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NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 3: Types of Nanoparticles Used in Cancer Therapy

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Abstract

Cancer therapy continues to be challenged by tumour heterogeneity, systemic toxicity, multidrug resistance, inadequate drug penetration and biological barriers. Nanoparticle-based drug-delivery systems have therefore attracted considerable interest because their size, surface chemistry, composition and architecture can be engineered to influence pharmacokinetics, biodistribution, tumour accumulation and intracellular delivery. This chapter reviews the major nanoparticle platforms investigated in cancer therapy, with emphasis on organic systems such as polymeric nanoparticles, dendrimers, liposomes, solid lipid nanoparticles, nanoemulsions and cyclodextrin nanosponges, and inorganic systems such as carbon-based nanoparticles, quantum dots, metallic nanoparticles, magnetic nanoparticles and silica nanoparticles. The principles of passive and active tumour targeting are discussed, including the enhanced permeability and retention effect, ligand–receptor-mediated uptake and interactions with the tumour microenvironment. The potential of nanoparticles to improve drug exposure, facilitate combination therapy, address multidrug resistance and assist delivery across difficult biological barriers is also considered. Finally, the chapter summarizes the biological, technological, manufacturing and study-design challenges that limit clinical translation and outlines future opportunities for safer, more predictable and patient-oriented cancer nanomedicine.

Keywords: Nanoparticles; Cancer therapy; Targeted drug delivery; Tumour microenvironment; Nanomedicine; Multidrug resistance.





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1. Introduction

Cancer comprises a broad group of diseases characterized by uncontrolled proliferation of abnormal cells, invasion of surrounding tissues and, in many cases, metastasis to distant organs. Cancer development is influenced by interactions among genetic susceptibility, environmental exposures, ageing and lifestyle-associated factors. Genetic alterations involving DNA-repair pathways, tumour-suppressor genes and proto-oncogenes contribute to malignant transformation, while inherited predisposition accounts for a proportion of cancers that varies with tumour type and the definition of hereditary disease [1,2].

Environmental and behavioural risk factors, including tobacco exposure, unhealthy diet, obesity, physical inactivity, alcohol consumption, radiation and exposure to carcinogenic agents, contribute to the global cancer burden. The World Health Organization has highlighted the continuing growth of cancer incidence and the need for effective prevention, diagnosis and treatment strategies [3]. Increasing age is also a major determinant of cancer risk because the cumulative acquisition of molecular and cellular alterations increases over time.

Current cancer-management strategies include surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy and endocrine or hormone therapy. These approaches have substantially improved outcomes for many malignancies, but limitations remain, including systemic toxicity, incomplete tumour selectivity, treatment resistance, heterogeneous responses and disease recurrence [4-7]. These limitations have stimulated interest in drug-delivery systems that can alter the pharmacokinetic profile of anticancer agents and preferentially expose tumour tissue or tumour cells to therapeutically relevant concentrations.

Nanoparticle-based delivery is one such strategy. By combining a drug or biological payload with an engineered carrier, nanoparticles can modify solubility, stability, circulation, cellular uptake and release behaviour. The approach does not eliminate all of the limitations of conventional therapy, but it provides a platform for integrating targeting ligands, stimuli-responsive release, combination therapy and imaging functions within a single nanoscale construct.

2. Nanoparticles for Cancer Therapy

Precision cancer medicine seeks to match therapy with tumour biology while limiting damage to healthy tissues. However, tumour heterogeneity, multidrug resistance, variable target expression, limited penetration into solid tumours and toxicity remain important barriers to successful treatment [8,9]. Immunotherapy has produced durable responses in selected cancers, but immune-related adverse events and the immunosuppressive tumour microenvironment may limit treatment benefit in other patients [10-12]. The extracellular matrix of solid tumours can further restrict the transport and migration of immune cells and therapeutic agents.

Nanoparticles can provide several complementary advantages. They may protect a payload from premature degradation, extend circulation, alter biodistribution, increase local or intracellular drug exposure and support controlled release. Surface engineering can be used to





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modulate interactions with plasma proteins and phagocytic cells, while ligands can be incorporated for cell-selective binding [13-15]. Nevertheless, nanoparticle delivery is dependent on the composition and architecture of the carrier, the physicochemical properties of the drug, the route of administration and the biological characteristics of the patient and tumour.

The value of nanomedicine is therefore best understood as a formulation strategy rather than as a universal targeting mechanism. A successful nanoparticle system must achieve a clinically meaningful balance between drug loading, stability, circulation, tissue penetration, cellular uptake, controlled release, manufacturability and safety.

3. Nanoparticles

Nanoparticles are commonly described as materials with at least one dimension in the nanoscale range, often approximately 1–100 nm, although the practical definition used in biomedical research can depend on the material and intended application. Nanomaterials may also be categorized according to dimensionality as zero-, one-, two- and three-dimensional structures [17]. In drug delivery, nanoparticles may exist as solid particles, vesicles, branched macromolecules, porous materials or composite structures.

The small size and high surface-to-volume ratio of nanoparticles allow the surface to be functionalized with polymers, targeting ligands, imaging agents or other components. These changes can alter protein adsorption, cellular interactions, circulation half-life and tissue distribution [15,22,23]. Polyethylene glycol (PEG), for example, is frequently used as a hydrophilic surface modifier to reduce nonspecific interactions and delay clearance by phagocytic systems, although PEGylation can also introduce formulation- and patient-dependent limitations.

An important concept in cancer nanomedicine is the enhanced permeability and retention (EPR) effect. Abnormal tumour vasculature and impaired lymphatic drainage can permit the accumulation of some nanoscale carriers within tumour tissue. However, the magnitude of the EPR effect is highly variable and should not be treated as a uniform property of all human tumours [26-25]. Particle size, shape, surface properties, circulation time, tumour vascularity, extracellular matrix density and interstitial fluid pressure all influence nanoparticle transport and retention.

4. Mechanisms of Nanoparticles for Cellular Targeting

Effective tumour delivery requires nanoparticles to navigate a sequence of biological barriers, including vascular transport, protein adsorption, clearance, extravasation, diffusion through the tumour interstitium, cellular uptake and intracellular trafficking [18-21]. These processes are governed by both carrier properties and tumour biology. Accordingly, a nanoparticle designed for cancer therapy should ideally show sufficient stability in the circulation, controlled interactions with the mononuclear phagocyte system, appropriate tumour accumulation, effective penetration and efficient intracellular drug release [20-23].





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4.1 Passive Targeting

Passive targeting relies on pathological features of tumour tissue rather than on a specific ligand–receptor interaction. Solid tumours frequently contain abnormal, tortuous and heterogeneous blood vessels with altered permeability. Together with impaired lymphatic drainage, these characteristics can favour the extravasation and retention of appropriately designed macromolecules and nanoparticles within some tumours.

The EPR effect is the classical mechanistic framework for passive tumour targeting. Its magnitude, however, varies substantially between experimental models and patients. Tumour type, vascular permeability, stromal composition, interstitial pressure, nanoparticle size, shape, surface chemistry and circulation time can all influence the degree of accumulation [26,27]. Consequently, passive targeting should be regarded as a probabilistic and tumour-dependent process rather than a guaranteed delivery mechanism.

The tumour microenvironment can also be used to design stimuli-responsive carriers. Altered tumour metabolism may produce a relatively acidic extracellular environment, and differences in pH between tumour-associated compartments and normal tissues can be incorporated into pH-sensitive formulations. Such systems can be designed to change particle stability, membrane permeability or drug release under acidic conditions [42,43]. Fig.1 illustrates the conceptual difference between nonspecific passive accumulation and cell-selective active targeting.

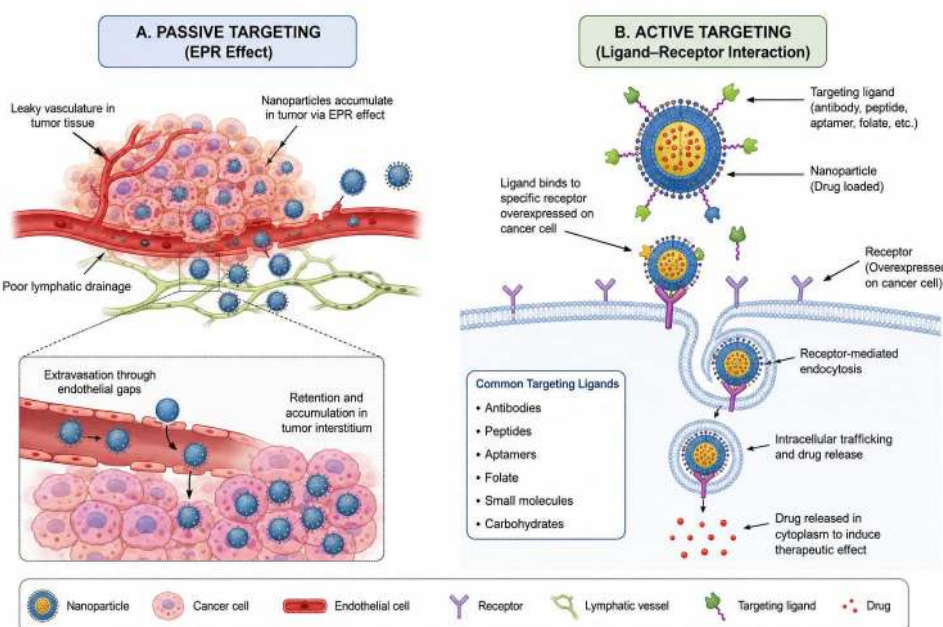


Fig.1 Conceptual representation of passive and active cellular targeting by nanoparticles





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4.2 Active Targeting

Active targeting involves the attachment of a ligand to the nanoparticle surface to promote recognition by a receptor expressed or overexpressed on selected cells. Commonly investigated ligands include antibodies, peptides, aptamers, proteins, carbohydrates and small molecules such as folic acid. Following ligand–receptor binding, the nanoparticle may undergo receptor-mediated internalization, potentially increasing intracellular drug delivery [29-33].

Transferrin and transferrin-receptor-mediated delivery have been extensively investigated because the transferrin receptor participates in iron uptake and can be increased in rapidly proliferating cells. Transferrin-functionalized nanocarriers may therefore exploit receptor-mediated uptake to improve the intracellular delivery of therapeutic agents [34-36].

Folate is another widely studied targeting ligand. Folate receptors, particularly folate receptor-alpha, are expressed at elevated levels in several malignancies, and folate-functionalized nanoparticles can bind these receptors and undergo receptor-mediated endocytosis [32-38]. Other approaches target receptors associated with tumour vasculature and angiogenesis. Such strategies may affect the supporting vascular compartment in addition to, or instead of, the malignant cells themselves [39, 40].

Active targeting should not be interpreted as a mechanism that automatically dictates whole-body biodistribution. Ligand density, receptor expression, binding affinity, accessibility of the target, nanoparticle size, surface chemistry, protein corona formation and route of administration all influence targeting performance [30,33]. The multivalent nature of nanoparticles may strengthen overall surface interactions, but excessive ligand density can also alter colloidal stability, protein adsorption or clearance.

5. Nanoparticles in Cancer Therapy

Nanoparticle systems used in cancer delivery can be grouped broadly into organic nanoparticles, inorganic nanoparticles and hybrid systems. The principal platforms discussed in this chapter are summarized in Fig.2.





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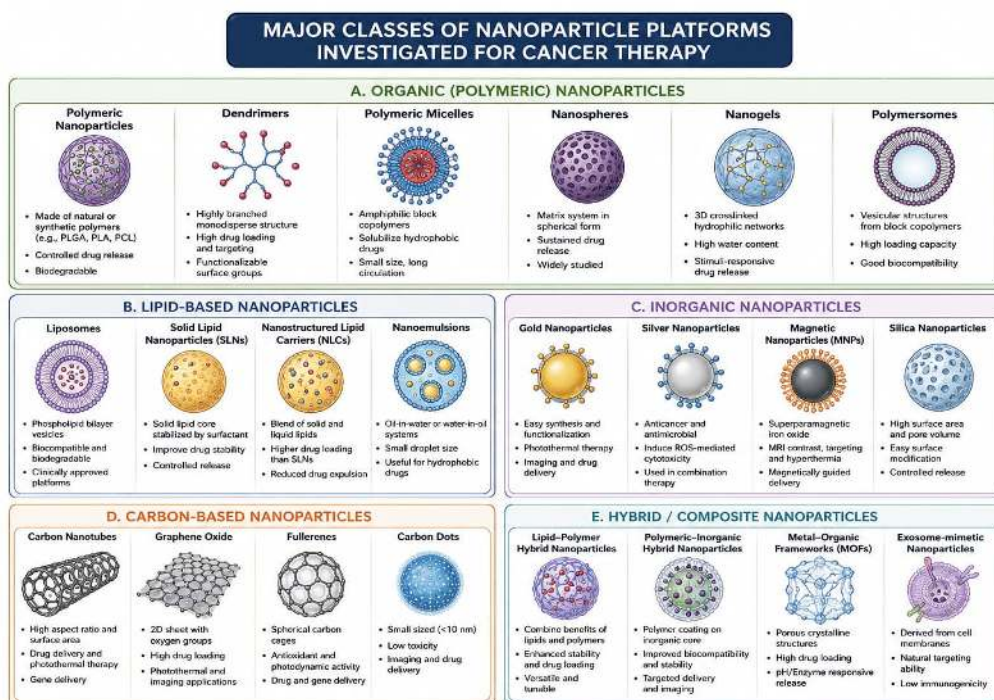


Fig.2. Major Classes of nanoparticle platforms investigated for cancer therapy

5.1 Organic Nanoparticles

5.1.1 Polymeric Nanoparticles

Polymeric nanoparticles are colloidal systems in which the therapeutic agent can be encapsulated within a polymeric matrix, embedded in a core, adsorbed onto the surface or chemically linked to the carrier. Early systems employed non-biodegradable polymers such as polystyrene and polymethylmethacrylate, whereas current biomedical development often emphasizes biodegradable and biocompatible materials, including poly(lactic acid), poly(amino acids), chitosan, alginate and albumin [44,46].

The polymer composition and particle architecture can be adjusted to control drug loading, degradation and release. Surface modification may alter protein adsorption and cellular interactions. Polymer-based nanocarriers have also been investigated for delivery across difficult biological barriers, although performance depends strongly on particle size, surface chemistry and the biological environment.

5.1.2 Dendrimers

Dendrimers are highly branched, approximately spherical macromolecules with a central core, repeated branching units and a high density of terminal surface groups. Their defined architecture and large number of modifiable end groups allow researchers to attach drugs,





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nucleic acids or targeting ligands. Polyamidoamine (PAMAM) and polypropyleneimine (PPI) are among the best-known dendrimer families used in nanomedicine research [45,46].

Generation, size, surface charge and terminal-group chemistry can be adjusted to influence drug loading and cellular interactions. At the same time, cationic surfaces may increase nonspecific interactions and toxicity, making careful surface engineering and biological evaluation essential.

5.1.3 Liposomes

Liposomes are spherical vesicles surrounded by one or more phospholipid bilayers and enclosing an aqueous internal compartment. Their amphiphilic architecture allows them to carry hydrophilic compounds within the aqueous phase and hydrophobic compounds within the lipid bilayer. Their biological compatibility, formulation flexibility and capacity for surface modification have supported the development of clinically relevant liposomal medicines [44-46].

Liposomes can improve apparent drug solubility, alter distribution and reduce exposure to some non-target tissues. However, leakage, aggregation, oxidation, limited loading for some drugs and uptake by phagocytic cells may affect performance. Long-circulating and ligand-functionalized liposomes have therefore been investigated to improve delivery.

5.1.4 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are lipid-based colloidal carriers in which the drug is associated with a solid lipid matrix or core. Typical components may include triglycerides, fatty acids, waxes, steroids and other physiologically compatible lipids, together with emulsifiers or surfactants [47].

SLNs can offer biocompatibility, protection of labile compounds and sustained or controlled release. Their limitations include restricted drug loading for some compounds, potential drug expulsion during lipid crystallization and physical instability. These characteristics need to be considered during formulation development and storage.

5.1.5 Nanoemulsions

Nanoemulsions are dispersions of immiscible phases with nanometre-to-sub micrometre droplet sizes. Common forms include oil-in-water, water-in-oil and bicontinuous systems. They can improve the dispersion of poorly water-soluble compounds and may serve as platforms for surface modification or combination delivery [44,47].

Preparation may involve high-energy processes such as high-pressure homogenization or microfluidization. These methods can improve droplet uniformity but may require specialized equipment and careful control of temperature and processing conditions. Long-term stability, coalescence and chemical degradation of susceptible components should also be assessed.





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5.1.6 Cyclodextrin Nanosponges

Cyclodextrin nanosponges are cross-linked cyclodextrin-based porous systems that provide cavities and a network capable of accommodating poorly soluble molecules. They have been investigated for improving drug solubility, stability and controlled release. Examples include paclitaxel-loaded beta-cyclodextrin nanosponges and systems designed to improve the solubility of camptothecin [48].

5.2 Inorganic Nanoparticles

5.2.1 Carbon Nanoparticles

Carbon-based nanomaterials include graphene and graphene oxide, carbon nanotubes, fullerenes and related structures. Their optical, mechanical, electrical and surface properties have encouraged investigation in imaging, drug delivery and photothermal or other therapeutic approaches. Graphene-based materials can interact with aromatic drug molecules through pi-stacking and can be functionalized with additional chemical groups [49].

Despite these advantages, the biological fate and safety of carbon nanomaterials depend on their dimensions, purity, surface chemistry, dose and route of administration. Long-term accumulation, inflammatory responses and reproducibility of functionalized materials remain important considerations.

5.2.2 Quantum Dots

Quantum dots are nanoscale semiconductor or carbon-based materials with distinctive optical properties, including broad absorption and relatively narrow, tunable emission. These characteristics have made them useful for fluorescence imaging and tracking. Carbon-related forms include graphene quantum dots and carbon quantum dots, while other quantum dot compositions are based on semiconductor materials [49].

In cancer research, quantum dots have been explored for imaging, theranostics and targeted delivery. Their potential usefulness must be balanced against concerns related to composition, stability, surface coating, biodistribution and possible toxicity of certain semiconductor components.

5.2.3 Metallic Nanoparticles

Metallic nanoparticles, including gold-, silver-, copper- and iron-containing systems, exhibit optical, electrical, magnetic or catalytic properties that can be exploited in diagnostics and therapy. Gold nanoparticles can be functionalized with drugs, polymers or targeting ligands, while nanoscale metal structures can also support imaging and Photothermal approaches [49, 50].

The ability to tune metal nanoparticle size and surface chemistry has supported investigations in targeted delivery and combination therapy. However, surface coatings, oxidation state,





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particle dissolution, accumulation and clearance can strongly influence safety and should be included in formulation characterization.

5.2.4 Magnetic Nanoparticles

Magnetic nanoparticles are commonly based on iron oxides or other magnetic materials and may be coated with polymers, lipids or other stabilizing layers. Their response to an external magnetic field can support magnetic resonance imaging, magnetic guidance and magnetic hyperthermia. Functionalization with targeting ligands has also been investigated for tumour-selective delivery [50].

Magnetic hyperthermia uses alternating magnetic fields to generate heat within magnetic nanoparticles, providing a way to damage tumour cells or enhance other therapies. The clinical value of magnetic systems depends on magnetic properties, heating efficiency, particle distribution, field parameters, safety and reproducibility.

5.2.5 Silica Nanoparticles

Silica nanoparticles, particularly mesoporous silica nanoparticles, provide high surface area, tunable pore structures and modifiable surfaces. They have therefore been investigated for drug loading, gene delivery, immunotherapy and stimuli-responsive release. Surface functionalization with amino-silane chemistry can modify cellular interactions and nucleic-acid loading, while mesoporous structures can accommodate small-molecule drugs [51,60].

Stimulus-responsive mesoporous silica systems are being explored for tumour and brain-tumour delivery, where changes in pH or other local conditions can be used to trigger release. Nevertheless, particle degradation, clearance, pore accessibility, surface chemistry and long-term safety remain important translational questions [51,60].

5.2.6 Hybrid Nanoparticles

Hybrid nanoparticles combine two or more material classes to integrate complementary functions. Organic components may provide biocompatibility, drug encapsulation or responsive release, whereas inorganic components may provide imaging, magnetic response or photothermal activity. The concept is attractive for multifunctional and theranostic systems, but the added structural complexity can increase characterization, manufacturing and regulatory requirements.

6. Mechanism of Nanoparticles in Overcoming Drug Resistance

Drug resistance is a major reason for treatment failure in oncology and can be broadly described as intrinsic or acquired. Intrinsic resistance reflects pre-existing biological features that reduce treatment sensitivity, whereas acquired resistance emerges during treatment through additional genetic, epigenetic or microenvironmental changes. Mechanisms include drug efflux, altered





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drug targets, impaired apoptosis, enhanced DNA repair and protective interactions with the tumour microenvironment.

Nanoparticles may help address resistance by increasing drug concentrations at the target site, improving cellular uptake, bypassing some efflux mechanisms, protecting labile payloads and enabling co-delivery of multiple agents. Co-encapsulation of drugs with complementary mechanisms can be particularly useful when resistance arises from more than one biological pathway. Targeting ligands and stimulus-responsive release may further increase intracellular exposure or alter the spatiotemporal distribution of therapy [8,10,16,52].

The potential mechanisms by which nanocarriers can counteract resistance are illustrated in Fig. 3.

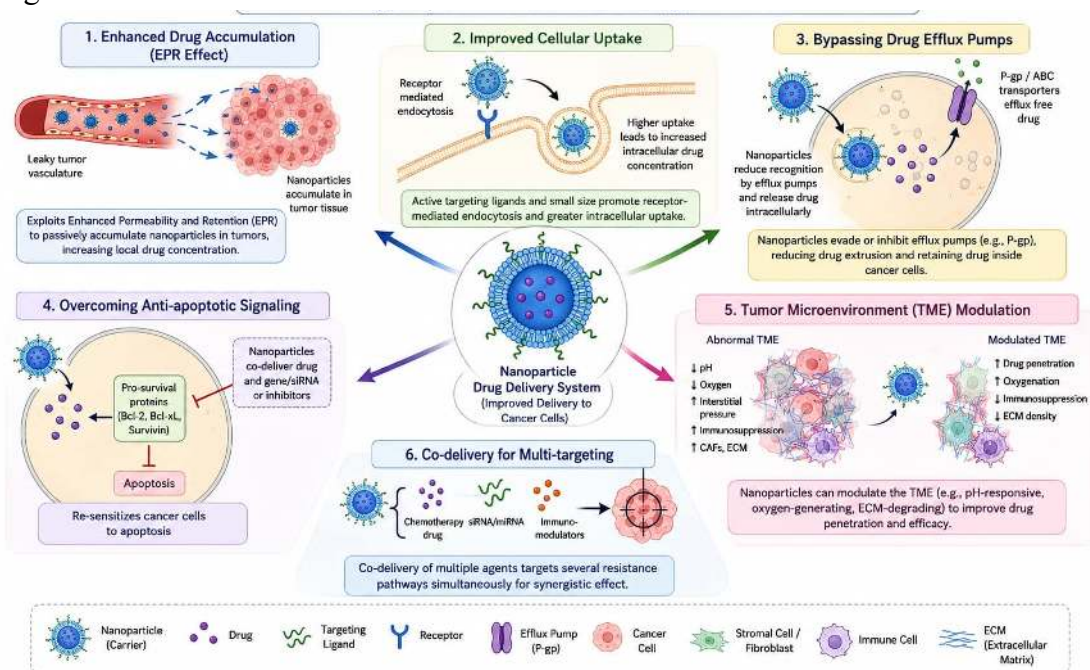


Fig.3 Conceptual mechanisms by which nanoparticle delivery may help overcome cancer drug resistance.

7. Advantages of Nanoparticles in Cancer Therapy

Nanoparticles can modify several properties of anticancer drugs, including apparent solubility, stability, circulation time, tissue distribution and intracellular concentration. Surface engineering can be used to modulate interactions with plasma proteins and phagocytic cells, while ligands can be added to promote cell-associated recognition [14,15,18,21].

Stimuli-responsive nanoparticles provide another important advantage. PH-sensitive systems can respond to acidic tumour or intracellular compartments, whereas temperature-responsive and magnetic systems can use externally applied stimuli or local heating to alter drug release.





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These strategies aim to improve spatial and temporal control of therapy rather than relying solely on the intrinsic distribution of a free drug.

Nanoparticles may also support combination therapy, including the co-delivery of small molecules, nucleic acids, imaging agents and immune-modulating components. In principle, a single platform can therefore integrate therapeutic and diagnostic functions. However, the degree of benefit is formulation-specific and must be demonstrated experimentally rather than assumed from nanoparticle size alone.

Biological barriers remain central to cancer drug delivery. The mononuclear phagocyte system can remove nanoparticles from the circulation, while the blood–brain barrier restricts access to brain tumours. Surface modification, receptor-mediated transport and other strategies have been investigated to increase delivery across these barriers [53– 55].

8. Nanoparticles in Cryosurgery

Cryosurgery uses controlled freezing to damage tumour tissue, but excessive freezing can also injure adjacent healthy structures when a tumour is located close to sensitive organs. Nanoparticle-based phase-change materials have been investigated as a way of modifying the thermal environment around the treatment zone.

Microencapsulated phase-change systems, including liposome-based approaches, may provide thermal buffering because of their latent-heat characteristics and low thermal conductivity. In principle, these materials can help protect selected regions from unwanted freezing while allowing the intended tumour-directed treatment to proceed. The concept remains dependent on formulation stability, heat transfer, particle distribution and safe removal after treatment [56].

A conceptual representation of the role of nanoparticle-based phase-change systems in cryosurgery is shown in Fig.4.

9. Significant Challenges in the Clinical Application of Nanoparticles

Despite extensive preclinical research, the clinical translation of nanoparticle systems remains difficult. Major challenges can be grouped into biological, technological/manufacturing and study-design or translational challenges [57–61]. These issues are interconnected: a particle that performs well in a simplified cell model may behave differently in blood, tumour tissue or a patient, and a formulation that is effective at laboratory scale may be difficult to manufacture consistently.





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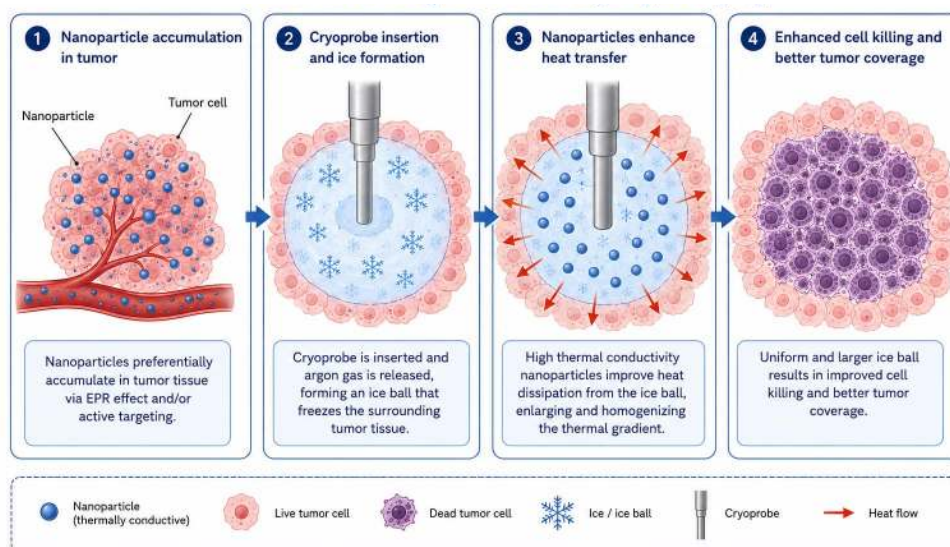


Fig.4 Conceptual representation of nanoparticle-assisted thermal management during cryosurgery

9.1 Biological Barriers

Nanoparticles administered systemically encounter plasma proteins, immune cells and endothelial barriers before reaching the tumour. Opsonization and uptake by phagocytic cells in organs such as the liver and spleen can reduce the fraction available for tumour delivery. After reaching tumour tissue, dense extracellular matrix, elevated interstitial pressure, poor perfusion and heterogeneous vascular permeability can limit penetration. These processes explain why increasing particle circulation time alone does not guarantee efficient tumour delivery [17, 20, 23, 64].

Biological safety is another major concern. Toxicity can be affected by particle size, surface area, shape, solubility, aggregation, composition, dose and route of administration. Oxidative stress, inflammatory responses, immune activation and organ accumulation have been reported for particular nanoparticle classes, emphasizing the need for material-specific toxicological evaluation [58-60].

9.2 Technological and Manufacturing Challenges

Scale-up is a major obstacle because many experimental formulations are developed in small batches using laboratory-scale equipment. Translation to larger manufacturing volumes requires reproducible control of particle size distribution, drug loading, surface properties, sterility, residual solvents, aggregation and stability. Changes in mixing, homogenization, solvent removal or purification can modify the final product. Manufacturing controls and analytical methods therefore need to be established early in development [61,62].





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Predicting *in vivo* performance from physicochemical characterization alone is also challenging. The biological identity of a nanoparticle changes after interaction with proteins and cells, and this dynamic behaviour can affect biodistribution and uptake. Standardized characterization and safety-assessment approaches are consequently important for comparing formulations across laboratories [60,63].

9.3 Study-Design and Translational Challenges

Many nanoparticle studies use simplified two-dimensional cell culture systems or animal models that do not fully reproduce human tumour heterogeneity, extracellular matrix architecture, immune interactions or metastatic disease. Consequently, promising efficacy *in vitro* or in a selected animal model may not translate directly into patients [61,64]. Better model selection, clinically relevant endpoints and appropriate treatment schedules are needed.

Clinical development must also account for patient-to-patient variability in tumour vascularity, receptor expression, immune status, prior treatment and organ function. Personalized nanomedicine could eventually use these variables to select carrier composition or targeting strategies, but this increases the complexity of study design, manufacturing and regulatory control [8,62].

10. Conclusion and Future Perspectives

Nanoparticles provide a flexible platform for cancer drug delivery because their composition, size, surface properties and internal architecture can be engineered for different therapeutic objectives. Organic, inorganic and hybrid systems have all been investigated for improving drug stability, altering pharmacokinetics, enabling targeted uptake, supporting stimulus-responsive release and facilitating combination therapy [14,19,64]. Their potential is particularly relevant to problems such as multidrug resistance, poor tumour penetration and delivery across restrictive biological barriers.

At the same time, nanoparticle accumulation within tumours is heterogeneous, and neither passive EPR-based accumulation nor active ligand targeting should be considered universally reliable. Clinical performance depends on the interplay between carrier design, tumour biology, treatment schedule and patient-specific factors [18,25,64]. Future development should therefore emphasize rational design supported by mechanistic understanding and clinically relevant models rather than relying solely on particle size or *in vitro* cytotoxicity.

Important future directions include multifunctional and theranostic systems, stimulus-responsive carriers, biomimetic platforms, nanocarriers for nucleic-acid delivery and approaches that combine targeted delivery with immune modulation. Advances in precision formulation, predictive modelling and manufacturing science may help connect nanoparticle properties with pharmacokinetic and pharmacodynamic outcomes. However, these innovations





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must be accompanied by rigorous assessment of long-term toxicity, immunogenicity, biodegradation, manufacturing reproducibility and regulatory acceptability [60-64].

The future of cancer nanomedicine will depend not simply on developing more complex nanoparticles, but on designing formulations that solve clearly defined clinical problems with predictable benefit, acceptable safety and scalable manufacturing.

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