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Review Article

Nanotechnology in Cancer Drug Delivery

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ABSTRACT

Cancer treatment is often limited by the inability to deliver an effective drug concentration to malignant tissue without damaging healthy organs. Many anticancer medicines have poor water solubility, are rapidly removed from the circulation, or cause serious adverse effects because they distribute throughout the body. Nanotechnology offers a way to modify drug delivery by packaging medicines in very small carriers and controlling their circulation, tissue distribution and release. This review summarizes the main biological barriers encountered by nanoparticles, important lipid, polymeric, inorganic and biomimetic carrier systems, and methods used to target tumors. It also discusses carriers that respond to changes in pH, redox state, enzymes, temperature, light or ultrasound. Current applications include delivery of conventional anticancer drugs, immunemodulating agents, RNA and gene-editing systems, as well as combined imaging and treatment. Clinically used products demonstrate that nanocarriers can improve formulation properties and, in selected settings, reduce toxicity or improve therapeutic performance. However, variable tumor accumulation, immune recognition, manufacturing complexity, long-term safety and patient-topatient differences remain important obstacles. Better biological models, quality control, companion diagnostics and data-guided formulation design may help translate promising systems into reliable treatments.

INTRODUCTION

Cancer is a group of diseases in which abnormal cells grow without normal control and may invade nearby tissues or spread to distant organs. Surgery, radiotherapy, chemotherapy, targeted medicines and immunotherapy are used according to cancer type and stage. Although these approaches have improved outcomes, systemic anticancer treatment can be difficult because many drugs affect healthy cells as well as tumor cells. Bone marrow, intestinal lining and hair follicles are particularly sensitive to medicines that damage rapidly dividing cells. Several anticancer drugs are poorly soluble in water. To prepare injectable

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formulations, conventional products may require solvents or surfactants that can contribute to infusion reactions and other adverse effects. Free drug molecules may also be cleared quickly, metabolized before reaching the tumor, or distributed to tissues that do not require treatment. These limitations can reduce the amount of active drug reaching cancer cells while increasing toxicity. 1Nanotechnology applies materials and structures at the nanometre scale to pharmaceutical delivery. Nanocarriers can encapsulate a drug, attach it to a carrier surface, or associate with it through chemical or physical interactions. Their size and surface properties can be adjusted to influence drug solubility, circulation time, cellular uptake and release. PEGylated liposomal doxorubicin (Doxil) was an early milestone in clinical cancer nanomedicine. Since then, research has expanded to polymeric particles, lipid nanoparticles, albumin-bound drugs, inorganic materials and cell-derived vesicles. The purpose of this review is to explain the major delivery principles and carrier types in clear, organized form, while outlining clinical examples, limitations and future directions. Nanomedicines should not be considered universally superior to conventional drugs: their value depends on the medicine, carrier design, tumor biology and clinical setting.

2. Biological Barriers to Tumor Delivery

2.1 The CAPIR delivery sequence:

After intravenous administration, a nanocarrier must complete several connected steps: circulation in blood, accumulation at the tumor, penetration through tumor tissue, internalization by target cells and release of the active drug. This sequence is often described as the CAPIR cascade. Failure at any stage can reduce the final therapeutic effect. A carrier that circulates for a long time may still be ineffective if it cannot enter the tumor or release its payload.

2.2 Protein corona and immune clearance

Blood contains albumin, antibodies, complement proteins, lipoproteins and many other molecules. These can rapidly adsorb onto a nanoparticle surface and form a protein corona. The corona changes the biological identity of the particle and may cover targeting ligands that were added during manufacture. When immune proteins mark the particle for removal, macrophages in the liver and spleen can take it up through the mononuclear phagocyte system, also called the reticuloendothelial system. Polyethylene glycol (PEG) is commonly used to create a hydrated surface layer that reduces protein adsorption and slows immune clearance. However, some individuals have pre-existing or treatmentinduced anti-PEG antibodies. These antibodies may contribute to accelerated clearance or complement-related infusion reactions. Alternative surface materials, including zwitterionic polymers, polyglycerols and cell-membrane coatings, are being studied to improve circulation and reduce unwanted immune recognition.

2.3 Passive accumulation and the EPR effect

The enhanced permeability and retention (EPR) effect describes the tendency of some macromolecules and nanoparticles to accumulate in tumors because tumor blood vessels can be abnormal and lymphatic drainage may be poor. In principle, gaps or defects in tumor vessels allow suitably sized carriers to leave the bloodstream and remain in tumor tissue. This mechanism has been important in the development of many nanomedicines. The EPR effect is not uniform. Tumors differ in blood supply, vessel structure, stromal density and lymphatic function. Animal tumor models may show greater vascular leakiness than many human cancers. Clinical imaging has demonstrated substantial variation in nanoparticle accumulation between patients and even between lesions in the same patient. Research also indicates that active transport across endothelial cells, including caveolae-associated transcytosis, may contribute to nanoparticle entry. Therefore, tumor delivery should not be explained by passive leakage alone.

2.4 Tumor penetration and cellular uptake

After reaching tumor tissue, nanoparticles may remain close to blood vessels because of high interstitial fluid pressure, dense extracellular matrix and tightly packed cells. Collagen, hyaluronic acid and other matrix components can restrict movement, especially for larger particles. Strong binding to the first tumor cells encountered can also create a binding-site barrier: carriers are retained near vessels instead of spreading into

deeper regions. Active targeting uses antibodies, peptides, aptamers, folic acid or other ligands to recognize receptors that are more abundant on selected cancer cells or tumor vessels. Examples include folate receptor, transferrin receptor, HER2, integrins and prostate-specific membrane antigen. Targeting ligands can improve cell binding and uptake, but do not automatically increase the total amount of nanoparticle entering a tumor. Once internalized, a carrier may enter endosomes and lysosomes. This is useful for releasing some small-molecule drugs, but nucleic acids often need to escape from endosomes to reach the cytoplasm.

3. Major Nanocarrier Systems

3.1 Liposomes

Liposomes are spherical vesicles made from one or more phospholipid bilayers surrounding an aqueous compartment. Water-soluble drugs can be carried in the inner aqueous space, while lipidsoluble drugs can associate with the bilayer. Their composition, size and surface coating can be adjusted to control stability and drug release. PEG-coated liposomes generally remain in circulation longer than early, uncoated formulations. Doxil is a PEGylated liposomal formulation of doxorubicin used in selected cancers. Encapsulation changes the distribution of doxorubicin and can reduce some dose-related toxicities, including cardiac toxicity, compared with conventional doxorubicin. Onivyde is a liposomal irinotecan formulation. Vyxeos (CPX-351) co-encapsulates cytarabine and daunorubicin at a fixed molar ratio for certain 3forms of acute myeloid leukemia. These products illustrate how liposomes can alter drug exposure or maintain a planned combination ratio.

3.2 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles contain a lipid matrix that remains solid at room and body temperature. They can protect drugs and may offer improved physical stability for some formulations. A limitation is that the lipid matrix can become more ordered during storage and may push the drug out of the particle. Nanostructured lipid carriers combine solid and liquid lipids to create a less ordered matrix, which can provide more space for drug incorporation and reduce drug expulsion.

3.3 Lipid nanoparticles for nucleic acids

Lipid nanoparticles (LNPs) are widely investigated for delivery of mRNA, siRNA and gene-editing components. A typical formulation includes an ionizable lipid, cholesterol, a helper phospholipid and a PEG-lipid. During preparation, the ionizable lipid helps associate with negatively charged nucleic acids. It is designed to be relatively neutral in blood and become positively charged in acidic endosomes, supporting membrane disruption and release of the payload into the cytoplasm. LNPs have enabled clinically important RNA delivery and are being adapted for cancer vaccines and other oncology applications.

3.4 Polymeric nanoparticles and micelles

Polymeric carriers can be made from biodegradable materials such as poly (lactic-co-glycolic acid) (PLGA), polylactic acid (PLA) and polycaprolactone (PCL). Their degradation rate, drug loading and release profile can be modified by changing polymer composition and molecular weight. Polymeric micelles are formed by amphiphilic block copolymers: a hydrophobic inner core can carry poorly soluble drugs, while a hydrophilic outer layer stabilizes the structure in water. A key challenge is preventing micelles from dissociating too early after dilution in blood.

3.5 Dendrimers and polymer–drug conjugates

Dendrimers are highly branched, tree-like polymers with a central core and many terminal surface groups. These groups can be modified to attach drugs or targeting molecules. Their uniform structure is useful for controlled design, but positively charged surfaces may damage cell membranes or blood cells unless carefully modified. Polymer–drug conjugates attach a drug to a water-soluble polymer through a linker. The linker may be designed to break under particular conditions, allowing the active drug to be released after delivery.

3.6 Inorganic nanoparticles

Inorganic materials provide functions beyond drug carriage. Gold nanoparticles can absorb nearinfrared light and convert it into heat for photothermal treatment. Mesoporous silica particles have 4pores that can store drugs and be fitted with gates that open in response to a trigger. Superparamagnetic iron oxide

particles can support magnetic resonance imaging and are studied for magnetic targeting or hyperthermia. Hafnium oxide nanoparticles can act as radiosensitizers by increasing the local physical effects of radiation. Their major concerns include biodegradation, longterm retention and possible toxicity.

3.7 Protein-based and biomimetic carriers

Albumin-bound paclitaxel (nab-paclitaxel; Abraxane) uses human serum albumin as a carrier and avoids the need for the solvent Cremophor EL used in some conventional paclitaxel formulations. Albumin may interact with natural transport pathways in the body. Exosomes and other extracellular vesicles are cell-derived structures that naturally transport biological material. They may be engineered to carry therapeutic molecules, although isolation, purification, variable composition and large-scale production remain difficult. Cell-membrane-coated nanoparticles use membranes from red blood cells, platelets, immune cells or cancer cells around a synthetic core. The coating may provide biological recognition or reduce rapid immune clearance. These systems are promising research platforms, but reproducible manufacturing and control of biological components are essential before broad clinical use.

4. Stimuli-Responsive Nanocarriers

Stimuli-responsive systems are designed to remain relatively stable during circulation and release their payload when they encounter a selected biological or physical trigger. The goal is to reduce premature leakage while improving drug availability at the tumor. Triggering conditions vary between tumors and patients, so the response must be sufficiently reliable and safe.

4.1 Endogenous triggers: pH, redox and enzymes

Tumor tissues and intracellular compartments may be more acidic than blood. pH-sensitive polymers, acid-cleavable linkers and charge-changing coatings can therefore be designed to alter their structure or release a drug in acidic environments. The difference in pH between tumor and normal tissue is often modest, so the carrier must be carefully tuned to avoid unwanted release. The cytoplasm generally contains more reduced glutathione than the extracellular environment. Disulfide-containing linkers can be cleaved under reducing conditions, helping release a drug after cellular uptake. Other chemical groups respond to reactive oxygen species. Enzyme-responsive systems use molecules that can be broken down by enzymes found at elevated levels in some tumors, such as matrix metalloproteinases or cathepsins. Enzyme-cleavable linkers can be used to release drugs or to break larger particles into smaller units that penetrate tissue more effectively. Hypoxic regions have low oxygen availability and may contain enzymes capable of reducing specially designed chemical groups. Hypoxia-responsive carriers aim to release drugs in these difficult-to-treat regions. However, oxygen levels and enzyme activity vary across tumors, which can affect performance.

4.2 Exogenous triggers: heat, light and ultrasound

External physical triggers provide an opportunity to control where and when drug release occurs. Thermosensitive liposomes can release their payload when heated locally, for example by focused ultrasound or radiofrequency methods. Light-sensitive carriers may use near-infrared light to activate photosensitizers, generate heat or break light-sensitive bonds. Ultrasound can produce mechanical effects, improve local permeability or activate phase-change droplets. These techniques require suitable equipment and careful control to limit damage to surrounding tissue.

5. Therapeutic Applications

5.1 Delivery of anticancer medicines

Nanocarriers can improve the formulation of poorly soluble drugs, protect unstable compounds and change drug distribution. Liposomal doxorubicin, liposomal irinotecan and albumin-bound paclitaxel are examples of clinically used formulations. The clinical benefit differs by product and indication; improved formulation does not guarantee a better outcome in every cancer.

5.2 Cancer immunotherapy and vaccines

Nanoparticles can deliver immune-stimulating molecules to tumor tissue or antigen-presenting cells. Some chemotherapy and photodynamic treatments cause immunogenic cell death, releasing signals that help

immune cells recognize tumor material. Nanocarriers may help localize these effects and reduce exposure of healthy immune tissues. Lipid nanoparticles are also being studied for personalized mRNA cancer vaccines. In such approaches, tumor mutations are analyzed to identify neoantigens, and mRNA encoding selected antigens is delivered to stimulate an immune response. These strategies are generally being evaluated in clinical trials and should not be confused with established standard treatment for all cancers.

5.3 RNA interference and gene editing

Small interfering RNA (siRNA) can reduce the production of a selected protein by directing cellular machinery to degrade a matching messenger RNA. This offers a way to investigate or suppress cancer-related genes that may be difficult to inhibit with conventional drugs. LNPs and polymeric carriers can protect RNA from degradation and help it enter cells. CRISPR/Cas systems are also being explored for cancer research and treatment. Delivery remains challenging because the components must reach the correct cells, escape endosomes and avoid unintended genetic changes.

5.4 Cancer theranostics Theranostic

systems combine diagnostic imaging and treatment in one platform or in closely matched formulations. Imaging can help measure where a carrier travels, whether a tumor takes it up and how treatment changes the target tissue. Fluorescent, magnetic, radioactive and photoacoustic components have been investigated. In the longer term, imaging-based selection may help identify patients whose tumors are more likely to accumulate a particular nanomedicine.

6. Clinical Translation and Examples

Clinical translation has produced several approved nanomedicines, particularly liposomal and albumin-based formulations. Doxil/Caelyx contains liposomal doxorubicin; DaunoXome contains liposomal daunorubicin; Myocet is another liposomal doxorubicin formulation used in some regions. Abraxane is albumin-bound paclitaxel. Onivyde is liposomal irinotecan, and Vyxeos is a liposomal combination of cytarabine and daunorubicin. Hensify (NBTXR3) is a hafnium oxide nanoparticle product used with radiotherapy in selected settings in certain regions. Approval status and indications differ between countries and may change over time. Clinical experience also shows that a promising nanoparticle can fail if the patient group is not selected appropriately or if the carrier behaves differently in humans than in laboratory models. A targeted carrier may require confirmation that its receptor is present in the patient's tumor. A formulation may also release its drug too early, remain trapped near blood vessels or fail to improve a clinically meaningful endpoint. These lessons support the use of biomarker testing, imaging and realistic patient-relevant models during development.

7. Major Challenges and Limitations

7.1 Biological variability

Tumors vary in blood flow, vascular permeability, receptor expression, immune-cell composition, extracellular matrix and oxygen level. A carrier that works well in one tumor model may perform poorly in another. Even multiple lesions in one patient may show different delivery patterns. This variability limits the usefulness of a single universal targeting strategy.

7.2 Manufacturing and quality control

Nanomedicines are complex products. Small changes in mixing speed, temperature, raw materials or process conditions can alter particle size, size distribution, surface charge, drug loading and release. Scale-up from laboratory batches to commercial production must preserve these critical quality attributes. Good Manufacturing Practice (GMP), validated analytical methods, stability testing and reproducible batch records are essential.

7.3 Safety and toxicology

Nanoparticles may accumulate in the liver, spleen or other organs. Their effects depend on composition, size, surface chemistry, dose, route and degradation. Potential concerns include complement activation, infusion reactions, inflammation, oxidative stress and long-term retention of non-biodegradable materials. Safety evaluation should consider both the active drug and the carrier, including repeated dosing and delayed effects.

7.4 Regulatory and economic considerations

Complex nanomedicines can be difficult to compare with conventional generic medicines because particle structure and performance may depend on manufacturing details. Regulators therefore require evidence that the product is consistently manufactured and performs appropriately. Development costs, specialized equipment, cold-chain requirements and complex testing may also affect affordability and access.

7.5 Limitations of current research models

Many early studies use rapidly growing tumors implanted under the skin of laboratory mice. Such models do not fully reproduce the architecture, immune environment or slow development of human cancers. More representative models, including patient-derived systems, orthotopic tumors and carefully designed clinical imaging studies, can provide better information about delivery and treatment response.

8. Future Perspectives

The future of cancer nanomedicine is likely to emphasize precision rather than simply increasing carrier complexity. Companion diagnostics may help identify tumors with suitable receptor expression, vascular access or nanoparticle uptake before treatment. Imaging with magnetic or radioactive tracers could support patient selection and help monitor delivery. Such approaches may reduce exposure of patients who are unlikely to benefit. Artificial intelligence and machine learning can analyze relationships between formulation composition, manufacturing conditions and biological performance. High-throughput screening and in vivo barcoding methods may compare many formulations more efficiently than traditional one-byone testing. Predictive models could assist in selecting lipid structures, polymer composition, particle size and surface properties. These tools will be most useful when trained on reliable experimental and clinical data. Other promising directions include biodegradable inorganic materials, biomimetic carriers, multistage particles that change size inside tumors, and combinations of nanomedicine with radiotherapy or immunotherapy. Translation will require simpler and more reproducible designs, clear clinical advantages, appropriate patient selection and long-term safety evidence.

CONCLUSION

Nanotechnology has expanded the possibilities of cancer drug delivery by changing how medicines are formulated, transported and released. Liposomes, lipid nanoparticles, polymeric systems, inorganic particles, albumin carriers and cell-derived vesicles each offer distinct advantages. Stimuliresponsive platforms and nucleic-acid delivery may enable more controlled and specialized treatments. Clinical products such as liposomal doxorubicin, albumin-bound paclitaxel, liposomal irinotecan and Vyxeos demonstrate that selected nanomedicines can provide practical benefits. Important barriers remain, including uneven tumor accumulation, protein-corona formation, immune clearance, limited tissue penetration, manufacturing complexity and uncertain long-term effects. Nanotechnology is therefore not a replacement for clinical judgment or established cancer care. Its greatest future value will come from matching a well-characterized carrier to the right drug, tumor biology and patient, supported by reliable manufacturing, diagnostics and clinical evidence.

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