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Advancements in nanomedicine: Targeted drug delivery systems for cancer treatment

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***Abstract*---Background:** Nanomedicine has emerged as a revolutionary approach in cancer treatment, enabling targeted drug delivery that enhances therapeutic efficacy while minimizing systemic toxicity. The rapid advancement in nanotechnology has led to the development of sophisticated drug delivery systems that optimize the pharmacokinetics and pharmacodynamics of anticancer agents. **Aim:** This article aims to review the progress in nanomedicine, focusing on targeted drug delivery systems developed for cancer treatment, highlighting their mechanisms, types, and clinically approved formulations. **Methods:** A comprehensive literature review was conducted to collate data on the history, mechanisms of action, types of nanomedicines, and their clinical applications in cancer therapy. Key databases were searched for relevant studies, clinical trials, and regulatory approvals of nanomedicines. **Results:** The review reveals a significant evolution in the field of nanomedicine since its inception,

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with various nanocarriers, including liposomes, dendrimers, and polymeric nanoparticles, being developed to enhance drug solubility and improve therapeutic targeting. Clinically approved formulations such as Doxil® and Abraxane® exemplify the successful integration of nanotechnology into oncology, demonstrating improved patient outcomes and reduced side effects. **Conclusion:** Advancements in nanomedicine have paved the way for innovative cancer therapies that leverage targeted drug delivery systems to improve treatment efficacy and safety. Continued research and development in this field hold promise for overcoming current limitations in cancer treatment, thereby enhancing the quality of care for patients.

***Keywords*---**Nanomedicine, cancer treatment, targeted drug delivery, clinical applications, drug formulations.

Introduction

Cancer ranks as the second-leading cause of death, responsible for one in six global fatalities. In 2020, an estimated 19.3 million new cancer cases emerged globally (18.1 million excluding nonmelanoma skin cancer), with over 10 million resulting in death (9.9 million excluding nonmelanoma skin cancer); notably, 70% of these cases occurred in low- and middle-income countries [1]. The poor outcomes associated with cancer are largely due to the lack of early detection methods and limitations in effective therapies. Present diagnostic and treatment protocols typically involve standardized screenings for a limited array of cancer types, followed by interventions such as surgery, radiotherapy, and chemotherapy [2]. Alongside these conventional approaches, newer treatments like immunotherapy, hormone therapy, gene therapy, and stem cell therapy have gained significant research interest in recent years.

Despite these advancements, chemotherapy remains the most potent and cost-efficient approach, especially for advanced-stage cancers. While recent biological and clinical progress has led to better treatment responses, most chemotherapy drugs still produce adverse and often severe side effects, which can hinder treatment continuity and diminish patients' quality of life [3]. Chemotherapeutics function by disrupting various phases of cell division, targeting rapidly proliferating cancer cells. However, due to insufficient specificity for cancer cells, high doses are required to achieve therapeutic effects, thereby inducing numerous dose-related side effects as they also impact other fast-dividing healthy cells. Common side effects include neuropathy, nausea, general malaise, myelosuppression, hair loss, kidney toxicity, and heart toxicity. Moreover, the limited water solubility of many chemotherapeutics complicates formulation and yields suboptimal pharmacokinetics, including low bioavailability [4]. A further challenge is that cancer cells often acquire resistance to chemotherapy. Nanotechnology has demonstrated potential in overcoming several limitations of traditional chemotherapy, offering promising avenues for enhancing cancer treatment effectiveness. Typically, drug molecules are solubilized, adsorbed, entrapped, encapsulated, or attached to nanomatrices. Thanks to their nanoscale dimensions (typically under 500 nm) and substantial surface-area-to-volume

ratios, nanocarriers can favorably modify the intrinsic properties and bioactivity of their contents [5]. Furthermore, nanoparticles can enhance the bioavailability of poorly soluble drugs, while promoting targeted tumor accumulation. Critically, nanoformulations help concentrate chemotherapeutic agents in tumors, thus improving therapeutic efficacy and reducing systemic toxicity.

The utilization of nanocarriers in cancer treatment largely hinges on enhanced permeability and retention (EPR) effects, initially identified by Matsumura and Maeda in 1986 [6]. The EPR effects arise from high vascular permeability and reduced lymphatic clearance in solid tumors, facilitating passive targeting and extended nanoparticle retention at the tumor site. Consequently, nanomedicines significantly boost treatment outcomes and mitigate the dose-dependent toxicity associated with chemotherapeutic agents. Over the years, EPR effects have formed the foundation of nanocarrier-based cancer therapies, resulting in the approval of multiple nanomedicines [7]. Additional nanocarrier-based therapies, including ABI-009 (albumin-bound rapamycin nanoparticles) [8], CPX-351 (cytarabine and daunorubicin liposomes) [9], and DoceAqualip (nanosomal docetaxel lipid suspension) [10], have shown promising anticancer effects in clinical trials. Although EPR-based nanomedicines have generated considerable excitement in cancer therapy, challenges persist, such as nonspecific distribution, inadequate tumor targeting, and both intra- and inter-tumoral as well as individual variability. Additionally, several stromal barriers—such as a dense extracellular matrix, elevated interstitial fluid pressure, growth-induced solid stress, and hypoxia—can exacerbate the heterogeneity in EPR-based tumor targeting. Given variations in tumor blood flow and vascular permeability, the EPR effect may not be suitable for all solid tumors. Clinically, tumor size often obstructs tumor blood flow; smaller, early-stage tumors exhibit more consistent EPR effects, whereas larger tumors display more variability. A recent study also highlighted that 97% of nanoparticles penetrate tumors through active transport via trans-endothelial pathways from blood vessels to tumor tissue [11].

In response, researchers have focused on innovating next-generation nanocarriers with greater practical application, such as ligand-based active tumor-targeting and tumor microenvironment (TME)-responsive drug delivery. The ligand-based approach involves ligands on nanocarriers binding directly to overexpressed receptors or antigens on cancer cells, enhancing nanocarrier uptake. For instance, nanoparticles conjugated with cetuximab have been designed to actively target epidermal growth factor receptor (EGFR)-overexpressing colon cancer cells [12]. However, the absence of such receptors in healthy cells reduces interactions between these cells and ligand-decorated nanocarriers, minimizing uptake by normal cells. Alternatively, TME-responsive systems enable on-demand drug release in response to the altered physiological traits of the TME, distinguishing it from healthy tissues. For instance, the TME of solid tumors presents an acidic pH, hypoxic conditions, an altered redox state, and elevated reactive oxygen species (ROS) levels [13,14]. Furthermore, the physicochemical properties of nanocarriers and their interactions with biological systems can be favorably tailored by modifying composition, shape, size, and surface characteristics. For example, surface modification with polyethylene glycol (PEG) can extend the circulatory half-life of drugs, thereby increasing bioavailability at the tumor site [15].

History of Nanomedicines in Cancer Treatment:

The origins of nanomedicine can be found in historical customs that used colloidal gold particles for therapeutic effects (16). Medicine pulverization, which is now known to produce nano-scale compounds, is used in the production techniques described in historical medical writings (17). Richard Feynman's 1959 Caltech talk, "There is plenty of room at the bottom," which suggested atomic arrangement as a potential future development, predicted the current idea of nanomedicine (18). Robert A. Freitas first used the term "nanomedicine" in 1999, and it has since gained prominence in technical literature. Nanomedicine is the application of nanotechnology in the 1–100 nm range to medical science (19). The drawbacks of conventional cancer medications, including their low specificity, quick clearance, degradation, and targeted restrictions, led to the need for nanomedicine (20). Then, nanocarriers were presented as a cutting-edge substitute for controlling release mechanisms and delivering medications only to tumors (21). A chronology of nanoparticle advancements is starting with doxorubicin-loaded liposomes for breast cancer and progressing to polymers, dendrimers, siRNA-encapsulated particles, and solid lipid nanoparticles created for efficient and focused treatment (22). Later, quantum dots and gold nanoparticles were added for cancer bio-imaging, and nanobots might be used in future developments (23).

Chemistry, biology, physics, engineering, and medicine are only a few of the disciplines where nanotechnology has spread. One notable example is the improvement of medication administration for complex disorders in clinical applications (24–26). Nanomedicine is a cutting-edge field of nanotechnology that has produced effective methods for treating illnesses and delivering biologic drugs. Although nano-drug delivery has generated interest in painless injections, targeted administration, and increased blood-brain barrier (BBB) penetration, biologics, such as therapeutic peptides, proteins, and antibodies, are typically supplied by injection (27). Lipid nanoparticles are becoming more widely known for their ability to transform synthetic molecules into nano-drugs, while liposome-based drug delivery methods, such as nano-sized formulations of CabiliviTM and Doxorubicin, demonstrate recent advancements in nanomedicine (28). The use of nanoparticles such as acid-base complexes, extracellular vesicles, and modified exosomes for immunotherapy and immunological regulation expands the therapeutic uses of nanomedicine (29). However, a deeper comprehension of the interactions between nanomaterials and biological tissues and organs is necessary for the safe clinical application of nanomedicine (30).

Targeted nanotherapy has proven to be more effective than traditional cancer treatments, with reduced toxicity, greater permeability, and increased retention. By extending the plasma half-life of nanoparticle medications, this technique influences their biodistribution and promotes a preferential accumulation in tumor tissues (31). The prolonged plasma half-life of nanoparticles is caused by their size surpassing the renal excretion threshold, which lowers clearance rates, and their selective accumulation in tumor tissues, which increases drug concentration in tumors over plasma or other organs and is dependent on both tumor size and time (32). This dynamic combines plasma presence and pharmacological activity to produce long-lasting therapeutic effects (33). The

benefits of nanotechnology in medication delivery, imaging, and diagnostics have increased interest in using it to treat cancer (34). A number of nanoparticle-based treatments, such as polymeric micelles, liposomes, and albumin nanoparticles, have been authorized for use in oncology; each has special advantages and disadvantages for certain clinical uses (35–37).

Types of Nanomedicines:

Lipid-based nanocarriers, inorganic materials, polymers, and biological possibilities like exosomes are just a few of the many nanoplatforms that have been investigated in cancer. Metallic nanocarriers, mesoporous silica carriers, carbon nanotubes, and graphene oxide particles are some examples of inorganic nanocarriers. The main kinds of nanomedicine that are currently being employed in preclinical and clinical research and each is covered in brief below.

Nanocarriers Based on Lipids:

Because of their high biocompatibility, biodegradability, and capacity to transport hydrophilic and hydrophobic medications with large load capacities, controlled release, and customizable features, lipid-based systems are widely used among the available nanocarriers for cancer therapies [38-41]. Based on their structure and characteristics, these are divided into three categories: liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).

Liposomes:

Liposomes can transport a variety of medications and are made up of one or more concentric lipid bilayers that encapsulate an aqueous core. They are made of biodegradable lipids, such as cholesterol and phospholipids, which provide compatibility and safety [42-43]. Agents can be added to liposomes to increase their circulation half-life, target certain cells, improve cellular absorption, and release in response to stimuli [44-47]. While some liposome formulations are in studies or awaiting approval, several are already in clinical use [48-49]. Despite these developments, the reticuloendothelial system (RES), particularly in the liver and spleen, is still able to absorb liposomal medications due to their quick clearance from plasma protein adsorption [50]. PEG-coated or other hydrophilic polymer-coated stealth liposomes withstand this clearance, prolonging circulation periods. PEGylated liposomal doxorubicin (Doxil®), for example, has a longer half-life than free doxorubicin, which allows for higher plasma concentrations and fewer adverse effects [51-52]. Tumor-targeting ligands such folic acid, hyaluronic acid, antibodies, and aptamers are frequently added to liposomes during cancer treatment. This improves drug accumulation in tumors while protecting healthy tissues [53–56]. Furthermore, certain liposomes are designed to release medications in reaction to conditions in the tumor microenvironment (TME). For the administration of irinotecan, Nunes et al. [57-58] created pH-sensitive, folate-conjugated liposomes, which demonstrate enhanced absorption and antitumor effectiveness against colorectal cancer. In addition to medication transport, liposomes have theranostic functions. For instance, a liposome functionalized with gadolinium and modified with folate was created for multimodal imaging and

drug administration in tumor therapy. It showed trimodal guiding, NIR-triggered release, and efficient tumor targeting [59].

SLNs, or solid lipid nanoparticles:

SLNs have exceptional stability and extended storage because of their solid lipid core, which is maintained by surfactants. Triglycerides, partial glycerides, fatty acids, steroids, and waxes are examples of common lipid materials. To improve stability and delivery qualities, surfactants such as lecithin and poloxamers are utilized [60]. By combining the benefits of liposomes, microemulsions, and polymeric nanoparticles, SLNs provide controlled release, high drug loading, and compatibility with a variety of drug types without the need for organic solvents [61-62]. High encapsulation and dose-dependent cytotoxicity against liver and lung cancer cell lines were demonstrated by one SLN formulation that contained linalool and cetyl esters [63]. Likewise, curcumin encapsulated in SLN demonstrated greater efficacy against breast cancer cells compared to the free medication [64]. RGD peptides and other targeting ligands increase the effectiveness of SLNs. Doxorubicin loaded into SLN that was pH-sensitive and modified by RGD, for instance, accumulated more tumors and was more effective than its non-targeted equivalents [65].

Nanostructured Lipid Carriers (NLCs):

NLCs represent a second-generation advancement in lipid nanoparticles, specifically designed to overcome limitations inherent to Solid Lipid Nanoparticles (SLNs), such as limited drug loading, polymorphic changes, crystallization of lipids over time, and drug leakage during storage periods [66]. Typically, NLCs are composed of a combination of solid and liquid lipids, surfactants, and other agents, such as co-surfactants and counter-ions, to enhance stability [67]. The solid lipid core is dispersed within a liquid lipid matrix, where the addition of liquid lipids modifies the solid matrix from a highly organized crystalline structure to a less structured lattice. This alteration enhances drug encapsulation efficiency and reduces drug leakage [68-69]. Similar to SLNs, NLCs utilize solid lipids, including triglycerides, partial glycerides, fatty acids, steroids, and waxes [70]. The liquid lipid phase often consists of digestible oils (e.g., corn, soybean, safflower, olive, coconut, and palm oils), medium-chain triglycerides (e.g., glyceryl tricaprate, glyceryl tricaprylate), fatty acids (e.g., oleic, linoleic, capric acids), and other compounds like Cetiol V, Miglyol 812, paraffin oil, isopropyl myristate, squalene, and various vitamins [70]. Numerous surfactants and their combinations are employed to boost the stability of NLCs in aqueous environments. Commonly used surfactants include various Tweens (e.g., Tween 20, 40, and 80), poloxamers (e.g., Pluronic F68, F127), Solutol HS15, polyvinyl alcohol, sodium salts of oleic, deoxycholic, and glycolic acids, polyglycerol methyl glucose distearate, TegoCare 450, egg lecithin, and soya lecithin [45]. Studies indicate that the structural stability, crystallinity, and cytotoxicity of NLCs are significantly impacted by the types of surfactants used [71].

Research has evaluated the antitumor efficacy of doxorubicin-encapsulated NLCs against liposome-encapsulated versions in a 4T1 breast cancer animal model, revealing that while liposome-encapsulated and free doxorubicin showed no

differences in tumor volume reduction, doxorubicin-loaded NLCs achieved superior suppression of tumor growth. Additionally, both NLCs and liposomes were capable of delaying the progression of lung metastases [72]. NLCs are increasingly explored as innovative drug delivery platforms in oncology [73]. Resveratrol, a naturally occurring polyphenol, demonstrates potent antiproliferative, antimetastatic, and anti-invasive effects across multiple cancer cell lines by targeting pathways such as P53, MAPK, caspases-3, 7, 8, 9, VEGF, and MMP-2 [74]. However, its clinical utility is limited due to low aqueous solubility, photostability, and extensive first-pass metabolism. A specialized NLC formulation of resveratrol was developed for targeted delivery to breast cancer cells [75]. Optimized resveratrol-loaded NLCs (RSV-NLCs) had an average particle size of 88.3 ± 3.1 nm with an entrapment efficiency of 88.0 ± 2.6%. These NLCs were further conjugated with folic acid to target folate receptors overexpressed in breast cancer cells. Folic-acid-modified NLCs (RSV-FA-NLCs) demonstrated significantly enhanced toxicity against MCF-7 folate-receptor-positive breast cancer cells compared to unmodified NLCs and free resveratrol. In A549 cells with minimal folate receptor expression, cytotoxicity was markedly reduced. Notably, folate-conjugated NLCs showed superior pharmacokinetics (t1/2: 12.04 h, AUC: 57.92 μg/mL·h) relative to unmodified NLCs (t1/2: 10.38 h, AUC: 27.11 ± 3.92 μg/mL·h) and free resveratrol (t1/2: 0.98 h, AUC: 6.37 ± 1.16 μg/mL·h) [76-85].

Nanocarriers that are inorganic:

Metals (such as gold and silver), metal oxides (such as iron, titanium, copper, and zinc oxide), mesoporous silica, graphene oxide, carbon nanotubes, and black phosphorus are examples of inorganic nanocarriers that offer unique advantages in drug transport and other therapeutic uses. They can take on a variety of shapes, such as nanoshells, nanorods, nanocages, nanostars, and nanospheres, which provide excellent stability and get around the drawbacks of lipid-based carriers, like the ease with which drug molecules can oxidize and leak. Despite certain biocompatibility and biodegradability issues, inorganic nanocarriers are appropriate for photodynamic (PDT), photothermal (PTT), and hyperthermia treatments due to their unique magnetic, electrical, and optical characteristics, controlled structural designs, and variable surface chemistry [86-92].

FeNPs, or iron nanoparticles:

Theranostic, therapeutic, and diagnostic applications of iron nanoparticles (FeNPs) are highly valued. FeNPs, which are mainly synthesized by the chemical coprecipitation approach, have superparamagnetic characteristics that are useful for magnetic particle imaging (MPI) and MRI applications [93-96]. They are also used in macrophage polarization, magnetic drug targeting, and magnetic hyperthermia. But the magnetic characteristics of FeNPs change depending on their form and content, therefore careful production techniques are required. Among the drawbacks are difficulties with effective tumoral distribution in vivo and long-term medication efficacy in target tissues [97]. One well-known use is the use of doxorubicin-loaded FeNPs to treat GBM, circumventing the limitations of the blood-brain barrier. Compared to free doxorubicin, in vitro experiments demonstrated markedly greater cellular uptake and cytotoxicity in malignant glioma cells, as well as increased drug release in acidic environments. A

multidrug-resistant cell model showed enhanced drug permeability under magnetic fields [98]. Nevertheless, self-agglomeration frequently limits the stability of SPIONs (superparamagnetic iron oxide nanoparticles) in vivo. Techniques that enhance biocompatibility and lessen immune system recognition include surface coatings with PEG, PLA, PLGA, chitosan, casein, or polycaprolactone [99-104]. Another use is gene therapy, particularly for triple-negative breast cancer (TNBC). In TNBC models, sericin-coated FeNPs were successfully used to deliver ROR1-targeted siRNA, resulting in decreased growth and enhanced tumor accumulation [105-108]. In addition to improved tumor-targeted doxorubicin administration and inhibition, a multifunctional FeNP platform (DOX@MMSN-SS-PEI-cit) also displayed MRI capabilities [109]. In addition to delivery, FeNPs cause cancer cell death by ferroptosis, an iron-dependent process that makes cancer cells more vulnerable to chemotherapeutics, particularly those that are resistant to them [110–112].

Gold Nanoparticles:

Due to their distinct physicochemical, optical, and electrical properties, gold nanoparticles (AuNPs) have garnered a lot of attention in the field of cancer diagnosis and treatment (113). Excellent biosafety, regulated dispersibility, enhanced stability, a high surface area for drug loading, and surface modification are only a few advantages that AuNPs offer as drug carriers (114). Furthermore, AuNPs can be shaped into a variety of shapes, each with unique properties, behaviors, and applications, such as nanorods, nanocages, hollow nanospheres, nanowires, nanoboxes, and nanostars. To generate novel hybrid materials that can be further capped, functionalized, or conjugated with pharmaceuticals or biological molecules for targeted cell delivery, they can be made entirely of pure gold or mixed or doped with other metals (115). Many chemical, thermal, physical, electrochemical, biological, or hybrid methods have been used to synthesize AuNPs (116-117). The most widely used chemical technique, the Turkevich method, reduces [AuCl4]− in water by employing a reducing agent such as citrate, tannic acid, or ascorbic acid (118). Common physical techniques, on the other hand, use radiation and laser ablation (117). While laser ablation at particular wavelengths encourages the creation of AuNPs, microwave, ultraviolet, or gamma irradiation provides heat and reducing conditions. Due to possible negative effects, the employment of these chemical and physical processes may be limited because they frequently call for high temperatures, pressures, and exposure to hazardous compounds (119). Because of this, scientists are favoring biological approaches that convert metal salts into stable, biocompatible metals by using microalgae, bacteria, fungi, or plants (120).

Because AuNPs can efficiently absorb and scatter light, their optical characteristics are very remarkable. Surface plasmon resonance (SPR) is the phenomenon where conduction electrons on their surface collectively oscillate when exposed to electromagnetic radiation due to resonant interaction with the electromagnetic field. Compared to non-plasmonic nanoparticles of similar size, AuNPs exhibit a noticeably larger SPR impact (121). A number of variables, including AuNPs' size, shape, composition, and concentration, affect their SPR (122). Their suitability for photothermal therapy (PTT) is increased by the fact that some AuNP forms are more effective at capturing photons than photothermal

dyes. Furthermore, by modifying their size and shape, AuNPs' resonance frequency can be modified, enabling the use of wavelengths that fall inside the "biological window" (650–1100 nm) with negligible effects on blood and other tissues (123). Because of its profound tissue penetration, near-infrared (NIR) light has been used extensively in PTT-mediated tissue ablation. The ability of AuNPs to absorb infrared light is directly linked to their PTT efficacy in treating deep-seated tumors (124). To attain high NIR absorptivity, AuNPs must be larger than 100 nm, which may lead to toxicity because of inadequate elimination and possible body buildup (125). Researchers have created tumor microenvironment (TME)-responsive AuNPs to solve this problem. These particles disperse at physiological pH and increase in size at low pH levels, improving NIR absorption (126). Coating AuNPs with cytochrome C and single-stranded DNA (ssDNA) at an ideal ratio of 1:400:1000 for AuNPs, ssDNA, and cytochrome, respectively, allowed for this pH sensitivity. CytC/ssDNA-AuNPs were found to cluster at pH 5.5, which is comparable to the pH of cancer cells. Electrostatic clustering and an increase in particle size were caused by a drop in zeta potential. In contrast to physiological pH, this aggregation is reversible at physiological pH (7.4), resulting in a red shift in the plasmonic absorption peak and amplifying photothermal effects at acidic pH. Under NIR irradiation, CytC/ssDNA-AuNPs demonstrated a temperature increase of 30 °C or more in cell culture media with a pH of 5.5, whereas only a 9 to 12 °C increase was noted in media with a pH of 7.4. Studies using in vitro PTT showed that CytC/ssDNA-AuNPs were highly cytotoxic to B16F10 melanoma cells while causing minimal harm to healthy cells. Furthermore, in colon cancer peritoneal metastases, PTT employing NIR-activated fluorouracil–AuNP complexes shown encouraging anticancer benefits (127).

Since AuNPs' surface characteristics can be altered to help them bind with a range of therapeutic agents for improved tumor targeting, they are also frequently used as drug delivery vehicles. Eugenol-conjugated AuNPs, for instance, displayed higher cytotoxicity against human prostate cancer PC-3 and human pancreatic ductal adenocarcinoma cells PANC-1 compared to free eugenol. This suggests that AuNP encapsulation improves the pharmacological potential and bioavailability of clove phytochemicals (128). Another illustration is the targeted administration of doxorubicin using hyaluronic acid-conjugated dendrimer-encapsulated AuNPs, which showed a fourfold increase in growth suppression in SK-OV-3 human ovarian cancer cell xenografts when compared to free doxorubicin (129). AuNPs also have the ability to deliver siRNA and chemotherapeutics. For example, triple-negative breast cancer (TNBC) cells were used to assess the anticancer activity of AuNPs loaded with doxorubicin and Bcl-2 siRNA (Dox-Bcl2-AuNPs) (130). While doxorubicin was coupled to siRNA through intercalation, Bcl-2 siRNA was joined to the AuNPs at the 3′-end by thiol conjugation. When compared to free doxorubicin, the combination nanocarriers greatly decreased cell proliferation and migration and resulted in a 40% reduction in Bcl-2 expression with a 50 nM siRNA dose.

Targeting Mechanism of Nanomedicine Vehicles:

The capacity of a nanomedicine formulation to precisely target malignant tissues while reducing negative effects on healthy tissues is a critical consideration when selecting one for cancer treatment. Different targeting strategies are used by

different nano-formulations to deliver anticancer medicines to tumor locations. Depending on the type of carrier, several medication delivery methods and advantages are offered by nanocarriers. Therapeutic medicines can be directly delivered into the bloodstream and reach their target location thanks to nanocarriers. They then cause DNA damage by producing too many reactive oxygen species (ROS), which may result in apoptosis and cell death [131-132]. Active targeting and passive targeting are the two main approaches for drug delivery using nanotechnology. The passive targeting technique concentrates nano-vehicles at the tumor by taking use of the intrinsic features of the tumor site. The characteristics of the tumor microenvironment (TME) and enhanced permeability and retention (EPR) are important variables. In contrast to normal cells, tumor cells have extensive holes in the arterial walls that favor passive targeting and promote neovascularization due to their rapid proliferation [133]. Insufficient angiogenesis allows particles to enter the tumor location and build up. Furthermore, EPR in tumors is caused by inadequate lymphatic outflow, which increases particle retention [134]. Nevertheless, the tumor microenvironment's high interstitial fluid pressure prevents nanoparticles from being absorbed and dispersed evenly [135]. Despite the fact that the EPR effect permits nanoparticles to preferentially accumulate in tumor tissues as opposed to normal tissues [136], the tumor microenvironment's irregularity and dysfunction frequently result in a heterogeneous distribution of nanoparticles [137], with the majority of them localizing in the tumor periphery and perivascular areas [4138]. To guarantee consistent drug delivery throughout the tumor, many nanocarriers additionally take use of TME properties such acidic pH, elevated redox potential, and variable production of lytic enzymes. The properties of tumor cells, particularly the cell surface receptors that cancer cells express, are used in active targeting. By adding other molecules that have hybridized with the carrier to bind to these receptors specifically, this technique accomplishes targeting. This section will examine the varied targeting modalities used by various nano-formulations, as well as the benefits and limitations of each.

Particle size, shape, and surface properties are some of the variables that affect passive targeting, which is often dependent on diffusion mechanisms. By prolonging circulation duration, particles in the 40–400 nm range have been found to improve bioavailability and decrease renal clearance. Maintaining a solid, spherical shape and a particle size between 50 and 200 nm significantly lengthens circulation duration while lowering renal clearance [139]. Ineffective lymphatic drainage networks, increased production of inflammatory mediators, and uneven neovascularization are all characteristics of tumor cells [140]. Nanoparticles can enter tumor tissues and stay in the tumor microenvironment for extended periods of time because of the porosity nature of the tumor vasculature and inadequate lymphatic drainage. Although the EPR effect promotes greater drug accumulation in tumor cells, the kidneys' glomerular filtration or the mononuclear phagocyte system (MPS) usually remove nanoparticles from healthy tissues. The transport of medications at the nanoscale is hindered by certain barriers, including aberrant tumor vasculature, solid stress caused by growth, and stress resulting from an aberrant stromal matrix [141]. Heterogeneous perfusion increased interstitial fluid pressure, and acidic and hypoxic conditions inside tumor cells eventually prevent nanoparticle penetration

[142]. By utilizing the EPR effect and TME features to optimize medication distribution, these difficulties can be overcome.

Enhancing the EPR effect requires maintaining the ideal nanoparticle size. Additionally, by enhancing plasma half-lives, the addition of neutral or negatively charged particles might lengthen circulation times and promote drug accumulation. Adjuvants such nitric oxide donors can also be used to increase the effects of EPR. The EPR effect is affected by a number of parameters, such as the extravascular tumor environment, tumor vasculature and biology, physicochemical characteristics, and extravasation, diffusion, and convection within the interstitium. Additionally, EPR varies in terms of vascular permeability, extravasation, penetration, hypoxic areas, and tumor blood flow. Nanoparticles travel through several phases when they enter the body, such as accumulation, endocytosis, and circulation. Additionally, depending on their properties, these particles are quite vulnerable to the opsonization process, which causes a protein corona to form surrounding the nanoparticles. Stealthy hydrophilic polymers (PEGylation) can be used to lessen opsonin absorption on nanoparticles in order to counteract this. Since Kupffer cells are specialized macrophages that aid in the uptake of foreign materials, an alternate strategy is to silence or deplete them in order to avoid the RES system [143]. PEGylated Prussian blue nanoparticles, which feature dual-enhanced photodynamic therapy with an oxygen-supplying property, have recently been found to reduce tumor hypoxia and modulate polyethyleneimine cytotoxicity. Notably, after laser irradiation, enhanced treatment efficacy has been found in tumor-bearing mice and breast cancer cells [144]. In a different study, PEGylated nanographene oxide-treated cancer cells showed significant necrosis and apoptosis, demonstrating a combined therapy example [145]. In a recent study, liposomes with PEG-coated 3 nm γ-Fe2O3 nanoparticles inside the bilayer were found to induce ferroptosis, an iron-dependently regulated cell death mechanism. The inclusion of doxorubicin improves the chemotherapeutic impact while permitting traceable magnetic resonance imaging and pH/ROS dual-responsive drug delivery. These particles also encourage the production of hydroxyl radicals, which results in efficient lipid peroxidation [146].

Changes in the tumor microenvironment (TME) and genetic/epigenetic modifications impact the course of tumors. Tumor cells, stromal fibroblasts, endothelial cells, immune cells, and extracellular matrix are all included in the TME. One possible tactic to stop tumor growth is to interfere with the way stromal cells and tumors communicate. Numerous strategies can be used, such as immune modulation/reprogramming, exosome/circulating tumor cell (CTC) targeting, anti-angiogenic treatments, ECM targeting, and carcinoma-associated fibroblast (CAF) elimination [147]. Another way to target tumor cells is to design medication delivery devices that are sensitive to pH. Large volumes of lactic acid are generated as a result of the Warburg effect, which promotes cellular development in acidic and low-oxygen settings. One intriguing method for targeting tumor cells is to develop a pH-responsive nanoparticle that degrades at tumor pH but is stable at normal pH [148]. Additionally, cancer treatment can benefit from the development of light-sensitive drug delivery devices. Many cancer cells exhibit overexpression of matrix metalloproteinases (MMP), which can be used as a tumor-specific trigger to modify the size of nanomedicines in order to

improve tumor penetration. Degrading the thick extracellular matrix is another possible strategy to enhance medication penetration [149].

Gelatin/nanochitosan/doxorubicin nanoparticles have recently been created by researchers for use in cancer treatment. MMP-2 breaks down gelatin as it reaches the tumor site, releasing smaller 4 nm nanochitosan/doxorubicin (ND) nanoparticles instead of the larger 178 nm GND. This improves tumor penetration and makes tumor cell endocytosis more effective. Finally, MMP-2 activity and low pH cause the release of doxorubicin. Additionally, this study established the drug's biocompatibility in a tumor-bearing mice model [150]. To evaluate its tumor penetration in pancreatic ductal adenocarcinoma cells, an aptamer-decorated hypoxia-responsive nanoparticle (DGL)@Apt co-loaded with gemcitabine monophosphate and STAT3 inhibitor HJC0152 has been created. In the TME, this particle has the ability to reverse its charge and shrink in response to hypoxia [151].

Immunotherapy, which involves modifying immune responses unique to tumor cells, is thought to be a viable method of treating cancer. Tumor-associated macrophages (TAMs) and other immunosuppressive cells are seen in the TME. Targeting TAMs has thereby improved cancer treatment [152]. Macrophages, which are drawn to the tumor site by the surrounding microenvironment and release cytokines, can make up as much as 50% of solid tumors. Local anoxia, inflammation, and lactic acid levels may all have an impact on this recruitment process [153]. M1 (proinflammatory and antitumor) and M2 (anti-inflammatory and protumor) are the two subsets of TAMs [154]. It has been seen that immune cells and nanoparticles interact to activate the immune system, which may improve treatment results. Reprogramming M2-type TAMs to M1-type can slow tumor growth by enabling these TAMs to act as drug depots for the accumulation of nanoparticles, which will facilitate local delivery [155]. In both in vitro and in vivo settings, polyethylene glycol-conjugated gold nanoparticles have been shown to have anti-tumor effects by suppressing M2 polarization of TAMs through lysosomal malfunction and autophagic flux inhibition [156]. In a different study, in vivo examination revealed that treatment with a biodegradable nanoparticle called ONP-302 caused changes in TAM gene expression toward the M1 phenotype and induced apoptosis in cancer-associated fibroblasts. The material used to create these negatively charged particles was poly(lactic-co-glycolic acid) (PLGA) [157].

Status of Approved Drugs and Those Under Clinical Trials

Clinical trials represent the final phase of drug development, where drug formulations undergo testing on human subjects to ascertain their actual efficacy and side effects, ultimately seeking approval for commercial use [158]. The clinical trial process encompasses several phases, all of which must be successfully completed sequentially to achieve medical approval for the drug against specific diseases. The duration of each phase, the conditions involved, and the number of participants are determined by regulatory authorities; typically, four distinct phases of clinical trials precede medical approval. Phase I involves testing with fewer than one hundred individuals, which may include healthy subjects as control groups, focusing on assessing the drug's safety and

appropriate dosage. However, in trials for cancer-related drugs, it is obligatory to include individuals diagnosed with the specific cancer type [158]. Following successful completion of Phase I, the drug advances to Phase II, where it is evaluated on several hundred individuals with the targeted cancer. The primary objective during this phase is to assess efficacy and side effects, commonly employing double-blind studies with placebo control groups. Phase III also aims to investigate side effects but emphasizes long-term and less frequent adverse reactions, involving a larger participant pool of up to a few thousand individuals and lasting 3 to 4 years. Upon successful conclusion of Phase III, the drug formulation can receive approval and proceed to marketing for medical use. Continuous monitoring occurs in Phase IV, where all reported adverse reactions are scrutinized to evaluate the drug's overall safety and efficacy.

Approved Nano-Formulations for Cancer Therapy

Since the early 1990s, various nano-formulations have received marketing authorization for cancer treatment. The polymer–protein conjugate Zinostatin stimalamer was first approved in Japan for hepatocellular carcinoma, followed by the pegylated liposome Doxil®, which was authorized in the United States as an anti-ovarian cancer drug formulation [159-160]. Over time, an array of other nano-formulations, including liposomes, metal and metal oxide nanoparticles, polymeric micelles, and lipid nanoparticles, have been developed and cleared for medical use by various regulatory agencies globally, with many more undergoing different stages of clinical and preclinical trials. A summary of the approved nanomedicine drugs for cancer treatment includes several formulations. For instance, Zinostatin stimalamer is a polymer protein conjugate containing styrene maleic anhydride neocarzinostatin (SMANCS), approved in Japan in 1994 for primary unresectable hepatocellular carcinoma, noted for its enhanced accumulation and EPR effect, albeit with slight toxicity leading to liver dysfunction. Doxil (Caelyx), which consists of doxorubicin hydrochloride in a pegylated liposome, was approved by the FDA in 1995 for ovarian cancer and AIDS-related Kaposi's sarcoma, offering prolonged drug circulation time and improved tumor targeting, although long-term use may predispose patients to oral squamous cell carcinoma. DaunoXome, a liposomal formulation of daunorubicin, received FDA approval in 1996 for HIV-related Kaposi sarcoma and is recognized for its lack of polyethylene coating and slow release into circulation, albeit associated with adverse cardiac effects.

Further, Lipo-Dox, another liposomal formulation of doxorubicin, was authorized in Taiwan in 1998 for Kaposi's sarcoma, breast, and ovarian cancers, recognized for its longer half-life and better tolerance. Myocet, also a liposomal formulation containing doxorubicin, received EMA approval in 2000 for breast cancer, highlighting reduced cardiotoxicity with equal anticancer activity. Mepact, which consists of muramyl tripeptide phosphatidyl ethanolamine in a liposome, gained EMA approval in 2009 for non-metastatic osteosarcoma, showcasing a longer half-life with less toxicity. Lipusu, a liposomal formulation containing paclitaxel, was approved in 2013 by the EMA for breast cancer and non-small-cell lung cancer, known for modulating paclitaxel toxicity without compromising its antitumor activity. NanoTherm, composed of Fe2O3 nanoparticles, was also approved by the EMA in 2013 for glioblastoma, prostate, and pancreatic cancers,

offering high blood circulation time and tumor uptake with moderate adverse effects. Other formulations such as Ameluz, Depocyt, and Genexol-PM have been authorized for various malignancies, highlighting the breadth of approved nanomedicine drugs in the oncology landscape.

Doxil® holds the distinction of being the first liposomal formulation approved in the U.S. in 1995 for treating ovarian cancer and AIDS-related Kaposi's sarcoma [160]. Subsequently, NeXstar Pharmaceuticals developed daunorubicin-loaded nanoparticles (DaunoXome®) for treating HIV-associated Kaposi sarcoma. In 2000, Myocet®, containing doxorubicin and cyclophosphamide, received EMEA approval for metastatic cancer treatment. Later, Marqibo® gained FDA approval for treating non-Hodgkin's lymphoma and leukemia. The year 2013 saw the introduction of Lipusu, which incorporated paclitaxel for gastric, ovarian, and lung cancer treatment [160]. It has been noted that the addition of compounds such as cholesterol and PEG can enhance the desired properties [161]. Furthermore, Takeda Pharmaceutical Limited developed mifamurtide-loaded liposomes to treat high-grade non-metastatic osteosarcoma. The FDA approved Vyxeos in 2017, a liposomal formulation combining daunorubicin and cytarabine, tested on 309 patients with an average age of 60 to 75, targeting acute myeloid leukemia (t-AML) or acute myeloid leukemia (AML) with myelodysplasia-related changes (AML-MRC) [162]. Alongside, Irinotecan-loaded PEGylated liposome (Onivyde) and cytarabine-loaded liposome (DepoCyt) also gained approval for pancreatic adenocarcinoma and lymphomatous meningitis, respectively [163].

In comparison to liposomal preparations, other types of approved nano-formulations are fewer in number. Nonetheless, attention has also been given to other nano-formulations, with some achieving clinical approval. Styrene maleic anhydride neocarzinostatin (SMANCS), a polymer protein conjugate, received approval in Japan in 1994 for renal carcinoma [164]. Eligard®, composed of leuprolide acetate in a polymeric nanoparticle, was authorized by the FDA in 2002 for prostate cancer [165]. Another formulation, Nanoxel®, which consists of N-isopropyl acrylamide and vinylpyrrolidone monomers loaded with docetaxel, received approval in India for treating metastatic breast cancer, ovarian cancer, non-small cell lung cancer, and AIDS-related Kaposi's sarcoma [166]. Apealea is a paclitaxel-containing polymeric micellar formulation that received EMA approval for epithelial ovarian cancer, primary peritoneal cancer, and Fallopian tube cancer [167]. Ferucarbotran and Ferumoxide, two iron oxide nanoparticles, received approval for cell labeling, particularly in the U.S. [168]. NanoTherm, approved by EMA for glioblastoma, prostate, and pancreatic cancers, is composed of superparamagnetic iron oxide nanoparticles coated with aminosilane, showing moderate adverse effects while improving blood circulation time and tumor uptake [169].

Conclusion

Nanomedicine has significantly transformed cancer treatment by introducing targeted drug delivery systems that enhance therapeutic efficacy and minimize systemic toxicity. The historical evolution of nanomedicine in oncology showcases a remarkable journey, beginning with the initial conceptualization of nanoscale systems to the current era of clinically approved formulations. These

advancements have revolutionized how oncologists approach treatment, shifting from traditional methods to more sophisticated strategies that leverage the unique properties of nanoparticles. The various types of nanomedicines, including liposomes, polymeric micelles, and dendrimers, have been instrumental in improving drug solubility and bioavailability. Their mechanisms of action—such as passive targeting via the enhanced permeability and retention (EPR) effect, as well as active targeting through specific ligand-receptor interactions—have led to significant improvements in tumor accumulation and retention of therapeutic agents. These innovations have resulted in formulations like Doxil® and Abraxane®, which have garnered regulatory approval and showcased their efficacy in clinical settings, providing patients with enhanced treatment outcomes and reduced adverse effects. Despite these advancements, challenges remain in the field of nanomedicine. Issues such as scalability in manufacturing, regulatory hurdles, and the complexity of biological interactions necessitate ongoing research. Moreover, the variability in patient responses to nanomedicine indicates a need for personalized approaches tailored to individual patient profiles. Looking ahead, the integration of nanomedicine into clinical practice presents exciting opportunities for advancing cancer therapy. Future research should focus on overcoming existing limitations, optimizing formulation strategies, and enhancing our understanding of the biological interactions of nanomedicines. By doing so, we can unlock the full potential of nanotechnology in oncology, ultimately leading to improved patient outcomes and a new paradigm in cancer care.

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التقدم في تكنولوجيا الادوية المتناهية الصغر: أنظمة توصيل الأدوية المستهدفة لعلاج السرطان

الملخص:

خلفية :لقد برز تكنولوجيا النانو كنهج ثوري في علاج السرطان، مما يتيح توصيل الأدوية المستهدفة التي تعزز الفعالية العلاجية مع تقليل السمية الجهازية. أدت التطورات السريعة في تكنولوجيا النانو إلى تطوير أنظمة متقدمة لتوصيل الأدوية التي تعمل على تحسين الحركيات الدوائية والخصائص الدوائية للعوامل المضادة للسرطان.

الهدف :يهدف هذا المقال إلى استعراض التقدم في تكنولوجيا النانو، مع التركيز على أنظمة توصيل الأدوية المستهدفة التي تم تطويرها لعلاج السرطان، مبرزًا آلياتها وأنواعها وتركيباتها المعتمدة سريريًا.

الطرق :تم إجراء مراجعة شاملة للأدبيات لتجميع البيانات حول التاريخ وآليات العمل وأنواع تكنولوجيا النانو وتطبيقاتها السريرية في علاج السرطان. تم البحث في قواعد البيانات الرئيسية عن الدراسات ذات الصلة والتجارب السريرية والموافقات التنظيمية تكنولوجيا النانو.

النتائج :تكشف المراجعة عن تطور ملحوظ في مجال تكنولوجيا النانو منذ بدايته، حيث تم تطوير مجموعة متنوعة من ناقلات النانو، بما في ذلك الحويصلات الدهنية، والأغصان النانوية، والجسيمات النانوية البوليمرية، لتحسين قابلية ذوبان الأدوية وتعزيز الاستهداف العلاجي. تركيبات معتمدة سريريًا مثل ®Doxil و ®Abraxane تجسد التكامل الناجح لتكنولوجيا النانو في علم الأورام، مما يظهر تحسين نتائج المرضى وتقليل الآثار الجانبية.

الخاتمة :لقد مهدت التقدمات في تكنولوجيا النانو الطريق لعلاجات مبتكرة للسرطان التي تستفيد من أنظمة توصيل الأدوية المستهدفة لتحسين الفعالية والسلامة العلاجية. تحمل الأبحاث والتطورات المستمرة في هذا المجال وعدًا لتجاوز القيود الحالية في علاج السرطان، وبالتالي تعزيز جودة الرعاية للمرضى.

الكلمات المفتاحية :تكنولوجيا النانو، علاج السرطان، توصيل الأدوية المستهدفة، التطبيقات السريرية، تركيبات الأدوية.