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Nanotechnology-based targeted drug delivery systems in cancer therapy

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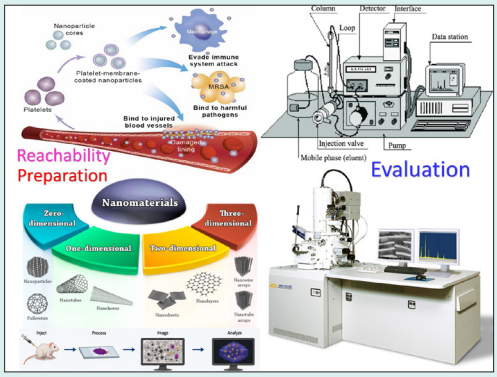
Abstract



Introduction: The treatment of cancer continues to face challenges because existing drugs do not target cancers effectively, cause harm throughout the body, and patients develop resistance to standard therapies. This review seeks to evaluate the latest developments in nanotechnology-based systems that deliver drugs in a targeted and controlled manner while providing personalized treatment through the investigation of nanocarrier development, Tumor Microenvironment (TME)-responsive systems, and multimodal cancer therapy techniques.

Methods: The research team conducted an extensive literature review by examining three databases, PubMed, Scopus, and Web of Science, to identify recent peer-reviewed studies that included both preclinical and clinical studies. The selected studies were assessed based on their nanocarrier physical and chemical characteristics, their two targeting methods, which included passive and active targeting, their TME-responsive systems, and their combined treatment methods, which included combination therapy and co-delivery methods.

Results: The use of nanotechnology-based drug delivery systems resulted in better pharmacokinetic and pharmacodynamic properties because tumors became more selective as their bioavailability increased, their circulation time extended, and their systemic toxicity decreased. The targeted ligand-based systems and TME-responsive technology allowed for precise drug release at specific body locations. The multimodal strategies, which included combination therapies and co-delivery systems, demonstrated their ability to produce synergistic outcomes that help to combat drug resistance while enhancing patient outcomes.

Conclusion: The field has made notable achievements, yet it faces multiple obstacles, including the need to counter tumor heterogeneity, the difficulties of deep tissue penetration and immunogenicity, the challenges in creating complex products, and the need to follow regulatory rules and the expense of developing products. The future of cancer therapy will be accomplished through the integration of artificial intelligence into nanocarrier design, the development of tailored nanomedicine, and the creation of new stimuli-responsive systems, which will result in better clinical outcomes.

Introduction

Cancer is at present the leading global cause of morbidity and mortality, notwithstanding the significant advances in targeted therapies and immunotherapy that have been made in oncology. This is largely because, wherever they originate in the body, all cancers show heterogeneity in the tumors, tend to metastasize, and resist treatment.[1] Allopathic treatments like chemotherapy and radiation kill off the cancer cells, but might lead to numerous harmful side effects.[2-5] Intrinsic and acquired resistance to drugs, mainly through mechanisms of drug efflux transporters' overexpression, altered drug targets, increased deoxyribonucleic acid (DNA) repair, and metabolic reprogramming, remains one of the major factors in the failure of treatment, especially in the case of heterogeneous and advanced solid tumors.[6] Incompletely dissolving in the aqueous medium, quickly being removed from the bloodstream, having limited penetration into tumor tissues, and suffering from biological barriers posed by the tumor microenvironment (TME) are additional challenges to

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effective drug delivery.[7] Hence, these factors highlight the need for improved drug delivery strategies that will enhance tumor selectivity while decreasing off-target effects.[8,9]

Nanotechnology-platformed controlled, systemic, and Multifunctional Therapeutics the newest generation of drug delivery systems (DDS).[10] These nanocarriers include liposomes, polymeric nanoparticles, dendrimers, lipid-based systems, metallic nanoparticles, and bio-inspired vesicles, which can improve their solubility or circulation time and rely heavily on either passive or active targeting to accumulate drugs at the tumor site.[11] Among them, the recently developed tumor microenvironment-responsive features and stimulus-triggered nanocarriers enable drug release, thereby overcoming many of the critical penetration and efficacy barriers.[12] This review summarizes recent developments in nanocarrier design, tumor microenvironment responsiveness, and multimodal therapeutic strategies for the physicochemical design of nanocarrier systems, tumor microenvironment responses, and multimodal therapeutic strategies for their clinical translation.[13]

Nanotechnology is a topic of multiple reviews as a recent delivery modality in oncology; this review is unique in that all design perspectives can be integrated into the systems, linking tumor microenvironment-responsive mechanisms to multiple therapeutic modalities via the physicochemical properties of a nanocarrier, all within a single framework. However, this does inform the type of review that the authors wanted; it critically discusses how some of these critical design parameters-particle size, surface charge, targeting ligands, responsiveness to pH, redox, or enzymatic cues-can affect the biological performance, clinical translation, and therapeutic efficacy of their targets within solid tumors. Strategies for passive and active targeting should now be placed within the context of systems for combination and co-delivery, which would explain why certain ones have managed to translate into clinical targets, whereas some have stayed at the preclinical stage. There is, for sure, a revival of extant knowledge at such stages that may completely redefine personalized nanomedicine and its integration with AI-assisted nanosystems design into a theranostic platform while taking into account new advances against age-old battles concerning tumor heterogeneity, barriers to tumor microenvironment penetration, immunogenicity, and scalable development.[14]

Thus, nanotechnology provides a remedy for therapies. In photothermal therapy (PTT) and photodynamic therapy (PDT), one process of the destruction of cancer cells involves the reactive oxygen species being activated under light excitation of the nanoparticles. Heating of the tumor site using magnetic nanoparticles excited in an alternating magnetic field is called magnetic fluid hyperthermia, an interesting alternative option. Interesting conversations could be held on the whole area of nanoscale delivery systems relating to the in and out of information exchange regarding small interfering RNA (siRNA), MicroRNA (miRNA), or clustered regularly interspaced short palindromic repeats (CRISPR) components involved in oncogene silencing or growth suppressor gene restoration, or everything about gene delivery via nanoparticles. Nanomaterials would also seek to circumvent any resistance to treatment by being able to evade the pump efflux mechanism, attain an intracellular-administered concentration above a critical level, or co-deliver other types of therapeutic agents operating under synergy.[15]

Nanomedicine remains an evolving field with most formulations in early stages of development. Despite promising pre-clinical outcomes, challenges in clinical translation persist. This review addresses these gaps by providing a design- based synthesis of nanocarrier systems and evaluating their translational potential, with emphasis on personalized nanomedicine and AI- assisted approaches.[16]

In its first part, this chapter defends these co-delivery strategies, which depend on a combination of the carrier technology together with anticancer drugs, nucleic acids, and phototherapy, and have demonstrated efficacy in experimental models for synergistic anticancer effects, if safety and toxicity profiles are adequately controlled. After a detour into clinically approved nanomedicines, the paradigmatic examples of the successful realization of nanotherapy for solid tumors in detail. The section reviews critically how the present nanomedicines failed due to toxin-related connotations, highly scaled-up regulatory issues, and barriers created by the TME, heterogeneous penetration, and distribution (Fig. 1). One dream so bright for future innovations in personalized nanomedicine rests on working concepts about multidimensional nanorobotic and theranostic platforms integrated with diagnostic and therapeutic components to further enhance precision and efficacy and thereby adaptability in next-generation therapy for cancer.[17]

Synopsis of nanotechnology in drug delivery

Definition and principles of nanomedicine

Nanomedicine is the study of the applications of nanotechnology for therapeutic and preventive purposes involving nanomaterials for medical applications. Most of these materials fall in the range of 1 to 100 nm in size and thus are considered for either intravascular delivery or local application at a pre-defined site of action. Nanomedicine thus proffers properties of overcoming a few major disadvantages to conventional means of administration. The definition of nanomedicine thus becomes the design, synthesis, and characterization of a plethora of engineered nanoparticles and DDS, including liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles (SLNs), nano-emulsions, and micelles, as well as inorganic nanoparticles that can load and protect the drug in their core from degradation and achieve its controlled release (CR) toward a particular target under environmental modulation. Quantum dots and nanosensors would then constitute the diagnostic arms of the nanomedicine-based theranostics system by dual triggering based on combination therapy and imaging.[19]

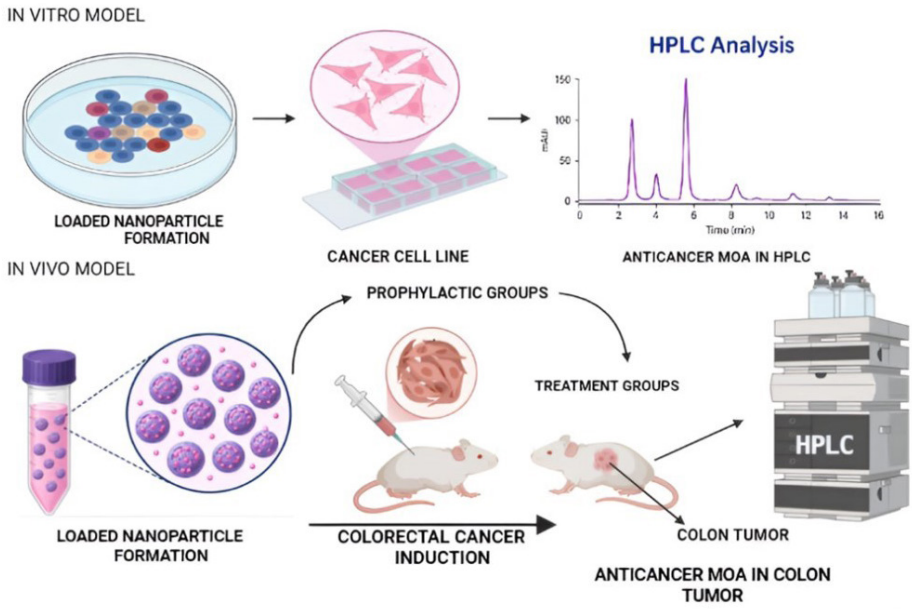

Fig. 1. Anticancer activity assessment and mechanism of action investigation of nanoparticle-based drug delivery systems: integrated *in vitro-in vivo* experimental workflow.[18]

Benefits

The historical advancement of drug special delivery systems signifies a lot of changes that have been undertaken in treating particular cancers and chronic ailments. Among the most obvious is the portal that affords nanomedicine delivery capabilities, more useful or minimal effects for those having the least side effects, targeting those with a lower surface area to volume ratio, and a tunable design. Typically, on the nanocarrier route of agent delivery, a drug must only accumulate into diseased tissues-that is, tumors-usually targeted through the enhanced permeability and retention (EPR) effect, where the leaky blood vessels allow the entry and retention of nanoparticles into the tumor microenvironment, whereas active targeting further improves their selectivity. Such opportunities bring with them all the better chances for delivery and bioavailability of the drugs. Normally, hydrophilic candidates tend to be very soluble in water and, thus, pose quite a barrier in their path towards clinic-ready, pain-free administration. Thus, such a carrier would provide sustained release in an orchestrated way. Control from the carrier can, therefore, be programmed for slowing down or triggering in response to different physiological stimuli like pH change, enzymes, and temperature change stimuli, or to external/internal stimuli like light or a magnetic field. This would mean that there would be fewer changes for the required adjustment of dosage concentration at the site of action to produce a pharmacological effect, thus further lowering inter-individual variability, tipping into either toxicity or therapeutic failure. This future comes with its greatest advantages: minimal toxicity, where cytotoxicity should not arise from targeting small amounts of diseased tissue while shielding healthy tissue.[20] It is imperative to incorporate haematological and gastrointestinal toxicities with small molecule-based chemotherapeutics.[21] The aim of the nanocarriers in extending the duration of effective drug action is to limit toxicity and possible enhancement of compliance. This is so because the nanocarriers are designed to avoid early destruction and rapid clearance, which are characteristic of pharmacokinetics influenced by the kidneys or liver. One increase in the shelf life of nanocarrier systems can come from different surface modifications, such as Polyethylene Glycol/PEG modification (PEGylation), which serve to stabilize them. These theranostic applications also favorably position these types of nanocarriers as multiplexed agents' delivery vehicles under a one multifunctional endowed approach that has imaging, tracing, or diagnostic abilities. Such a platform would permit flexibility of treatment with sustained potency.[22]

Physicochemical properties influencing therapeutic outcomes

Therapeutic effects of nanocarrier systems must have proper value judgments with respect to their various properties in the first place; those that govern how and when they cross biological fluids within the organism. Therefore, physicochemical characterization must be given a priority, from concept and design to formulation efficacy and safety, through targeting, to the design of nanomedicines. In these, attention will be given to size, and with much discrimination. Actually, it should be much less emphasized, as even the upper limits are more contested; thus, laying undue emphasis on the low selections of size, range from 20 to 100 nm, at the expense of those nanoparticles whose larger sizes really distinguish them in biodistribution, cellular uptake, and circulation. Contemporary notions consider that tissue penetrability and long circulation are low for both small and large particles, which quickly clear from the circulation due

to instability in electrostatic repulsion. In all such cases, nanoparticles belonging to the size range of 20-200 nm should possess improved permeability and EPR effect to accumulate and retain within tissue tumors characterized by pathologically leaky vasculature. On the other hand, those below 10 nm would quickly be disposed of through renal clearance and hence stand to benefit from therapy. Another such passive factor would be surface charge, since positively charged nanoparticles are electrostatically attracted onto the cell membranes, enhancing cellular uptake. Having more or less neutral charges would probably not help avoid toxicity and could, in fact, cause unwanted reactions in the bloodstream due to blood proteins. It certainly needs to maintain a near-neutral surface charge, especially if it is pegylated, since this behavior has the tendency to promote circulation with reduced immunogenicity and maximized therapeutic efficacy. Nanoparticle morphology and shape would also have effects on their behavior. The spherical nanoparticles seem to be the best, as they are easy to prepare and can be predicted in the behavior they will have; rod- or tube-type nanoparticles, on the other hand, will possibly improve cellular uptake because of prolonged circulation.[25] Several ligands will be utilized to actively target specific receptors in perturbed cells by functionalizing nanoparticles for reduced off-targeting effects and maximized intracellular transport inside the cells - antibodies, peptides, aptamers, or small molecules. Surface chemistry will determine which protein corona is adsorbed from circulation onto the nanoparticles and thus will decide the biodistribution, while the other one will activate the therapeutic action. Localization and kinetics of shuttling matter, indeed being propagated within a nanocarrier for little life assimilation with electronic control to be a shuttle for the drug without compromising the integrity of the agent, rather in stimulation by the pH, pertinently.[23-26]

Mechanisms of nanoparticle-mediated cancer targeting

Passive targeting

Passive targeting is one of the well-established passive methods that employs nanoparticles for nonspecific accumulation in tumor tissues without the requirement of a specific targeting ligand. Tumors exhibit a special physiological property called the EPR effect, which favors passive accumulation of the therapeutic agents in solid tumors with the help of this effect. Due to the abnormality of the vascular circulation within the tumor and the disruption of lymphatic drainage, these nanosized drug carriers will now distribute more into the tumor tissues.[27]

Blood vessels normally maintain control of tightly sealed endothelial cells in normal tissue, where any leakage of macromolecules through endothelial cells is inhibited. However, very rapid and rather careless angiogenesis, continuous in nature, results in the blood vessel network of a tumor. The EPR effect enables nanoparticle accumulation in tumors due to leaky vasculature and impaired lymphatic drainage, leading to enhanced retention. Therefore, nanoparticles engineered in such size ranges can easily blunder into the TME through these gaps. The principle of increased permeability is thus established.[28]

Drugs would be more efficacious because less would reach the systemic circulation and more would go to the tumor site, and there by side effects compared to conventional chemotherapy. Different types of nanoparticles, like liposomes, polymeric micelles, dendrimers, and SLNs, have been designed to harness the EPR effect for cancer therapy.[29]

On the contrary, the enhancement of nano-delivery, which itself may mean a major leap, should directly impact the therapeutic characteristics of nano-sized cancer drugs and create an opportunity for possible dose reductions for the drugs to be applied afterward in the therapeutic context of PIT.

Active targeting (ligand–receptor interactions)

Receptor-mediated endocytosis is a significant event in opening up access for targeted nanoparticles into the cytoplasm of a cancer cell, along with their cargo of drugs intended for uptake in high efficiency by the cancer cell while limiting exposure to normal tissue, thereby enhancing the therapeutic index while drastically reducing systemic toxicity.[30] Active targeting pertains specifically to over-expressed receptors in cancers, such as folate receptors in ovarian cancer, human epidermal growth factor receptor 2 (HER2) receptors in breast cancer, or EGFR in lung tumors, while also achieving distribution among angiogenic blood vessels, where integrins are expressed. Hence, these are promising new modalities in personalized treatment, into which active targeting will provide a very direct, inflammatory means of treatment.[31]

Some strategies are believed to actively drive the resistance waves against the underlying drugs. But it must enter the cancer cell and avoid excretion via efflux pumps in the membranes in the case of an active target being neutralized by antitumor resistance mechanisms. Also, some patient-related and average-related issues are likely to emerge due to heterogeneities regarding the expression of the receptors and the possibility of degradation within the blood circulation before reaching the target tissue. Mechanisms of active targeting using affinity ligands probably remain one of the most attractive paradigms for nanomedicine, with promise for selectivity, control over delivery, and perhaps an improved therapeutic index for cancer treatment.

The studies of both *in vitro* and *in vivo* systems demonstrate that active targeted nanoparticles of chemotherapeutic formulations or conventional medicines that get endocytosed and/or exhibit cytotoxicity via receptor-mediated mechanisms can increase cellular drug uptake directed toward the cancer cells. This additional plethora of advantages endowed by such targeting mechanisms provides for a much better efficacy and safety over standard homogeneous nanoparticle platforms and also those conjugated to non-targeted chemotherapeutics. Active targeting nanoparticles are considered multipronged because they ensure better accumulation of the drug and

thus anticancer efficacy inside the cancer cells, less drug selectivity toward cancer cells in order to minimize side effects on normal cells, and better control of drug release. The major limitation of active targeting nanoparticles is that these types of nanoparticles can only have clinical applicability for certain types of cancers that have specific cell surface receptors.

In theory, targeting involves having the drug accumulate such that when it interacts with the matrix proteins, it will then procure more efficient transport to the diseased organ, with the passive release achieved by EPR effects in diseased tissues, where drug concentrations may suffice to allow for improved retention and absorption. This is assessed in relation to the drug carriers-the nanoparticles, liposomes, micelles, or dendrimers-with surfaces richly decorated with high-affinity ligands to receptors overexpressed more dominantly in target cells found most often in infected and diseased or tumor tissues. These ligands include, for example, antibody fragments and antibodies, peptides, aptamers, carbohydrates, and some vitamins such as folic acid, epitopes of common ligands to target a receptor type that is practically absent for that class of ligands: folate, transferrin, epidermal growth factor receptor (EGFR), or integrins, or the virtually always upregulated receptor in disease conditions, cell surface glycoprotein (CD44). Perhaps the outcome of the active targeting technique would vary with the dynamics, indicating differences in donor-acceptor interaction with respect to density and absolute area and orientation, stability of ligand-receptor binding in normal physiological conditions, receptor heterogeneity and down-regulation, and immunogenicity, which may be mentioned as one of the great sophisticated challenges that need to be engaged with during design considerations. Overall, active targeting appears to have the most definitive theoretical promise of any means of enhancing both safety and efficacy in modern DDS, particularly with respect to cancer therapies and other forms of targeted therapy (Table 1).

Stimuli-responsive targeting (pH, temperature, enzymes, redox)

Among the advanced strategies, one of the most developed in DDS is understood as new-generation responsive targeting in nanomedicine, an innovative technique applicable only in releasing the therapeutic agents of a carrier system through stimuli-based triggering, either internal or external.[32] These triggers activate anti-tumour drugs in a restricted spatio-temporal manner; thus, they are improved in terms of efficacy, selectivity, and effectiveness with minimum damage to the healthy tissue for the treatment of cancer.[33]

The acidic nature of the TME and pH, which is an important aspect to be considered, is estimated to range from 6.5 to 6.8, an extraordinarily low acidic value compared to normal physiological pH at 7.4. Endosomes and lysosomes are also acidic in nature. The rationale for using pH-sensitive nanoparticles is that under acidic conditions, acid-sensitive bonds or coatings involved would either degrade or swell, with a subsequent release of drug products within the region of the tumor or cancer cell.[34]

Thermomodulating systems can optimize therapeutic outcomes of tumor tissue sensitivity to mild hyperthermia or enhance the external heat application with a combination of thermosensitive polymers being used as a nanocarrier during the application of mild hyperthermia (40-43 °C). The polymer has undergone structural transitions at specific temperatures through which it is capable

Table 1. Passive and active targeting in nanomedicine: targeting ligand receptor interactions for precision drug delivery

Category	Key elements	Functional role	Clinical relevance
Targeting strategy	Ligand–receptor interaction	Enables selective recognition of diseased cells	Improves the specificity of anticancer therapy
Cellular uptake pathway	Receptor-mediated endocytosis	Internalizes nanoparticle–drug complexes into the cytoplasm	Ensures high intracellular drug availability
Drug carrier systems	Nanoparticles, liposomes, micelles, dendrimers	Serve as vehicles for ligand and drug conjugation	Allow controlled and site-directed drug delivery
Target receptors	Folate receptor, HER2, EGFR, integrins, CD44	Overexpressed on tumor or angiogenic cells	Facilitates cancer- and tissue-specific targeting
Targeting ligands	Antibodies, peptides, aptamers, carbohydrates, vitamins	Bind selectively to target receptors	Reduces off-target drug distribution
Mechanism against drug resistance	Bypass of efflux pumps	Enhances intracellular drug retention	Helps overcome multidrug resistance
Comparison to passive targeting	Independent of the EPR effect	Provides active cellular internalization	Enhances uptake beyond vascular permeability
Design parameters	Ligand density, orientation, stability, and affinity	Determines targeting efficiency	Critical for reproducibility and efficacy
Biological challenges	Receptor heterogeneity, downregulation	Limits uniform response across patients	Impacts patient stratification
Systemic challenges	Ligand degradation, immunogenicity	Affects circulation time and safety	May reduce clinical translation
Therapeutic outcomes	High selectivity and controlled delivery	Increased therapeutic index	Reduced toxicity to normal tissues

of enabling the release of the drugs into the tissues on demand. Such treatment is applicable nowadays in modern photohyperthermias or magnetic hyperthermias that apply other thermal combinations.[35]

Another such example is an enzyme-responsive targeting strategy, where overexpression of specific enzymes presents in tumor tissues, such as cathepsins, hyaluronidases, and matrix metalloproteinases, is exploited by using cleavable linkers attached to drug nanoparticles for localized release in invasive or metastatic tumors where relatively high concentrations of the enzymes are found.

These systems rely on the very basic principle that, because redox potentials differ between healthy and cancer cells, in reality, cancer cells typically accumulate large amounts of glutathione, enabling it to cleave disulfide or polysulfide links by internalizing nanoparticles that allow the localized release of the drug within cancer cells and remaining stable in the bloodstream.

Some will become activated by the specific features of the TME, while others may engage trigger application from outside; this advantage pertains to target specificity, systemic toxicity, or enhanced therapeutic gains concerning cancer treatment.[36]

One of the challenges that multifunctional and responsive nanocarriers have to face involves stimuli from the body itself. Stimulation in this case would include physiological changes such as variations in pH values in certain diseased organs and sometimes even in some healthy ones, differences in the presence of stimuli-specific protein marks in the healthy cells, etc. Thus far, certain diseases have shown promise with nanocarrier-associated delivery; however, these nanocarrier-based delivery systems still face restrictions in terms of poor absorption and frequent patient injections of the nanomedicine. There may also be cases where they are physically entrapped or enzymatically degraded before reaching their targets, thus reinforcing the need to gain a better understanding of the environmental physiology of healthy and diseased cells and to further complement the development of drug design systems delivered via nanocarrier-based applications toward therapeutic targeting (Fig. 2).

Types of nanocarriers used in cancer therapy

Polymeric nanoparticles

Nanocarriers are independent of nanoparticles used in chemotherapy; rather, they support one another. Thus, the polymeric anticancer treatment working systems to be considered in this work-polylactides, polyglycolic acids, poly (lactic-co-glycolic acids), and poly (ethylene glycols)-along with other biocompatible and biodegradable polymers such as chitosans and gelatins to act as carriers for anticancer therapeutics, present an argument in favor of using these polymers as partners in cancer-targeted therapy with added benefits of protection and CR.[40]

Polymeric nanoparticles chemically maintain their solubility and stability under conditions when the respective drugs are poorly soluble in water and/or decompose rapidly in a physiological environment. The beauty of polymeric drug encapsulation is that it allows prolonged circulation time for drug accumulation at the tumor site while the polymer is gradually degraded during the same treatment period. The CR may also take place, either by way of simple diffusion or some kind of stimulus. For instance, there are pH-sensitive polymers that can be used to formulate acid-sensitive drugs, which will liberate their active form in an acidic environment at the tumor site, minimizing adverse effects to surrounding normal tissues.[41]

Mostly, this surface-modification approach is identified as an active targeting strategies that redesign the polymeric nanocarrier system with different targeting ligands, including antibodies and peptides, or even small molecules engineered to bind the nanoparticles to a receptor commonly found on a cancer cell but not in others. Another consideration could be settings at the surface; this is PEGylation, hence evading recognition by the immune system and increasing circulation time.

Polymeric nanoparticles are the best-suited class of nanoparticles for co-delivery of chemotherapeutics and

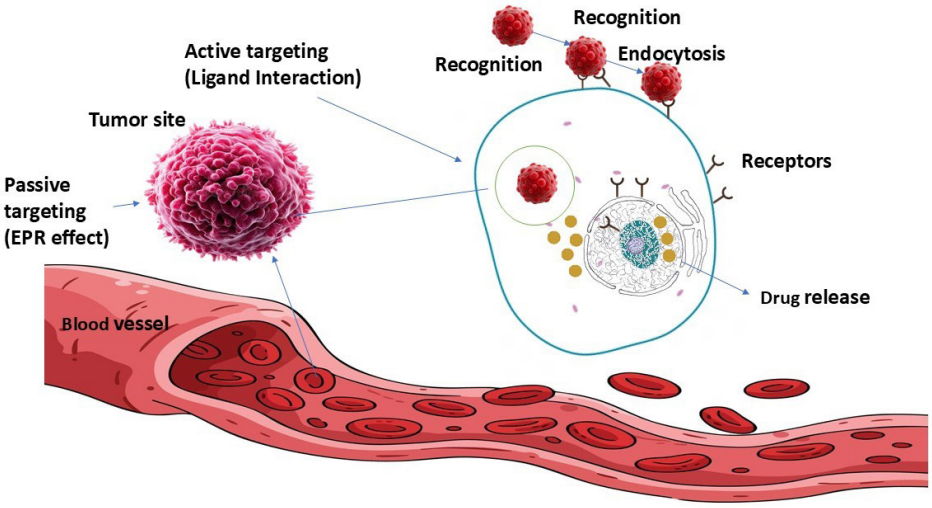

Fig. 2. Nanoparticle-mediated cancer targeting mechanisms: passive and active strategies, tumor microenvironment interactions, and clinical translation.[37-39]

gene therapies against cancers with potential synergistic actions. So far, these nanocarriers has shown potential in pre-clinical studies in crossing some barriers of the DDS, probably the most notorious barrier the world has ever confronted in the treatment of cancer. This works synergistically to broaden treatment windows through, for example, co-administration of gene silencing molecules targeting the formation of resistance pathways with cytotoxic drugs to enhance therapy.[42]

Designing poly-lactide nanoparticles should thus exhibit flexibility concerning design, biocompatibility, and an equally controlled direct delivery system. Among the most exciting picks, they would, without a doubt, rank at the topmost competition within the current hot pool of hopeful-but-admittedly-highly-plastic nanocarrier systems being devised to augment precision and effectiveness in oncotherapeutics.

Liposomes and lipid-based nanoparticles

For sure, the oldest and the largest application of nanocarriers in cancer treatment has been liposomes, and now expanded to lipid nanoparticle carriers for drug delivery. Mainly, they mimic biological membranes like phospholipid bilayers so that they can encapsulate hydrophilic and lipophilic drugs. Thus, they have a lot of compatibility with the cellular constituents, which makes lipid nanocarriers biocompatible, flexible, and very efficient in anticancer agent delivery in compliance with intracellular environments.[43]

The bioavailability of liposomes and lipid nanoparticles is further increased. Thus, this manipulation of liposomes with PEG chains gives them the name "stealth" nanocarriers, which escape rapid clearance by the immune system. These nanoparticles show passive targeting of the cancerous cells into the leaky tumour vasculature with this long circulation behaviour through EPR phenomena.[44] However, it can also be modified to achieve active targeting by attaching some ligands, such as antibodies, folic acid, or peptides, onto its surface. The ligand would then bind specifically to receptors that are overexpressed on cancer cells; therefore, an enhanced therapeutic impact will be accompanied by a concomitant decrease in unwanted effects. One more design is the so-called stimulus-sensitive lipid nanoparticles, granting release of content under selected stimuli like pH, temperature, or certain enzymes, further strengthening directed control of drug release that is triggered by the tumour microenvironment.[45]

However, aside from the common liposomes, other lipidic matrices may also be: SLNs and nanostructured lipid carriers (NLCs). Formulation of these matrices has been developed to improve the stability, increase the drug-load capacity, and elaborate a safety mechanism for certain delivery profiles, especially for poorly soluble anticancer agents in good design, which counteract the multidrug resistance in cancer cells.

Recently, the spotlight has dimmed on lipid nanoparticles, the most-promoted genetic therapy, like siRNA and mRNA, as they can shield nucleic acids from being degraded by agents and also participate in cellular uptake.[46]

After these two, SLNs and NLCs, probably no other lipid system would be thought of as a potential candidate in this area. The system is promising since most anticancer agents can achieve very high encapsulation efficiencies (EEs) with a good burst effect toward the target tumor. Moreover, biodistribution and biocompatibility are the crucial issues that could propel the use of lipid polymer hybrid nanoparticles or NLCs made from fats and surfactants, which have some acceptable standing in quasi-research and preclinical applications. Moreover, the toxic effects imposed by the lipids are lower compared to the polymeric and metallic accounts, which have been in use for nanocarrier systems in systemic applications.[47]

SLNs operate with solid lipids at ambient room temperature and an aqueous environment of body temperature. Based on these SLNs, attempts were made to suppress the quick precipitation of therapeutic concentrations of lipophilic drugs undergoing early burst release from further drug release via matrix diffusion. The crystallinity, being the second drug-release retarding parameter, might extend to the limit, which does not exceed the possible loading capacity of SLNs.[48]

In the formation of NLCs, liquid lipids are combined with solid lipids to afford the polymeric counterpart; the matrix would thus be characterized by high-grade so-called torpedo-like imperfections and disorders aimed toward solving the problems guided by the new generation of NLCs. With all these modifications to the structure, these may afford the NLCs an even greater capacity for drug loading and, conversely, a lesser release of the drugs. Relative to SLNs. NLCs are much more stable and have a CR behaviour. Increased interest has been shown in the application of NLCs for the delivery of anticancer drugs, including hydrophobic ones, genetic materials, or combined therapies.[49]

Both SLNs and NLCs essentially employ microencapsulated lipid systems, which function as nanocarrier delivery systems that target the tumor sites by the mechanism of the EPR effect. The nano carriers allow for a selective engraftment of tumor tissues. Besides that, conjugating with targeting ligands such as folate, transferrin, antibodies, etc, may also be attempted on the carriers for this active targeting. This would bring in additional advantages concerning binding to receptors of cancer cells with lesser therapeutic effects and safety against nontargeted cells.

Both SLNs and NLCs may actually be some of the best and most versatile candidates for nanomedicine delivery in cancers, placing them in a position for effective and selective delivery of anticancer chemotherapeutics. Our research into design systems to benefit patients will thus keep patient care alive on the personalized surgical management front for cancer therapies.[50]

Dendrimers

By branching dendrimers into highly branched nanoscale synthetic polymers, which give them a tree-like architecture,

meaning they are categorised by a well-defined three-dimensional structure in which a central core is found with repeating branching units that are called generations, and the number of surface terminal functions. This shape provides the next unique features of dendrimers, and they are well defined with accurate molecular weights and high density of functional groups; thus, providing an ideal condition for nanocarrier application for DDS and cancer therapy.[51]

One of these advantages is that dendrimers have the potential for combinational and synergistic therapy. These polymers offer high potential for drug payload capacity since they may either be loaded by encapsulation of the drugs inside the internal cavities of dendrimers or through chemical conjugation of drug molecules through the surface functional groups. Such dual-loading methods allow carrying multiple therapeutic molecules into the dendrimers in an effort to follow a combination therapy toward synergistic effects and improved outcomes.

Highly modified with either polyethene glycol or hydrophilic groups, the biocompatibility and solubility of dendrimers are great. Their smaller sizes were for the earlier generations, from 1 to 10 nm in size, which helped in cellular uptake and penetration in tissues.[52]

In cancer therapy, dendrimers overcome drug resistance, improve pharmacokinetics, and reduce systemic toxicity by means of a controlled and targeted DDS. Typical dendrimers such as PAMAM (polyamidoamine) and polypropylene imine have already shown good promise in the delivery of anticancer drugs, genes, and imaging agents.

Nevertheless, because of their tunable structural features and multifunctional characteristics, their limited DDS capacity has been proven to provide a versatile and potent platform in nanomedicine-derived therapies.[53]

Metallic nanoparticles (gold, silver, iron oxide)

Nanoscale metallic particles exhibit an entire range of the earliest optical, magnetic, and chemical properties useful in applications from medicine and electronics through catalysis and to environmentally oriented applications. These include specific nanoparticles that are good at doing some of these specific things: gold (Au), silver (Ag), and iron oxide nanoparticles (Fe_3O_4 or γ-Fe_2O_3). Gold nanoparticles are structurally stable enough and exhibit properties in surface plasmon resonance that make them suitable for biological materials; this accounts for these specific optical gold characteristics indeed. Research in current subjects relevant to this area includes PTT, which is the process by which light is converted into the favourable killing of tumour cells, with the input of microsizing, biosensing, imaging, and DDS, while surface functionalization will promote easy attachment onto biomolecules, for instance, antibodies or Deoxyribonucleic acid, for targeted applications.[54]

Silver nanoparticles are known for their antibacterial and antiviral effects related to nanoparticles. Microbial cells are killed as silver ions come off to impair the support of the membranes and inhibit certain aspects of cellular metabolism. Thus, they are generally used in medical dressings, textiles, coatings, and water purification. Like those, the state of plasmon also contributes to sensor and imaging technology.

The unique ferromagnetic characteristic of super-paramagnetic iron oxide nanoparticles is that they will never be magnetic when an external magnetic force is not applied. This quality gives these nanoparticles contrasting agents in magnetic resonance imaging (MRI), a method to modify DDS through magnetic guidance, hyperthermic cancer therapy, and cleansing of the environment. Biocompatibility, coating, or functionalization of nanoparticles through the entire spectrum of sciences and technologies strengthens their applicability.[55]

Carbon-based nanomaterials (carbon nanotubes, graphene)

It is indeed quite optimistic for nanotechnology, particularly over time, regarding carbon-based nanotechnology such as carbon nanomaterials, which include carbon nanotubes (CNT) and graphene, all of which have special properties in terms of mechanical, electrical, and thermal properties. CNT is a carbon nanotube, which is a cylindrical, rolled-up sheet of graphene; either one-wall or multi-wall variations are also available. The reason for this is the arrangement of carbon atoms, which creates a situation of immense tensile strength, excellent electrical conductivity, and thermal stability, so that they are good candidates for fabricating nanoelectronics, conductive films, energy storage devices, and composite materials for aerospace and automotive applications.[56]

Graphene is by far the most recognized among 2D materials and consists of a monolayer completely built by carbon atoms and organized like a honeycomb structure in two dimensions. In particular, the percolation threshold of graphene can be compared favorably to that of CNT. The high electrical conductivity, large surface area, flexibility, and transparency clearly distinguish it as an important material to be used in flexible electronic devices, high-performance batteries, super-capacitors, sensors, and advanced coatings.[57] Biocompatibility and inherent chemical tunability for applications in DDS, biosensing, and tissue engineering also strongly favor graphene for such uses.

High adsorption capacity is being further evaluated for CNT and graphene for environmental applications, in addition to water purity and sensing pollutants. Naturally, carbon nanomaterials continue to transform the field of electronics and energy, medicine, as well as material engineering, despite the issues of mass production, economic feasibility, and toxicological assessment.[58]

Niosomes and transfersomes

Niosomes are nanosized vesicular DDS, being made of non-ionic surfactants, usually in combination with cholesterol for stability. These look like liposomes structurally, but are, however, more stable, less expensive, and easier to store because they do not contain phospholipids that can

oxidise quickly. Niosomes are structured into amphiphilic bilayers that could house all types of hydrophilic as well as lipophilic drugs. This makes them adaptable due to their ability to encapsulate both hydrophilic and lipophilic drugs.[59] They increase bioavailability by protecting the drug from degradation and facilitating controlled or targeted release. With excellent biocompatibility, which is relevant for transdermal delivery, anticancer therapy, ophthalmic formulations, and vaccine delivery, among many, are niosomes.[60]

Transfersomes, a new derived type of classical vesicle, are ultra-deformable or elastic vesicles designed to penetrate skin better. Such units are formed by phospholipids further treated with edge-activator surfactants such as sodium cholate or Tween to provide added flexibility to the membrane. This property of deformability enables them to squeeze through narrow intercellular spaces of the stratum corneum, which makes transfersomes an effective vehicle for transdermal and intradermal DDS applications carrying large, hydrophilic molecules that otherwise are usually poorly penetrated by the skin. Thus, increasing systemic absorption, hence needing less dose and generally better therapy. This will come in handy, especially whenever the drug is intended to be proteins, peptides, anti-inflammatory agents, or analgesics.[61]

Exosomes and bio-inspired nanovesicles

The class of microvesicles (30-150 nm), which underlie intra- and inter-molecular structures known as exosomes, is involved in intercellular communication. Such exosomes could be a rich source of proteins, lipids, and nucleic acids, making them preferable agents to deliver drugs to cells and genes to cells as micron-sized biocompatible carriers. Exosomes, being of natural origin, will usually face less difficulty regarding such aspects as immunogenicity, stability, or even the capacity to cross biological barriers, such as the blood-brain barrier. Bio-inspired nanovesicles could either be developed through manipulation of the cell membrane or by mimicking the architecture of exosomes.[62] Biomimetic nanovesicles draw inspiration from the characteristics of natural vesicles while affording them the greater flexibility associated with selection of their scale and customization (Fig. 3). Both novel vector systems allow for the targeted delivery of therapeutic agents, increasing the therapeutic benefits and reducing their toxic effects; hence, both have attracted considerable attention in advanced cancer nanomedicine.[63]

The various types of Nanocarriers and their merits and pitfalls used for cancer treatment are listed in Table 2.

Formulation and characterisation of nanocarriers

Particle size, zeta potential, and morphology

Particle size

It is also a very important parameter in determining the stability of the system: Smaller particles are said to be relatively more stable in suspension, as they are less prone to sedimentation and aggregation. Likewise, it is believed that smaller-sized nanocarriers have greater surface area and thus facilitate drug release.[76]

Zeta potential

Zeta potential refers to the surface charge of the nanocarrier; hence, it is one of the main criteria for establishing colloidal stability. At very high values of the surface charge (+30 mV or -30 mV), there is a good electrostatic repulsion preventing any aggregation. On the contrary, as zeta potential approaches neutrality (-10 to +10 mV), aggregation may happen in the absence of steric stabilisers like polyethylene glycol.[77]

Morphology measuring techniques

Dynamic light scattering allows the determination of size and polydispersity index (PDI), whereas the analytical method of Nanoparticle Tracking Analysis provides size distribution based on measuring the collective motion of individual particles. The shapes and surface structural features constitute the morphology of the nanocarrier system.[78]

Drug loading capacity and its encapsulation

Drug loading capacity

The quantity of drug successfully unified into the nanocarrier in terms of the weight of the final nanoparticle formulation represents drug loading capacity. Thus, the amount of drug carried per unit of weight of the delivery system is indicated.[79]

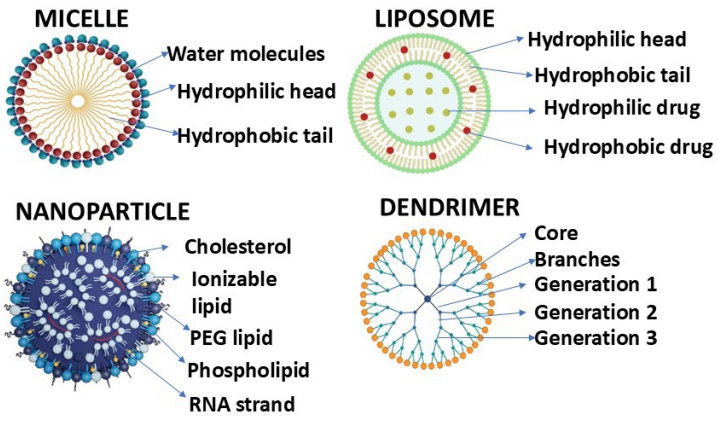

Fig. 3. Various types of Nanocarriers showing the morphology used in cancer therapy.[64,65]

Table 2. Nanocarrier platforms for cancer therapy: material composition, structural design, functional advantages, and translational challenges

Nanocarrier type	Description	Examples	Advantages	Limitations
Liposomes	Spherical vesicles with lipid bilayers	Doxil, DaunoXome	Biocompatible, can carry both hydrophilic & hydrophobic drugs	Stability issues, rapid clearance by the Reticuloendothelial System (RES)[66]
Polymeric Nanoparticles	Made from biodegradable polymers	Polylactoglycollic acid, PEGylated nanoparticles	Controlled release, good stability	Possible toxicity, complex manufacturing[67]
Dendrimers	Branched synthetic polymers	PAMAM dendrimers	High drug-loading capacity, precise structure	Expensive, potential toxicity[68]
SLNs	Solid lipid core stabilised by surfactants	Compritol SLN	Good stability, controlled release	Low drug-loading, potential expulsion on storage[69]
Nanomicelles	Self-assembled amphiphilic molecules	PEG–PLA micelles	Solubilise hydrophobic drugs, small size	Dilution instability in the bloodstream[70]
Carbon Nanotubes	Cylindrical carbon structures	Single-walled CNT, Multi-walled CNT	High surface area, effective delivery	Biocompatibility & toxicity concerns[71]
Metal/Metal Oxide Nanoparticles	Nanoparticles of gold, iron oxide, etc.	Gold nanoparticles, Fe_3O_4	Imaging + therapy (theranostics)	Potential long-term toxicity[72]
Quantum Dots	Semiconductor nanocrystals	Cd, Se, and ZnS	Excellent imaging properties	Toxic heavy metals[73]
Nanogels	Hydrophilic polymer networks	PNIPAM gels	High loading, responsive release	Limited penetration in dense tumours[74]
Exosomes	Natural extracellular vesicles	Exosome-based carriers	Biocompatible, low immunogenicity	Difficult large-scale production[75]

Encapsulation efficiency

The EE states the percentage of an initial amount of drug that gets successfully entrapped within or allied with the nanocarrier during the course of formulation.[80]

Release kinetics

Such kinetics mean the rate and conditions under which the therapeutic agent will be released into the body from the nanocarrier over the span of time. The knowledge of release behaviour is essential in predicting the therapeutic effect, frequency of dosing, and the *in vivo* performance.[81]

Stability studies

Stability studies have to assess the physical integrity, chemical integrity, and biological integrity of the nanocarriers over time, under different environmental conditions of the environment. The term stability testing denotes the formulation and characterization of nanocarriers, as distinct physical, chemical, and biological properties need to remain unchanged during storage and usage. Hence, it sets the main goal of defining shelf-life, storage conditions, and robustness for the formulation.

Physical stability measurements could be particle size, PDI, and zeta potential (both marking the presence or absence of aggregation or sedimentation of nanoparticles) and also visual aspects, colour changes, and phase separation, while chemical stability would pertain mainly to the intact encapsulated drug and carrier substances in drug content, degradation products, a pH change, and also oxidation or hydrolytic changes (by different analytical techniques like HPLC or UV).

Surface functional technique

The above is descriptive of action-oriented nanoparticle behavior, stability, and targeted biocompatibility and dexterity in drug delivery through surface functionalization. Surface functionalization is one of the principal design principles for nanoscale carriers for advanced therapy and diagnostic applications.[82]

Nanotechnology for combination and co-delivery therapy

Co-delivery of chemotherapeutics

Chemotherapeutics could refer to the simultaneous encapsulation and delivery of two or more anticancer drugs using a single nanocarrier system. Nanocarriers can drive drugs with different solubilities, mechanisms of action, and pharmacokinetics to the tumour site in an efficient manner.[83]

Combination of drugs with nucleic acids (siRNA, miRNA, CRISPR)

By combining traditional pharmaceutical formulations and nucleic acid molecules, such as siRNA, miRNA, and CRISPR components, cancer therapy can be focused towards targeting not just genetic pathways but also cellular pathways. siRNA and miRNA can control the expression of specific genes or silence oncogenes and restore the activity of tumour suppressors, thereby making drugs work better.[84] CRISPR has made it possible to make precise changes in the genome to repair mutated genes or to switch off genes that drive cancer. When these nucleic acids are co-delivered using nanocarriers, their effects on chemotherapeutic drugs complement each other, foremost to overcoming resistance to chemotherapeutics, reducing dosage, and improving specificity (Table 3). This is an excellent approach for personalising and effectively treating cancer patients with high efficacy.[85]

Table 3. Nanotechnology-based platforms for combination and co-delivery cancer therapy: system types, functional descriptions, and representative therapeutic payloads

Type of nanotechnology	Description	Combination payloads delivered
Liposome-based co-delivery	Lipid bilayer vesicles that can carry hydrophilic & hydrophobic agents together	Drug–Drug, Drug–Gene[86]
Polymeric nanoparticles	Biodegradable polymers (PLGA, PEG) are used to load multiple agents	Drug–Drug, Drug–siRNA, Drug–Protein[87]
Dendrimers	Branched polymers with multiple binding sites for co-loading	Drug–Drug, Drug–Gene, Gene–Gene[88]
Polymeric micelles	Self-assembled amphiphilic polymers for hydrophobic drugs	Drug–Drug, Chemo + Photodynamic agents[89]
Nanogels	Cross-linked hydrophilic polymer networks enabling high loading	Drug–Drug, Drug–Protein[90]
Metallic nanocarriers	Gold, iron oxide, or hybrid metal nanoparticles for therapy + imaging	Chemo + Photothermal, Drug–Drug[91]
Hybrid nanocarriers	A combination of lipids, polymers, and metals for multifunctional delivery	Drug–Drug, Drug–Gene, Chemo + PTT/PDT[92]
Exosome-based delivery	Natural vesicles offering biocompatibility and targeting abilities	Drug–Drug, Drug–Gene[93]
Carbon nanomaterials	CNTs, graphene for multi-agent loading	Drug–Drug, Chemo + Photothermal[94]

Role of nanoparticles in combination therapies with radiotherapy

The introduction of nanoparticles stands to benefit combined cancer therapy with radiation. One of the major obstacles to the success of radiation therapy is that it causes collateral damage to surrounding normal tissues. The extra burden arises from the radioresistance of tumor cells. These hurdles in radiation therapy could be bypassed through nanotechnological delivery systems, holding the ability to target the tumor (e.g., enabling hypoxic tumors).

Thus, the nanoparticles would further act as radiosensitizers to increase the sensitivity of malignant tissue to ionizing radiation further. Upon irradiation, the high-Z nanoparticles, that is, gold, silver, hafnium oxide, and bismuth nanoparticles, enhance local dose deposition through photoelectric and Compton effects, thus amplifying DNA damage and reactive oxygen species (ROS)-generated tumor cell death. Thus, the amount of radiation required to control a tumor would be reduced, and the toxicity to the normal tissues would probably be reduced.

Co-delivery systems enable simultaneous delivery of multiple therapeutic agents, enhancing synergistic effects and overcoming drug resistance. When encapsulated within nanoparticles, drugs such as cisplatin, doxorubicin, or poly (ADP-ribose) polymerase inhibitors gain superior stability and improved accumulation in tumors based on the EPR effect, with slight synchronization of drug release during the radiation exposure period, all of which may together target DNA damage induction inside the tumor cells while probably blocking their repair systems and favoring apoptosis.[95]

The treatment-oriented radiotherapy protocols can be aided with the use of nanoparticles, primarily with regard to solid tumors under hypoxia-responsive or pH-sensitive nanocarriers, which can modulate oxygen levels or preferentially release radiosensitizers in those hypoxic tumor regions known to act as roadblocks to radioresistance. An array of possibilities concerning the delivery of immunomodulators alongside radiotherapy through nanoparticles should bring about the stimulation of antitumor immune responses, thereby confirming the abscopal effects.

Nanoparticle-mediated imaging will invariably benefit these considerations for utmost precision, efficacy, and safety of combination treatments in radiotherapy.

Comparative evaluation of nanocarrier-based systems and conventional anticancer treatments

Nanocarriers have been studied a lot over the past few decades because they seem really good at helping to deliver drugs. Nanocarriers increase the therapeutic efficacy while reducing side effects, prolonging release, and targeting delivery. These qualities and much more make them interesting for drug delivery applications. Additionally, because their physicochemical properties can be modified depending on composition (organic, inorganic, or hybrid), size (small or large), shape (sphere, rod, or cube), and surface properties (surface charge, functional groups, PEGylation or other coating, attachment of targeting moieties), nanocarrier systems are of considerable interest in drug delivery. The overriding philosophy of nanocarrier-based DDS is to eradicate a disease with the least possible side effects. Anticancer medicines have some problems when they are given to people in the usual way. These problems include not working well, the cancer being very harmful to the body, and the cancer becoming resistant to the medicine. Many anticancer drugs are just not as good as they could have been. Nanocarriers can take the drug directly to the tumor, exploiting the physiological conditions that are found in the tumor. They make the drug more efficient in humans with cancer. The surface receptors on the tumor cells possess many surface receptors that helps these tiny carriers locate the tumor cells and deliver the drug to them.[96]

The tiny carriers are very good at getting the anticancer medicines into the tumors. Tiny carriers and anticancer medicines are helping us to fight cancer in a way. Several nanocarrier-based products have been approved for the treatment of various tumors, and many others are in different phases of clinical trials.

Clinical applications in cancer using nanotechnology

Food and Drug Administration (FDA) approved nanomedicines.

All of these nanomedicines are pivotal studies with respect to the FDA, helping and improving cancer therapy through enhanced delivery of drugs while reducing toxicity and maximising therapeutic benefit. Some examples include liposomal doxorubicin (Doxil®), which is a liposomal formulation of doxorubicin; the alternative specification, Albumin-bound paclitaxel nanoparticles (Abraxane®), which improves the solubility and raises the tumour uptake of the albumin-bound paclitaxel nanoparticle; and nano liposomal irinotecan (Onivyde®), a nanoliposomal formulation of irinotecan used in treating metastatic pancreatic cancer. These nanomedicines use the EPR effect, prolonged circulation time, and lowered systemic side effects to improve delivery, thus using advanced properties that nanotechnology brings to modern oncology.[97]

Various formulations of nanomedicine for anticancer treatment have progressed from research to clinical use. With this, the translatability of nanotechnology in oncology is asserted. The pegylated liposome formulation of doxorubicin manufactured by Orthobiotech/Schering-Plough may well be regarded as the first nanomedicine to win the FDA's approval in November 1995 for treating ovarian and breast cancers. Abraxane, the albumin-bound nanoparticle formulation of paclitaxel developed by Abraxis Bioscience, then entered the scene in January 2005, thus enabling the first series of approvals for treating various cancers, whereas further approvals were gained in September 2013 for treating metastatic pancreatic cancer in combination with gemcitabine. Gilead Sciences obtained the approval for DaunoXome in April 1996 after establishing the liposomal form of daunorubicin for Kaposi's sarcoma associated with AIDS; conversely, the FDA sanctioned Depocyt in April 1999 for the treatment of lymphomatous meningitis with liposomal cytarabine prepared by SkyePharma/Enzon. One other was for Oncaspar in 1994 for the combinatory upon PEGylation of asparaginase from Enzon for targeting acute lymphoblastic leukemia. Currently, numerous nanomedicines are in clinical trials, besides the already approved agents by the FDA; for example, Onco-TCS, a liposomal formulation of vincristine for non-Hodgkin lymphoma; LEP-ETU, a liposomal paclitaxel presently being developed for tumors of the ovary, breast, and lung; Aroplatin, a liposomal form of cisplatin under investigation for colorectal cancer; and OSI-211, a liposomal variant of lurtotecan under study for lung and recurrent ovarian cancers, all being in phase I or II clinical testing. These scenarios further reinforce the case for increasing efforts that will be placed on nanocarrier-based systems to improve the safety, efficacy, and clinical performance of anticancer therapies directly.

Nanoparticle-based preparations in clinical trial

Currently, the development of such a nanoparticle-based preparation is being explored for clinical trials in order to determine the best way to deliver drugs with reduced toxicity to improve cancer therapies. Such nanoparticle drug formulations are currently undergoing initial clinical trials in order to achieve targeted delivery of drugs with minimum toxicity for the betterment of cancer treatment. Clinical development is also going on with NK105 (paclitaxel formulated as nanomicelles) and lipid nanoparticles with siRNA for the treatment of solid tumours. Thus, these formulations would potentially exhibit better pharmacokinetic properties, improved penetration into tumours, and other treatment possibilities.[98]

Success stories and case studies

Nanotechnology has demonstrated improved drug-delivery efficiency in several studies. Abraxane® claims a superior response rate and better tolerability in terms of hypersensitivity reactions compared to conventional paclitaxel, and can therefore be found in almost all types of breast, lung, and pancreatic cancers. All these successes portray how potentially transformative nanomedicine will be to personalised cancer therapy.

Personalized therapy

Cancer therapy refers to the specific type of control in an individualized manner to cater specifically to people suffering from cancer. It was developed for the purpose of treating an individual with cancer, keeping the treatment specifically effective for the tumor and less toxic to other parts of the body. In fact, targeted therapy targets cancer cells and provides the necessary medicine to cause them to undergo cell death, with evaluation of cancer cells on the aspect that distinguishes them from other normal cells. For instance, there are actually a lot of receptors in an excess state appearing on cancer cells or are disturbed along the signaling pathways. These different aspects are targeted at killing the cancer cells. Now, that can be done by molecules that can locate cancer cells and deliver the medicine to them. Each of these is accomplished through using antibodies that are made to find cancer cells or with particles that can carry the medicine to the cancer cells. With the permeability and retention effect, these tiny particles can find the cancer cells because the cancer cells are different from normal cells, and the particles can get into the cancer cells more easily. Cancer-targeted therapy is the treatment of cancer patients; that is, targeting the cancer cells for death and not damaging other parts of the body. Controlled therapies, on the other hand, provide the right dose of medicine at the right time and place for the right person; after all, nanoparticles can also be programmed to release medicines when they encounter acids, enzymes, or other things, or even better, just when exposed to heat or light from outside. Then, the medicines are released in the area of the tumor, where the medicines can do their work and kill the bad cells. Today, this is the kind of therapy that could probably spare some healthy parts of the body from excessive medication. The therapy, being controlled, along with specially designed instruments, ensures that the medication reaches the tumor site and remains there; ultimately, this is a great boon for the comfort of people. Controlled therapy is one of the best ways

to prescribe medicine to individuals, as it is very accurate and minimizes the adverse effects of medicine on the rest of the body. However, personalized cancer therapy also includes all aspects related to the patient profile, type of tumor, stage of disease, and response to treatment. Targeted, controlled, and personalized therapies. Chemo targets the healthy parts of the body and does not always work for cancers responding to it; even cancers develop resistance to chemotherapy. Personalized cancer therapy stands on customizing cancer treatment for cancer patients. An integrated approach will solidify personalized oncology because it will cause drug design and delivery to be more closely linked to clinical decision-making, even to the most patient-specific biological feature of a particular cancer, than before, thereby improving therapeutic outcomes and quality of life.[99]

Toxicity, biocompatibility, and safety considerations

In vitro and in vivo toxicological assessment

In vitro and *in vivo* toxicity testing would be essential before any nanoparticle-based DDS was clinically used. *In vitro* tests involve cell cultures and measure cytotoxicity, oxidative stress, cell uptake, membrane integrity, and inflammatory response (Fig. 4). The results of these tests provide quantitative measures of dose-dependent toxicity with an emphasis on the mechanism of interaction. *In vivo* tests would necessarily involve animal models for the study of biodistribution, metabolism, clearance, organ accumulation, immunotoxicity, and prolonged effects (Fig. 5). Parameters such as haematology, histopathology, and behavioural changes will be monitored. Thus, this completes the evaluation of nanoparticles for biocompatibility, non-toxicity, and safety for regulatory approval and clinical translation.

Immunogenicity and off-target effects

Immunogenicity is described as the unexpected immune response generated in a host by a drug or its nanocarrier. These foreign particles activate the macrophages or activate

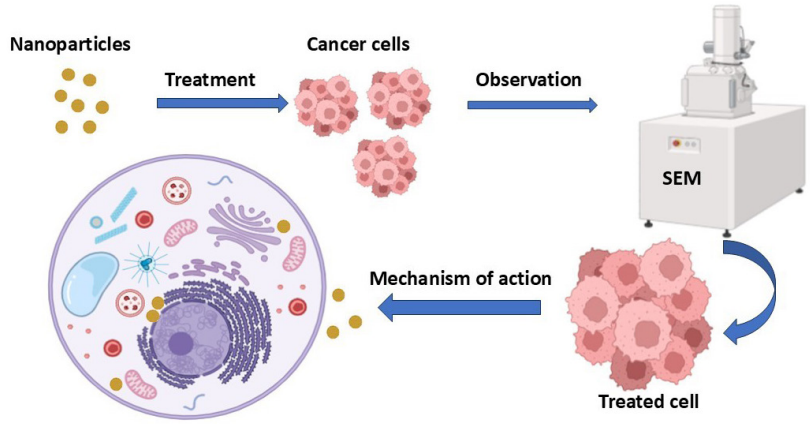

Fig. 4. Diagrammatic representations express that the process of exposure to a nanoparticle starts with its internalization inside the cell. Finally, cellular internalization and drug delivery at the target point produce quite an action scheme. SEM analysis has shown different modes of action of anticancer activity.[100]

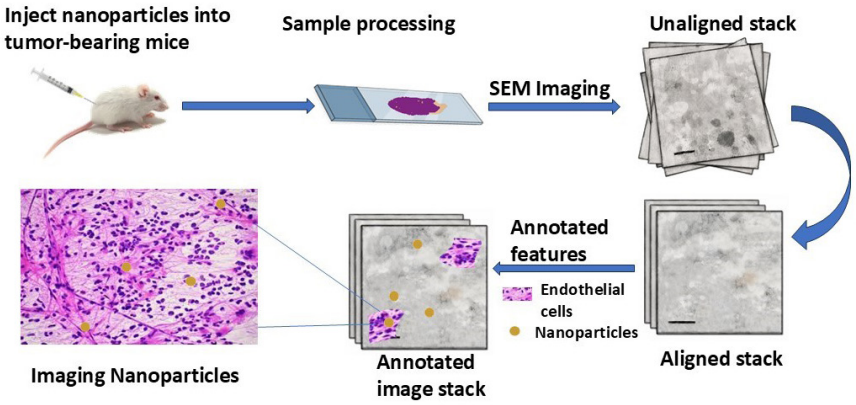

Fig. 5. Experimental work-up and image analysis pipeline overview for 3Dem-NPD. (A) Experimental workflow: through a vein, gold nanoparticles are injected into tumor-bearing mice. Tissues of the tumor are taken out and fixed before being embedded in resin. Tissues thus embedded are cut into 70-nm sections and successively deposited on a silicon wafer. The wafer is then placed into a scanning electron microscope (SEM), and each slice is visualized through backscattered electrons. The images thus produced are digitally processed through alignment algorithms and then annotated for endothelium and nanoparticles. This constitutes the creation of a three-dimensional model in three dimensions of endothelium and nanoparticles to be evaluated. (B) Here is the 3D representation stacked on 2D patterns of electron microscopy, tied with annotated endothelial cells whose shapes were visible through the removal of a few cells. Panel B-i shows a 2D slice of the annotated EM dataset on the 194th z-plane with a zoomed-in version in panel B-ii. (C) The 3-D model of the endothelium (colored) and nanoparticles (orange). This is panel C-i, which shows a 2D slice of the annotated electron microscope dataset that is set on the 194th z-plane, along with a zoomed version in panel C-ii. Scale bars are all 10 μm except for the zoomed-in ones that are 1 μm.[101]

other pathways for complement protein or antibody overproduction. Those avenues, in the end, might produce other side effects, such as rapid wear-and-tear clearance from blood, weakened therapeutic efficacy, hypersensitivity reactions, or inflammation. It has been realistically shown that immunogenicity is very much dependent on surface properties, dimensions, shapes, and compositions of the nanocarrier.

An interference of a drug or a nanomedicine with tissues or cells other than the foreseen targets is called off-target effects. This might occur due to nonspecific binding or missed targeting altogether. Accidental accumulation in organs, like the liver, spleen, or kidneys, may also contribute to the off-target effects of nanomedicine. Irrespective of impairment, these off-target effects can be fairly toxic, damaging the organs and diminishing the entire selective effect of the treatment. That is the good part; indeed, the strategies being pursued revolve around engineering of the targeting ligand, optimisation of particle size, or providing CR to reduce off-target interactions.

Biodistribution and clearance pathways

In the design of nanoparticles for therapeutic delivery, it is essential to learn about the clearance routes and biodistribution. Expectedly, following their administration, nanoparticles are distributed according to size, surface charge, and composition. Most of these are sequestered by the reticular endothelial system, primarily by the liver and spleen, thus reducing their targeting efficiency. Smaller particles are eliminated from the circulation through the kidneys (thereby measuring less than 10 nm), while larger or more hydrophobic particles are cleared from the body via the liver. Some surface modifications are made on the nanoparticles to prolong their circulation time in the blood and avoid opsonisation and uptake by the immune system (E.g., PEGylation).[102] Thus, their understanding is important in the scheme that considers the optimal design of nanoparticles that can penetrate into the tumors and exit the system from the body (Fig. 6).

Long-term safety concerns

Long-term safety concerns in relation to the presence of nanoparticles are linked with persistence in the body, accumulation within the body, and a chronic form of toxicity. Some of these nanoparticles, especially metallic nanoparticles or carbonless nanoparticles, would accumulate in the body for a longer duration. They would then lodge in the liver and spleen, or even lungs and brains, eventually initiating inflammation and delivering oxidative stress that is likely to result in tissue damage.[103] Chronic repeated exposures can lead to compromised immunity, followed by havoc created in cellular events. The other aspect deals with the interference of genetic materials, which tends to have negative impacts on reproductive/developmental health. Little is known about the long-term effects associated with the formation of associated proteins and the production of nanoparticles; hence, these need precise and extensive long-term investigations for safe transfer into the clinic.[104]

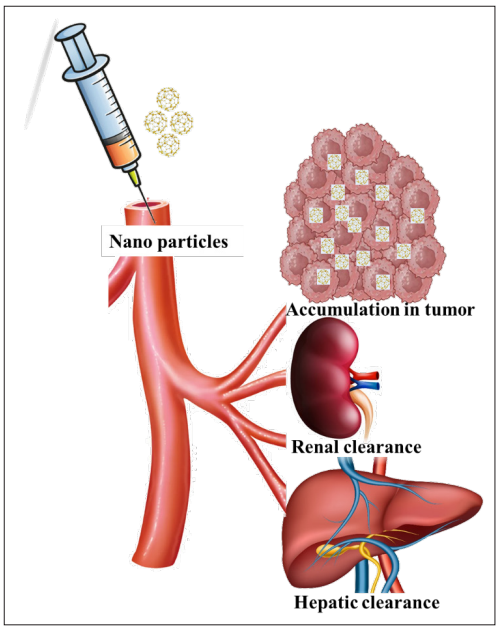

Fig. 6. Biodistribution and clearance pathways of nanocarriers: mechanisms, biological barriers, and clinical implications

Challenges in nanomedicine for cancer therapy

Scale-up and manufacturing risks

It is always a challenging task to increase production volumes of nanomedicines from laboratory level to industrial level, as it often faces strict controls with respect to size, shape, surface chemistry, and batch-to-batch uniformity of the particles. Such minute differences can create significant differences in terms of therapeutic and safety properties. The regulatory standards demand precise evaluation and quality assurance, which cannot easily be made for multifunctional or stimuli-responsive nanoparticles.[105] Large-scale synthesis should also guarantee the preservation of stability without aggregation, besides offering an extended shelf life. These disadvantages hamper the speed of progress towards commercialisation and necessitate the uniformization of nanofabrication technology, which should also be scalable and cost-effective.

Regulatory hurdles

The composite and multidimensional character of nanoparticles seldom fulfils fixed criteria for evaluating medicines. The regulatory bodies require extensive characterisation of the nanoparticles at least with respect to the size, composition, surface chemistry, stability, and interactions with biological systems, which are generally extremely difficult to standardise. In fact, matters specific to a nanoformulation that must be included in safety assessments include altered biodistribution, immune activation, and long-term accumulation.[106] The regulations are yet heterogeneous among countries. The great majority of discrepancies can be attributed to a total lack of harmonisation of testing protocols, which then becomes an issue when long-term toxicity is questioned, while having to deal with poorly defined critical quality

attributes. All of these elements, in turn, have increased the burden of regulatory approval with respect to time and cost, heavily discouraging the timely clinical translation of nanotherapies.[107]

Stability and reproducibility matter

In contrast to today's highly advanced nanomedicines, these are so unstable that high-energy surface free attractions encourage aggregation and make them very sensitive to environmental conditions such as pH, temperature, and ionic strength. Instability changes some of the properties related to particle size, surface charge, and drug-release profile, thereby affecting therapeutic efficacy and safety. Reproducibility is also yet another issue, since minor differences in the synthesis methodologies, raw materials, and storage conditions can cause an entire batch to give drastically different results. Control must even be exerted in excess in the manufacturing processes just to have the same particle shape, drug load, and physicochemical properties. Quality assurance, scale-up, and even possible approval for translation into a clinic become difficult.[108]

Tumour microenvironment walls

The efficient delivery of nanomedicines is deeply hindered by the tumour microenvironment. Dense extracellular matrix, irregular blood vessels, and increased interstitial fluid pressure are the typical characteristics of solid tumours that restrict nanoparticles from penetrating and uniformly distributing inside them.[109] Further, they can also hinder drug action or alter the behaviour of nanoparticles in hypoxic and acidic conditions. Moreover, the heterogeneity present in the tumour microenvironment might influence the response of different tumour regions to the same treatment modality, hence abating the net effectiveness.[110] All these biological barriers get in the way of effective targeting and delivery, thereby decreasing the therapeutic response anticipated from nanomedicines. Emphasis on bone marrow microenvironment, immune interactions, and circulation-specific challenges. A nurturing microenvironment exists in the histology of bones, where only tumor sustenance and resistance to treatment may be taking place. This niche system is itself complicated; it contains a number of components like stromal cells, osteoblasts, and endothelial cells, various types of extracellular matrix components, and soluble factors such as cytokines and chemokines. All these components work together to protect the tumor cells from dormancy and reduce penetration, therefore activating pro-survival signaling pathways for pharmacological effects. Hematologic malignancies with solid tumors that have metastases to the bone are even more complicated environments in which the effects of both conventional medicines and nanomedicines are greatly reduced.

More than that, immune interactions in the tumors within the microenvironment undermine treatment outcomes. As such, tumor cells can also be in control of immune responses by activation of suppressor T cells and inhibition of both the cytotoxic T cells and natural killer cells, while tolerizing immunosuppressive populations like regulatory T cells and myeloid-derived suppressor cells. Polarization of macrophages to a tumor-promoting (M2) phenotype encourages tumor growth; compromises therapeutic efficacy; and, in that, macromolecule-mediated DDS need to be developed in consideration of these immune-evasive situations.

There is a variety of impediments associated with the circulation of the drug. The major aspect is clearance through the mononuclear phagocyte system, nonspecific protein adsorption, and reduced time of circulation for all therapeutic agents, more so for nanoparticles. Moreover, shear stresses at blood vessels and opsonization also come into confrontation during reduced targeting efficiency. Hence, it raises, very rarely admittedly, the importance of circulation as a potential therapeutic target by contrasting obstacles against describing the capacity of circulating tumor cells and cancers prone to metastasis in overcoming hemodynamic and immune exertions for further disease progression.

Prospects and emerging trends

Personalised nanomedicine

Nanomedicine that is personal to the patient is yet another step forward in cancer therapy to provide treatment methods for every individual using nanoparticle systems equipped for genetic, molecular, and tumour-specific profiles. Personalised nanomedicine thus amalgamates genomic, proteomic, and metabolomic data for the optimal selection of drug compounds, doses, and delivery systems for maximum therapeutic effect, combined with the least side effects. Understandably, nanoparticles are smartly directed towards specific biomarkers and unique TME or switched to be triggered under stringent conditions for drug release.[111]

Future perspectives of artificial intelligence and machine learning

Artificial Intelligence and Machine Learning promise to achieve rapid advances in precision nanomedicine by supporting the development of sophisticated algorithms with massive data sets (genomic profiling, tumour biomarkers, imaging data, clinical outcomes) aimed towards the design of the most individualised patient-specific nanoparticles. They would determine what common principles would govern particle size, surface chemistry, and the optimum combination of ligands to create the most refined potential DDS, which would define computer-adaptive strategies to maximize the selectivity for tumours while minimizing off-target effects. The computer-assisted strategies will also employ ML models that can predict profiles of drug release, biodistribution, and eventually toxicity of "safer" and "more efficacious" formulations.[112]

Artificial Intelligence grapples with molecular signatures that will one day allow disease detection and identify nanocarriers that may be directed against these unique receptors or microenvironmental target characteristics in

tumors. Real-time patient-based data will be fed into the computational models so that every treatment plan can also be directed to a truly tailored single-target precision personalisation effort, adding unique therapeutic accuracy and improved clinical performance in outcomes.[113]

Future perspectives of nanorobotics and intelligent drug delivery

Nanorobotics has recently emerged, possibly from the expansive applications of precision medicine, into its orbit of focus possibilities, narrowing toward anti-cancer applications. However, as of yet, no such reports have emerged concerning any clinical translation of such autonomous nanoscale machines with the ability to perform complex decisions *in vivo*. On the contrary, however, much promise for the future is seen through the progress of nanofabrication, stimulus-responsive materials, and bioengineering, which augurs well for the actual construction of these nanorobotic systems. Such early primitive conceptual designs should respond to local biological clues like pH, enzymatic activity, or tumor-associated biomarkers for the site-specific triggering of active drug release. Things such as autonomous navigation, biological signal processing, and decision-making for therapeutics are useful applications that can be envisioned for nanorobots. Most of these applications remain largely hypothetical and are hindered by considerable technical, safety, and regulatory factors.

The proof-of-concept developed so far also claims to act as an intelligent drug-delivery system for experimental purposes, holding both the sensing and actuation features within a nanoparticle or micro-and nano-systems' stimuli-responsive capability. Such platforms allow the CR of drugs under some external stimuli; they could probably be made adaptable in real-time to certain variations in TME conditions. External systems' localization and penetration, which act, attract, or are guided by either magnetic fields or ultrasonic waves, remain largely preclinical.

Theranostics (combined therapy and imaging)

This venture puts therapy and diagnosis together in one sector, a treatment and monitoring of a disease. The agents used shall perform for the dual function of imaging and providing therapy (e.g., in case of nanoparticles, MRI-visible diagnostics, and loaded with therapeutic drugs).[114] Thus, tracking in real-time treatment response.

Theranostic application of designed nanoparticles

Nanoparticles have displayed immense potential in cancer treatment modalities involving tumor selectivity, radiosensitization, and treatment monitoring, to name a few. Engineered nanoparticles, by their very design impacting theranostics, are also expected to gain utility based on their ability to enhance therapeutic results.

For example, gold high-Z metal and hafnium oxide, when used as radiosensitizers in nanoparticle conjunction treatments, either extract extra local radiation or generate ROS to collect additional DNA damage in tumor cells. These therapeutic modalities, which are co-formulated with radiotherapy, are done so in many ways, for instance, through time-release with chemotherapeutics or by co-loading molecular inhibitors along with concurrent lesions generated by radiation-induced cytotoxicity and synergistic tumor control. Such methods drop off substantially with respect to non-targeted toxicity.

On such a basis of theranostic application, the nanoparticles will link their imaging modalities to their therapeutic payloads. Where gold and bismuth nanoparticles represent CT contrast, iron oxide nanoparticles facilitate MRI, while radionuclide-labeled nanocarriers will even be visualizable by positron emission tomography (PET)/ single-photon emission computed tomography (SPECT). Having been endowed with this imaging ability would lend to accurate tumor localization, thereby paving the way for treatment planning and thorough monitoring of biodistribution and accumulation of nanoparticles.

Theranostic nanoparticles would therefore be activated to release their radiosensitizers or drugs dependent on localized changes in pH, hypoxia, or enzyme activity to create real-time imaging feedback on therapeutic activation. Radiotherapy could gain extended time availability otherwise rendered unattainable through immunomodulation and imaging of nanoparticles, thus offering a robust platform to explore pathways of immune activation as well as prediction of possible abscopal effects.

It follows, therefore, that theranostic nanoparticles would enhance combination radiotherapy under a truly targeted treatment paradigm through imaging-guided administration and an unprecedented level of process observation from a real-time vantage point in precision safety and personalization for cancer treatment.

Conclusion

Nanotechnology-based systems for targeted, controlled, and personalized drug delivery have created a new method of cancer treatment, which enables doctors to deliver drugs directly to tumors while enhancing the effectiveness and decreasing overall body harm. The implementation of tumor microenvironment-sensitive nanocarriers together with multimodal therapeutic methods has reached a point of drug delivery improvement, which creates strong possibilities for medical use. The process of developing large-scale clinical applications faces ongoing difficulties because of tumor heterogeneity, tissue penetration limits, immunogenicity factors, and the challenges of manufacturing and regulatory requirements. The research work needs to establish valid processing methods that will help scientists create nanomedicine-based treatment methods. Researchers should continue developing advanced nanocarrier systems, which will help them move their findings from the laboratory to clinical use in order to create more effective, patient-specific treatments for cancer.

Authors' Contribution

Conceptualization: Hindustan Abdul Ahad.
Data curation: Hindustan Abdul Ahad.
Formal analysis: Hindustan Abdul Ahad.

Investigation: Hindustan Abdul Ahad.
Methodology: Hindustan Abdul Ahad.
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Competing Interests
The authors declare that they have no competing interests.

Data Availability Statement
Data supporting this study are included within the article.

Declaration of AI-Assisted Tools in the Writing Procedure
The authors declare that generative AI was used in the creation of this manuscript. During the preparation of this work, the authors used Perplexity in order to improve the writing process and to enhance the readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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