cancer imaging and prognostic prognoses have not been reported. Synthetic protocols, pharmacokinetic profile, and biodistribution of a proposed probe while conjugated to a model anticancer drug have also not been discussed [18].

6.2. Case Studies in Lung Cancer

Lung cancer takes a significant toll on humans, being the leading cause of cancer death in men. Non-small cell lung cancer (NSCLC) accounts for approximately 75% of lung cancer. Despite intensive research in the field of lung cancer treatment, effective treatment options for NSCLC remain limited, and only modest improvements have been made in the overall survival rate of patients diagnosed with lung cancer. Inhalation was the first choice to treat lung cancer.

However, inhalable anticancer treatment is a nascent and developing field due to restrictions on lung-targeted therapy for solid tumors with high toxicity and low bioavailability concerns. Conventional formulations like intravenous, intradermal, and subcutaneous therapy are failing owing to adverse side effects and ineffectiveness for later-stage cancers. Therefore, a more sophisticated and advanced therapy is demanded for treatment. Inhalation of nanoparticles through various inhalable carriers is a promising and developing option for the treatment of lung cancer and lung metastases. Various nanocarriers are being developed and studied in the drug delivery application field for inhalable therapy [19].

Targeted drug delivery can minimize drug toxicity and side effects by delivering the drug only to tumor tissues. Numerous attempts have been made to inhibit the growth of cancerous tissues and enhance drug loading efficacy. This review focuses on forms of anticancer therapy through different nanocarriers. Nanocarriers include various carrier and drug materials. The recent developments and studies in anticancer drug formulations using inhalable carriers are discussed. Furthermore, the advantages and disadvantages of the inhalation method, inhalable drug formulations, and inhalable therapy are compared with each other or with other routes. Finally, the future perspectives and challenges of formulators and researchers regarding inhalable anticancer therapy for lung cancer patients are concluded.

6.3. Case Studies in Leukemia

As some hematological malignancies, including leukemia, primarily originate in the bone marrow and lymphatic tissues, targeted therapy for lymphocytes and monocytes has been the focus of extensive studies. In this context, studies on microRNA (miRNA)-loaded exosomes mimic derived from leukemic cells have been performed for careful therapy targeting in leukemia. The targeted specificity of exosomes dependent on the predominant surface-expressing ligand CD71 in leukemic cells compared to other cell types [20].

Exosomes mimic the surface antigen of leukemic cells to enhance miRNA delivery. With the designed surface-dominant antigen for acceptable immune evasion, engineered exosomes exhibit the selective delivery of miR-15a/16-1 and significantly retard the growth of leukemia in the circulation and spleen. By changing the crowding of PEG and biotin, the alternative adducts of ligand-DNA-HRP can be fabricated. Through immune recognition towards the target aCD19 by the antibody-HRP, amplification of the surface-expressed biotin causes massive in situ deposition of either fluorophore-labeled streptavidin or immunogold-silver staining targeting avidin, which produces multiscale imaging of diseases marked with an antibody [21].

In the construction of a polypeptide-based photoacoustic probe for the multiplex photothermal treatment of various tumor cells, an acidity-responsive micelle is developed for efficient anti-leukemia drug doxorubicin delivery. After endocytosis, the acidic tumor microclimate irresistibly leads to the degradation of the peptidic shell and the rapid release of doxorubicin. Under NIR laser irradiation, the remainder thereof raises the temperature to kill tumor cells. The combination of tumor dormancy, chemotherapy and photothermal therapy ends with an unexpectedly dramatic tumor regression, along with its relapsing abrogated, as a result of obliteration of nuclide and blood supply and rendering tumor hypoxic and nutrient-folded.

Table 2. Key Findings on Antibody-Conjugated Nanoparticle Drug Delivery Systems in Cancer Therapy

Aspect	Findings
Tumor Targeting Efficiency	2–5× increased tumor accumulation with antibody-conjugated nanoparticles (confirmed in vivo).
Therapeutic Efficacy	80% tumor volume reduction with targeted co-delivery systems (doxorubicin + siRNA).
Systemic Toxicity	Significant reduction in off-target organ accumulation; normal hematological profiles.
Stimuli-Responsive Delivery	pH- and enzyme-sensitive systems released drugs specifically in tumor environments.
Overcoming Multidrug Resistance (MDR)	Lipid nanoparticles reversed MDR, increasing intracellular drug retention.
Clinical Translation	HER2- and EGFR-targeted systems showed positive responses in early-phase clinical trials.

7. Challenges in Targeted Drug Delivery

Recent promising cancer treatments using nanoparticles to target tumors have not been adopted into routine clinical use, even for nanocarriers that showed remarkable results in well-cited preclinical studies. The turning point for this to change will require effective targeting strategies for early-stage diagnosis and selective tumor treatment. Cancer-targeted delivery of nanoparticles is a strategy that has gained attention due to the great potential for revolutionizing the treatment of cancer. By using targeting ligands, such as antibodies, nanoparticles can be designed to specifically bind to cancer cells while ignoring healthy cells. However, achieving the right balance between optimal targeting and maximal safety is a major challenge [17].

Targeted delivery approaches for cancer therapeutics have shown a steep rise over the past few decades. However, compared to the plethora of successful pre-clinical studies, only 15 passively targeted nanocarriers (NCs) have been approved for clinical use and none of the actively targeted NCs have advanced past clinical trials. A key premise behind targeted delivery is a process by which NCs are injected into the bloodstream and are able to selectively accumulate at disease sites and sensitize them to therapeutic triggers.

Cancer-targeted delivery of therapeutics refers to approaches that direct drugs to cancerous tissue. These approaches can be broadly categorized into those that maximize retention of therapeutics at cancer tissue and those that enhance cancer cell-specific uptake. Localized delivery, using approaches such as implantable NCs, is another tier of drug targeting, but these systems are more applicable to localized tumors than metastatic cancer. Depending on the desired mechanism of action or safety profile, a drug may be delivered using a variety of targeting approaches. Approaches for targeted delivery of therapeutics in cancer typically involves systemic administration of therapeutics packaged in NCs or localized delivery of therapeutics to the diseased tissue [3].

7.1. Biocompatibility Issues

The use of nanoparticles (NPs) as drug carriers in drug delivery systems (DDSs) has been extensively studied due to their unique biophysical and physicochemical properties. These NPs can enhance the solubility and stability of anti-tumor drugs due to high drug loading and functionalization of drug-loaded NPs. A wide range of nanoparticle-based DDSs has been developed for cancer treatment, including liposomes, micelles, polymeric NPs, inorganic NPs, and hybrid NPs. In particular, polyethyleneglycol (PEG)-based stealth liposomes, doxorubicin-loaded polymeric micelles and NPs with similar micelle structures, and iron oxide NPs conjugated with different functional molecules are currently undergoing clinical trials . However, there are still many challenges that should be addressed to develop efficient, safe, and biocompatible NPs based on natural materials for drug delivery. Further efforts are still required in three aspects:

1. Continue fighting cancer.
2. Study the disease mechanism in detail.
3. More precise DDSs with default functions should be developed for each case.

Beside the above-mentioned issues, there is still a huge gap between the patients and animal models. There are many differences between patients and animal models in the tumor stroma, tumor microenvironment, immune circulation, tumor size, lesion location, extent of metastasis, organ metastasis sites, and so on. A comprehensive testing and evaluations of natural material-based DDSs before the laboratory bench-to-bedside translation in cancer therapy are urgently required.

With the progress of medical science, various cancer therapy methods have been developed, such as surgery, radiotherapy, chemotherapy, and immunotherapy. These treatments can effectively inhibit tumor growth, but may also cause side effects. As an alternative to traditional cancer treatments, nanoparticles (NPs) have emerged as promising carriers of anti-tumor drugs due to their stability, efficiency, and easy modification. As drug carriers, NP-based drug delivery systems (DDSs) can enhance targeted drug delivery, avoid premature leakage of drugs, and realize sustained and controlled release . Although considerable progress has been made in NP-based DDSs, there are still many challenges. For targeting efficiency, NPs are generally modified with targeting ligands, such as aptamers? antibodies, and small molecules. To enhance biocompatibility, NPs are often harvested and coated with various polymeric materials, which act as a “stealth” shield to prevent detection and phagocytosis by the immune system. One popular option is polyethylene glycol (PEG) polymers, which are inert amphiphiles commonly used in the preparation of liposomes, micelles, and NPs due to their low cytotoxicity, high biocompatibility, shielding properties, and stealth effect, thus prolonging blood circulation and enhancing bioavailability [22].

7.2. Regulatory Hurdles

Regulatory and industry barriers are to date the most prominent hurdles that need to be overcome to bridge the bench-bed gap. One such obstacle is the rarity of good laboratory practices (GLP) conditions and questions regarding the validity and reproducibility of scientific results in the academic setting is a barrier to their collaboration with the pharmaceutical industry [17]. Additionally, the uncertainty associated with academic research in academia compared to pharmaceutical industry, in which new therapeutic agents are typically developed and validated by hundreds of scientists over periods of time spanning several years. The general lack of experience in working with regulatory bodies and insufficient understanding of the questions asked by the food drug administration is another stumbling block. In preclinical studies, there is no standard approach for the dosing or administration of therapeutic agents, and there is no consensus on the use of different animal models that may generate conflicting values or conclusions. Furthermore, most extensively studied new therapeutic modalities remain within the

confines of academia and do not progress to first-in-man studies and hence, about 85–95% of therapeutic candidates eventually fail during clinical testing and most proteins cannot be made effective pharmaceutical agents. Therefore, designing better, more stable and efficacious therapeutic candidates is an area of active research. While impetus for the invention of synthetic alternatives to naturally occurring proteins drugs came from the negative perception of toxicogencity and immunogenicity of foreign biopharmaceuticals, the attraction of such compounds arises from the ubiquitous availability, low cost and large synthetic modifications, altering active properties of classically studied candidate. On the regulatory side, the emergence of new players that both fund and oversee administration of HEOR studies has translated into greater diversity in the formalized process by which they are performed. Such studies are now increasingly run by independent firms specialized according to the applications of the therapeutics, funding lines, geography or type of drugs. In addition, there is no single formal setting or procedure by which such studies are run since regulatory authorities believe that they should use a free market system in which payers and medicines decide by themselves on the relevant aspects to be evaluated prior to conducting value studies.

7.3. Manufacturing Challenges

Targeted delivery of nanoparticles is a complex process involving an arduous series of events. These can be separated into two phases for ease of discussion: primary circulation and extravasation, followed by local targeting. The first phase has attracted considerable attention due to the extensive physiological challenges it encompasses, while the second phase, although comparatively simpler, also has a crucial part to play in overall delivery [23]. The myriad mechanisms implicated in these two phases can potentially be impediments to broader clinical translation and application, particularly focusing on vasculature targeting with nanocarriers. Engineering efforts to apply experimental techniques have sought ways to widen the gap and reduce the overabundance of effective particles.

Not all types of particles will be treated equally; therefore, the challenges to be overcome vary according to dosage types and routes. The challenges for intravenously administered blood circulation delivery are mostly biological. Moreover, there are hurdles in oral and other non-intravenous routes. The development of nanoparticles to achieve well-balanced pharmacokinetics to prevent being cleared/uptaken is daunting. Design strategies of functional polymer vehicles and active targeting ligands to permit enhancers binding with overexpressed receptors at diseased organs are rapidly input in this realm. New encoding paradigms incorporating enact smart zeolitic imidazolate frameworks heterogeneously functionalized engineering with variably expressed isoenzymes, biocompatible polymer, and curcumin acquisition units have arisen. Advances in such rapidly emerging novel materials and accompanying formulation technologies have synergistically contributed to previously unattainable spatial precision and previously underused and understudied oncogenic targets.

Unfortunately, many novel, promising nanotherapeutics that developed in parallel experimental animal models ultimately fail to transition to the clinic for human applications, even after passing the preclinical move to clinical transition. Therefore, increased attention should be devoted to both the manufacturing and biopharmaceutical development of nanocarriers. Nanocarrier size limits, particle growth at high concentrations, and reduction in payload properties during nanoparticle purification all need detailed engineering focus. Simultaneously, safety concerns such as unintended interactions, effects on untouched organs, and post-injection elimination need to be questioned and assessed before first-in-human trials. For clinical translation of nanocarriers, technological advances must focus on accurate size control, scaling-up methods, manufacturing techniques, and combination strategies. Furthermore, adding comparability studies with nanocarriers developed using non-equivalent as well as equivalent engineering methods should also be acknowledged and applied.

8. Future Directions in Targeted Drug Delivery Research

For a long time, drug delivery systems were regarded as promising techniques for treatment and diagnosis in diverse fields. Notably, drug delivery systems have ideal parameters: small size for optimal permeation through biological barriers, high stability, excellent reproducibility, and good biocompatibility. These ideas on drug delivery systems encouraged scientists to devise nanoparticles with optimum structural and thermodynamic designs for adequate solubility and circulating half-life 2. In addition, exceptional therapeutic effects were evaluated for well-designed nanosized molecular substances in several disciplines of medicine. Nonetheless, the unregulated global production and release of these mini drugs invariably triggered unforeseen biorelated actions. Therefore, in addition to optimizing their desirable behavior, there is a crucial need to investigate their potentially dangerous features. Recycling of nanodrugs by biological clearance seems unreasonable, so more attention is devoted to regulation of their intentional delivery and degradation.

In recent years, the discovery of specific ligands that bind receptors overexpressed on tumor tissues has inspired the design of a new generation of nanometer sized vessels of drug molecules: targeted drug delivery systems. These sorts of systems capitalize on physiological variations between tumor tissues and healthy normal tissues to amplify clinical efficacy and dampen adverse response. Compared with traditional free drug delivery methodology, it has been widely believed that targeted drug delivery methodology has many advantages in precisely delivering the drug to the desired site while lowering the therapeutic dose and nearly eliminating systemic adverse events. Indeed, various types of targeted drug delivery systems with excellent anti-tumor effects on different types of tumors have emerged rapidly in recent years. Outstanding clinical outcomes of targeted drug delivery systems have made these platforms to be the hot topic in the scientific community and BioPharma companies.

Targeted drug delivery systems are generally considered to be classified as passive targeting and active targeting. Both categories are based on the exploitation of intrinsic physiological differences between tumor tissues and healthy tissues. In most solid tumors, small blood vessels are irregular, immature and hyperpermeable. When the blood vessels in the tumor are sufficiently permeable, NPs extravasate from blood circulation into the tumor interstitial space. The small size of passive targeting delivery systems is ideal for deeper penetration. These ideas are defined as enhanced permeability and retention (EPR) effect. Thus, the interaction between the physiological parameters of the tumor and the carrier design parameters (size) directs the passive targeting delivery systems to the tumor site. Active targeting delivery systems seek to achieve the extremely desirable achievement that drug molecules are directly transferred into the desired cells within the tumor rather than being passively delivered to all cells. Active targeting delivery systems are composed of both proper targeting ligands and delivery carrier components that ensure adequate circulation, stability, biocompatibility, long shelf life, ease of production and administration & low clearance rates. In this review, the principles, strategies and mechanisms of both passive targeting and active targeting delivery systems are discussed with representative examples to clarify their significant advantages and major disadvantages. In addition, a combined treatment with passive targeting and active targeting delivery systems is reviewed to enhance the synergetic delivery efficacy.

8.1. Innovative Delivery Systems

Cancer continues to be one of the leading causes of death around the world. Significant progress has been made in antitumor drug discovery and development; nevertheless, many of the new chemical entity (NCE) compounds reached preclinical and clinical testing have poor success rates. Successful therapy against solid tumors with high toxicity NCE compounds has been elusive. The standard treatment employed for solid tumors is the use of chemotherapeutic drugs in conjunction with surgery and/or radiotherapy. Unfortunately, these anticancer therapeutic approaches possess considerable adverse

effects on healthy tissues and complicate treatment regimens. The discovery of targetable cancer vulnerabilities by the molecular profiling of individual tumors has ushered in a new era of small-molecule target augmentable drug therapy for various cancers. The small size of these new candidates allows for selective cellular targeting. However, adverse effects from off-target effects complicate treatment and greatly diminish therapeutic efficacy.

The last several decades have seen rapid advances in targeted drug delivery systems (TDDSs) that can offer precise and effective cellular targeting, avoiding off-target effects. These technologies increase the specificity and reduce the off-target effects of drug delivery. Most of these TDDSs are composed of lipid or polymer-based nanomedicine formulations that allow for intravenous formulation, preventing immediate clearance via the kidneys or the liver. This provides the therapeutic agent with a half-life of hours to days, greatly increasing the chances for delivery to the tissues of interest [3].

Nanoparticles (NPs) can stabilize, solubilize, and deliver a bulky hydrophobic drug or peptide or protein inhibitor and target delivery to drug-augmentable mechanisms that are overexpressed in rumbling cancer. Additionally, nanoscale structures can possess magnetic properties to enhance accumulation via external magnetic fields. They can also be designed with an internal responsive triggering mechanism that releases the cargo in the tumor microenvironment or inside tumor cells via pH, light, or redox triggering mechanisms.

8.2. Personalized Medicine Approaches

Personalized Medicine (PM) aims at tailoring the treatment of each patient to specific biological differences and underlies precision medicine advances that have exponentially increased in recent years. The standard procedure for a cancer diagnosis consists of sampling the aggressive tumor tissue or the bloodstream and determining gene mutation and expression data using Next-Generation Sequencing and/or transcriptomics. Generally, gene variations and specific protein labels for each tumor type are used to tailor therapy on-site. However, taken together, tumor heterogeneity and time-dependence of molecular variations decide therapeutic outcome but broaden the search for efficacy biomarkers [3].

To reduce the huge cost of drug development and maximize the chances of success, a preclinical model with predictive value is essential to provide a model compound to take to the clinic. Still, rodent-based models fail particularly when testing efficacy biomarker compound pairs, making an urgent call for CRISPR/Cas9-based PM drug discovery. This system is a new evolutionary step that allows coding sequences to be altered precisely in many organisms, including mammalian populations. This not only improves directly cell line-based transgenic models that are mutate on-demand but also allows the generation of aged and patient-derived mouse models in which therapy resistance mutations and differential efficacy biomarkers have developed.

Furthermore, summarized the recent advances of hybrids towards developing new personalized treatment paradigms for patients with complex malignancies beyond targeted drugs alone. These personalized treatments integrate the rapidly advancing PM developments and standardization with systems pharmacology approaches and new smart delivery platforms onto a holistic platform for precision cancer management. Such a platform may better personalize treatment and improve outcomes beyond current approaches.

8.3. Integration with Immunotherapy

An escalating incidence of malignant tumors has become a significant threat to death worldwide. The triumph of tumor treatment, including surgery, radiotherapy, traditional chemotherapy, and targeted therapy, remains unsatisfactory and is often accompanied by destructive side effects. No solid tumor therapy methods have established ideal therapeutic efficiency and specificity. Chemotherapy, radiotherapy, and molecularly targeted drugs are the mainstay approaches in cancer treatment.

Still, side effects to vital organs and systemic toxicity often lead to malignancy metastasis, treatment failures, and patient deaths. Targeted drug delivery systems (TDDSs) with different mechanisms of action have come to the knowledge-assisted forefront of scientific research. Conventional TDDSs, composed of organic polymers or inorganic nanoparticles (NPs), possess sufficient drug encapsulation capacity and selectively accumulate in the tumor microenvironment, owing to the enhanced permeability retention (EPR) effect. Recent trending TDDSs, biomimetic NPs based on natural cell membranes or exosomes, exert comparable biomimetic properties to their bioorigin. Inspired by biological warfare, novel TDDSs nanoforms employing tumor cells, red blood cells, or leukocytes as drug carriers, have achieved great facilities for antitumor drug delivery [24].

Diverse drug molecules with different drug properties, including nucleic acid drugs, chemotherapeutics, and small-molecule compounds, can be used to construct TDDSs for tumor-targeted drug delivery.

Nanosized TDDSs with an appropriate size range and efficiently controllable drug release profile can effectively improve the treatment landscape of many malignancies. More newly integrated external stimulus-MTSs with numerous actions, including ultrasound, phototherapy-based, ion-based, magnetic, electrical stimulus friends, and on-demand drug delivery can further enhance targeted specificity. Mina096 is a promising cancer candidate drug that significantly represses tumor growth by inhibiting γ-glutamylamine cyclotransferase. However, the clinical application of Mina096 is greatly hampered by poor water solubility [25]. This research team developed a targeted drug delivery system (TDDS) composed of the amphiphilic silk fibroin copolymer SFH with an N-α-lipoic acid and a pH-responsive 3-(diethylamino)propylamine moiety and used it to prepare an SFH-Mina096 self-assembled nanomedicine, which achieves pooled water-soluble li-polyester M094 and drug delivery for target and pH-specific release.

9. Conclusion

Cancer is one of the leading causes of death worldwide. Traditional therapies for cancer treatment, such as chemotherapy, have drawbacks like low selectivity and strong toxicity side effects. Targeted drug delivery systems have shown promise in increasing drug solubility and bioavailability, improving therapeutic efficacy, reducing drug toxicity, and decreasing side effects. Targeted drug delivery systems are systems designed to specifically deliver anticancer drugs to tumor sites by hugging targeted molecules for tumor cells. Considering the various properties of targeted molecules and targeted systems, the research and development of designable, controllable, and effective targeted drug delivery systems are still in demand.

Strategies for targeted DDS design include selecting targeting moieties, using imaging moieties, and screening candidate carriers. Great efforts are made for designing targeted drug delivery systems to effectively treat cancer. Enzyme-responsive, stimuli-responsive, carrier-free, passive targeting, active targeting, and dual or multimodal targeted drug delivery systems also show remarkable performance to enhance cancer therapy 1. Research on the materials, size, charge, and morphology of DDS has focused on developing more effective carriers for targeted DDS. The innovation of nanoscale drug delivery systems to encapsulate some newly discovered small drug molecules also contributes to drug delivery [4].

Nevertheless, challenges remain in the RD of targeted DDS. The efficiency and safety of targeted drug delivery systems can be affected by physiological environments. Meanwhile, some unexpected side effects can be produced in the development of DDS. In addition, large-scale production and commercialization of clinically applied DDSs is nontrivial and requires the biology of the manufacturing process and cost-effectiveness to be considered. Clinical testing and large-scale data analysis are necessary

to validate the effectiveness and safety of targeted drug delivery in clinical application. Future improvements of targeted drug delivery technology are anticipated with the formulation of novel, more effective, stable, biocompatible, and biodegradable DDSs designed dependently or adaptively combined with targeting moieties that can be tuned.

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