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Nanotechnology integration in oncology for advanced nanoparticle based strategies in targeted cancer diagnosis and treatment

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Abstract

Cancer remains a major global health challenge. Conventional therapies are often limited by poor tumor selectivity, systemic toxicity, multidrug resistance, and suboptimal pharmacokinetics. Nanotechnology offers a transformative approach in oncology. It enables targeted drug delivery, controlled or stimuli-responsive release, and multifunctional platforms that combine therapy and diagnostics. Nanoparticles enhance drug solubility, prolong circulation, and improve intracellular uptake. These advances are achieved through passive enhanced permeability and retention (EPR) and active targeting mechanisms. Despite robust preclinical success, clinical translation remains inconsistent. Factors such as pronounced inter- and intratumoral EPR variability, long-term toxicity or biodistribution concerns, immune recognition, and stringent regulatory or manufacturing hurdles contribute to high attrition rates. Approved nanomedicines, such as liposomal doxorubicin (Doxil®) and albumin-bound paclitaxel (Abraxane®), have achieved meaningful clinical impact. Others, such as thermosensitive liposomal doxorubicin (ThermoDox®), have shown variable or limited benefits. This gap highlights persistent differences between promise and performance. This review critically examines nanoparticle synthesis strategies (bottom-up, top-down, microfluidic, and green methods); structural and physicochemical characterization techniques; tumor-targeting mechanisms; and major classes of organic (liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric, micelles, dendrimers), inorganic (carbon-based, metallic, silica, magnetic), and hybrid nanocarriers. Emphasis is placed on mechanistic insights, comparative performance, and translational limitations. Key issues include batch-to-batch variability, lack of standardized nanotoxicology protocols, patient-specific heterogeneity, and regulatory challenges. This review aims to guide the successful integration of nanotechnology into precision cancer therapy.

Keywords Nanoparticles, Nanomedicine, Targeted cancer therapy, Nanoparticle drug delivery

1 Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, accounting for a substantial and growing global disease burden. According to the most recent global estimates, cancer incidence and mortality continue to rise due to population aging, lifestyle factors, and environmental exposures, underscoring the urgent need for more effective and safer therapeutic strategies [1, 2]. Between 2022 and 2050, cancer cases are projected to increase from 10.3 million to 19 million (≥ 84%). Deaths are projected to increase from 5.4 million to 10.5 million (≥ 93%), with a greater than two-fold increase among men aged 65 years and older (≥ 117%) and for low Human Development Index (HDI) and medium-HDI countries/territories (≥ 160%) [3]. Conventional cancer therapies, including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, have significantly improved patient outcomes in many malignancies. However, their clinical efficacy is frequently constrained by fundamental limitations [4]. Systemic chemotherapy often suffers from poor tumor selectivity, resulting in dose-limiting toxicities and narrow therapeutic windows. Many potent anticancer agents exhibit unfavorable pharmacokinetics, rapid clearance, low aqueous solubility, or instability in physiological environments, leading to suboptimal bioavailability and reduced therapeutic efficacy [5]. Moreover, insufficient tumor penetration, off-target accumulation in healthy tissues, and the emergence of multidrug resistance continue to compromise long-term treatment success. Even newer targeted and immunotherapeutic approaches face challenges related to heterogeneous target expression, immune-related adverse events, and limited durability of response across patient populations. These unresolved clinical challenges underscore a critical gap between the intrinsic potency of anticancer agents and their effective delivery to tumor sites. In many cases, therapeutic failure arises not from lack of drug activity but from inadequate biodistribution, insufficient tumor accumulation, or unacceptable systemic toxicity. Addressing these unmet clinical needs has become a central focus in contemporary oncology research, driving the exploration of advanced drug delivery strategies [6].

Nanotechnology is an emerging approach in modern medicine. It enables the development of nanoscale systems that improve drug delivery, enhance therapeutic effects, and reduce toxicity. A nanoparticle (NPs) is a material measuring 1 to 100 nm in size [7]. Its unique properties are due to its small size. A nanocarrier is a nanoscale system designed to transport drugs or diagnostics to target sites in the body. NPs aim to help drugs accumulate more in tumors and enter cells. They leverage natural effects, such as leaky blood vessels, and lock onto targets with specialized molecules. Nanocarriers make it possible to control when drugs are released. They allow multiple treatments at once and can combine treatment and detection tools in a single system.

Nanotechnology-based drug delivery systems have demonstrated significant clinical potential across multiple therapeutic areas. Several nanomedicines have been successfully developed for applications beyond oncology. In ophthalmology, nanomedications like Restasis, Cequa® [8], and Cyclokat® [9] address dry eye syndrome. Durezol combats eye inflammation [10], while Ikervis® is used for acute keratitis [8]. For neurodegenerative conditions, treatments include Riluzole NPs for amyotrophic lateral sclerosis [11], and Glatopa® for multiple sclerosis [12]. Nanomedications such as DepoDur™ [13], and Exparel® [14] have enhanced pain management. The COVID-19 vaccines from

Pfizer–BioNTech and Moderna, utilizing lipid NPs for mRNA delivery, underscore nanotechnology's pivotal role in enhancing vaccine delivery [15].

Despite these advances, cancer remains a key area for nanomedicine. This is due to the complexity of tumor biology, limitations of conventional chemotherapy, and the need for targeted drug delivery strategies that minimize systemic toxicity. As a result, substantial research focuses on developing nanoparticle-based platforms. These aim to improve tumor targeting, enhance drug accumulation within malignant tissues, and overcome biological barriers in cancer therapy [16]. The present review critically examines NPs synthesis approaches, structural and physicochemical characterization, tumor-targeting mechanisms, and major classes of nanocarriers used in cancer therapy, with particular emphasis on translational challenges, regulatory considerations, and future directions for precision oncology.

2 Synthesis of nanoparticles

Various synthesis techniques have been developed to produce NPs with controlled morphology and functionality. These methods are generally classified into, Bottom-Up, Top-Down, Microfluidic and Green methods.

2.1 Bottom-up and top-down method

The bottom-up method, also referred to as constructive synthesis, involves assembling NPs from atoms, ions, or molecules into larger clusters. This method offers precise control over particle size, crystallinity, and chemical composition. Common techniques include sol–gel processing, chemical vapor deposition (CVD), plasma or flame spraying, laser pyrolysis, and various spinning methods [17]. In contrast, the top-down method reduces bulk materials into nanosized particles through physical or chemical means. Both strategies allow fine tuning of NP size, morphology, and surface charge by adjusting parameters such as temperature, reaction time, and energy input [18]. Top-down methods are generally more scalable and straightforward but frequently result in irregular particle shapes, surface defects, and contamination from milling media. Bottom-up methods, on the other hand, typically produce highly uniform particles with well-defined structures, although they often require complex reaction conditions and extensive purification steps. Moreover, the use of organic solvents, surfactants, or reducing agents in bottom-up processes can introduce residual toxicity if not completely removed, raising important biocompatibility and regulatory concerns that must be addressed during formulation and safety evaluation, (Fig. 1).

2.2 Microfluidic-assisted nanoparticle synthesis

Microfluidic techniques overcome several key limitations of conventional bulk synthesis methods by exploiting the small dimensions of microchannels and the resulting high surface-to-volume ratio. These features facilitate rapid and uniform mass transfer, providing superior control over nanoparticle characteristics [20]. Compared to traditional batch processes, microfluidics enables the production of highly stable, uniform, and monodisperse nanoparticles with improved encapsulation efficiency through precise manipulation of channel geometry and fluid flow rates [21]. The operating principle of microfluidic devices relies on the controlled flow of fluids through microscale channels and chambers of defined geometry, often integrating sample preparation, reaction,

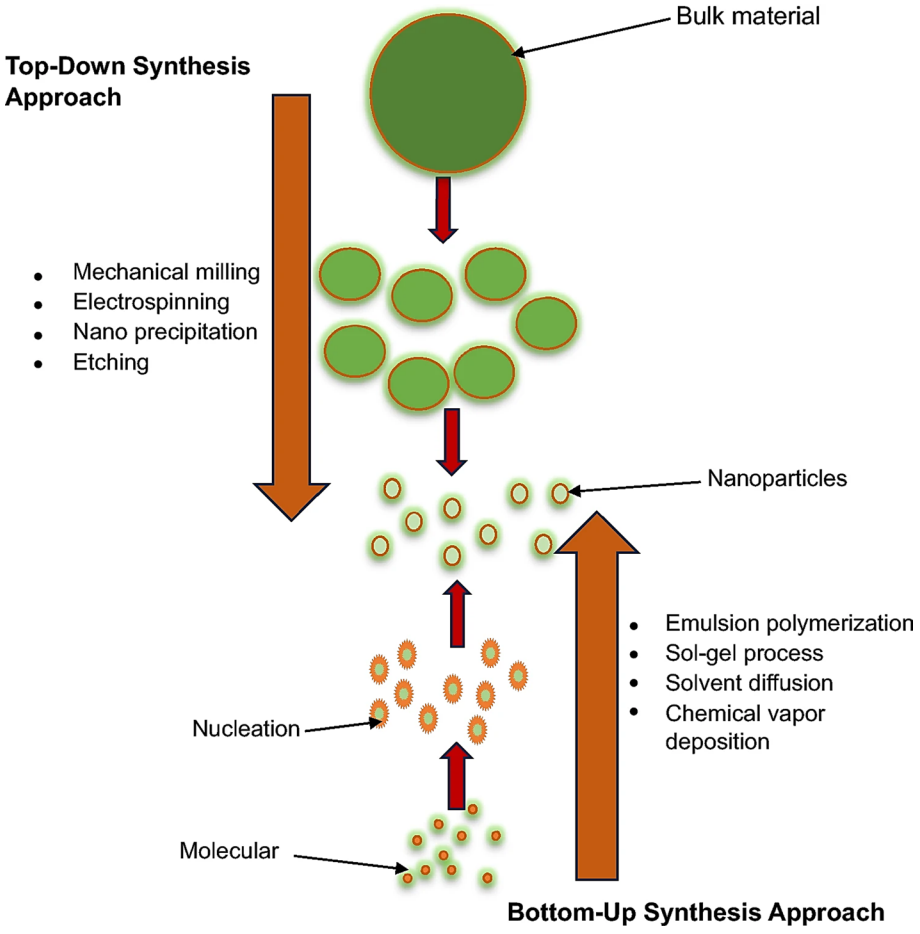

Fig. 1 Schematic illustration of NPs synthesis via top-down and bottom-up methods [19]

separation, and detection steps [22]. Depending on the flow pattern, microfluidic reactors are classified into two main categories: single-phase (continuous-flow microfluidics) and multi-phase (droplet-based microfluidics) systems, (Fig. 2).

2.3 Green synthesis method

Green synthesis is an environmentally friendly, economical, and clean approach to producing NPs using biological entities such as bacteria, yeast, fungi, algae, and plant extracts, as illustrated in (Fig. 3). These natural sources provide inherent reducing, capping, and stabilizing agents while often conferring additional antibacterial properties and minimizing environmental impact. From a regulatory perspective, NPs platforms synthesized via well-defined chemical processes are currently favored. This is due to their reproducibility, scalability, and compatibility with existing pharmaceutical manufacturing frameworks.

Despite these challenges, green-synthesized NPs frequently match or surpass their chemically synthesized counterparts in anticancer performance, often due to smaller particle size, distinct morphology, and enhanced biocompatibility. For example, Ag_2O NPs prepared using Datura innoxia leaf extract exhibited stronger anticancer activity (IC_{50} = 17.908 µg/mL) compared to chemically synthesized Ag_2O (IC_{50} = 23.856 µg/mL) [23]. Similarly, ZnO nanoparticles synthesized with Syzygium aromaticum (clove)

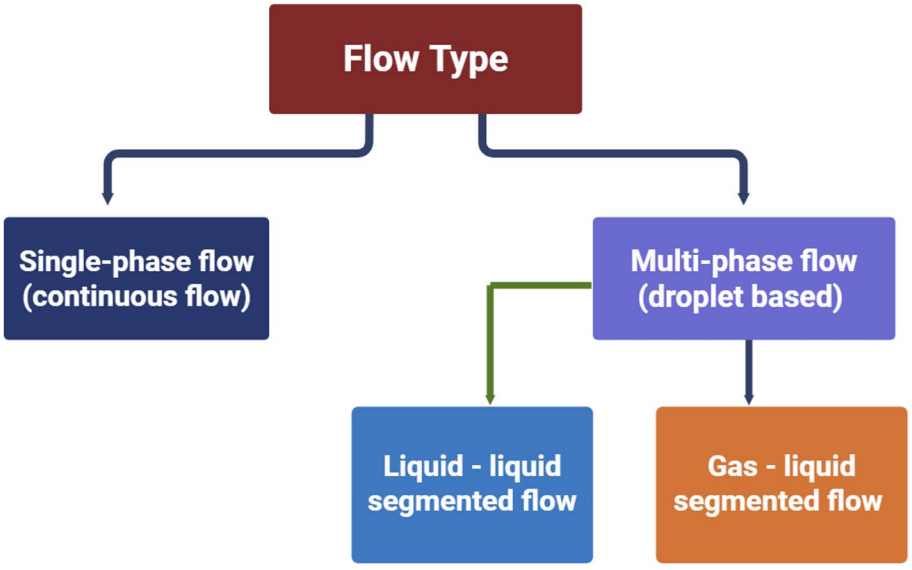

Fig. 2 Microfluidic techniques classification

Fig. 3 Various biological sources for green synthesis of NPs [25]

bud extract (CBE) showed superior cytotoxicity against HNO-97 cells at higher concentrations (IC_{50} = 73.35 µg/mL), likely due to bioactive compounds from the extract adsorbed onto the nanoparticle surface [53]. Bacteria release bioactive substances, such as enzymes, proteins, hormones, ions, polysaccharides, and pigments, which are crucial for NP formation. Sulfur-containing proteins and NADH-dependent reductases contribute to NP stability and reduction [24].

Successful synthesis of NPs with controlled size, morphology, and surface properties is essential for reliable physicochemical and biological performance. These attributes are rigorously evaluated using a suite of complementary characterization techniques, as detailed in the following section.

3 Characterization techniques of nanoparticles

NPs were characterized by using a variety of characterization tools, including X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), Raman spectroscopy (RS), Ultraviolet–visible spectroscopy (UV–vis), X-ray photoelectron spectroscopy (XPS), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Energy-dispersive X-ray spectroscopy (EDX), Brunauer–Emmett–Teller (BET), Zeta potential analysis (ZP), Dynamic Light Scattering (DLS), Vibrating-sample magnetometry (VSM), as shown below and summarized in Table 1.

3.1 X-ray diffraction analysis

XRD is widely used to determine the crystalline structure and phase composition of NPs. In this technique, a sample is irradiated with incident X-rays, and the scattered intensities at various angles are measured [26]. The resulting diffraction pattern reveals lattice spacing and crystallite size through Bragg's law. However, the resolution may decline when analyzing amorphous materials or extremely small NPs composed of only a few hundred atoms [27].

3.2 Fourier-transform infrared spectroscopy

FTIR spectroscopy measures the absorption or transmission of infrared radiation by a sample to identify its molecular bonds and functional groups [28]. Each material produces a characteristic spectrum, serving as a chemical fingerprint. FTIR is particularly useful for evaluating surface functionalization, organic coatings, and impurities, thereby confirming the chemical integrity and bonding environment of NPs systems [29].

Table 1 Nanoparticles characterization techniques in drug delivery and cancer nanomedicine

Technique	Key information provided	Role in cancer nanomedicine	Refs.
XRD	Crystal phase, lattice parameters, and crystallinity.	Determines the physical state of the drug (crystalline vs. amorphous), which affects solubility and release rates.	[49]
FTIR	Functional groups and molecular bonding.	Confirms the successful chemical attachment (conjugation) of targeting ligands or Polyethylene glycol (PEG) coatings to the NPs.	[50]
RS	Molecular vibrations and chemical fingerprints.	Used in SERS for ultra-sensitive detection of cancer biomarkers.	[51]
UV-Vis	Absorbance, concentration, and plasmonic peaks.	Measures drug loading efficiency and monitor the stability of metallic NPs (like gold) used in photothermal therapy.	[52]
XPS	Surface elemental composition and oxidation states.	Analyzes the top 1–10 nm of the NPs surface to ensure chemical purity and proper surface functionalization.	[53]
SEM	Surface topography and morphology.	Evaluates the overall shape and surface texture, which influences how NPs interact with cell membranes.	[54]
TEM	Internal structure, morphology, and actual size.	Provides high-resolution imaging to confirm the precise shape and size required for deep tumor penetration.	[55]
EDX	Elemental mapping and chemical identification.	Confirms the elemental makeup of the NPs (e.g., verifying the presence of silver or iron in a composite carrier).	[56]
BET	Specific surface area and pore size/volume.	Essential for NPs to determine how much internal space is available for drug "loading."	[57]
ZP	Surface charge (electrokinetic potential).	Predicts colloidal stability in the bloodstream and dictates interaction with negatively charged cancer cell surfaces.	[58]
DLS	Hydrodynamic size and Polydispersity Index (PDI).	Measures the "effective" size of the NPs in biological fluids, ensuring it won't be cleared too quickly by the immune system.	[59]
VSM	Magnetic properties (Saturation, Coercivity).	Crucial for magnetic NPs used in targeted drug delivery via external magnets or as MRI contrast agents.	[60]

3.3 Raman spectroscopy

Raman spectroscopy involves the inelastic scattering of monochromatic light, typically from a laser, as it interacts with molecular vibrations within a material. It provides detailed information on molecular structures, chemical bonds, and crystallographic orientation [30]. The enhanced variant, known as surface-enhanced Raman spectroscopy (SERS), significantly amplifies Raman signals, enabling sensitive detection of trace compounds and surface species [31]. Both Raman and SERS are valuable for probing optical and plasmonic properties of metallic NPs [27].

3.4 Ultraviolet–visible spectroscopy

UV–Vis spectroscopy is a simple and widely applied method for evaluating the optical properties of NPs. It measures light absorption or reflectance in the ultraviolet and visible regions, corresponding to electronic transitions between energy states [32]. Absorption peaks provide insights into particle size, bandgap, and aggregation behavior. Complementary photoluminescence measurements are often used to assess fluorescence and recombination processes in semiconductor and quantum dot NPs [33].

3.5 X-ray photoelectron spectroscopy

XPS is among the most accurate techniques for determining the elemental composition, chemical states, and bonding characteristics of NPs surfaces [34]. It operates on the principle of the photoelectric effect, measuring the kinetic energy of emitted electrons to identify surface elements. XPS is also widely used to investigate electron transfer dynamics in supported NPs. For example, platinum nanoparticles (Pt NPs) supported on cerium dioxide (CeO_2) have been shown to transfer one electron to the substrate for every ten platinum atoms, demonstrating strong metal support interactions [35].

3.6 Scanning electron microscopy

SEM provides detailed images of NPs morphology by scanning an electron beam across the sample surface under vacuum [36]. The emitted secondary or backscattered electrons are collected to form high-resolution images that reveal surface topology and particle size. This technique is rapid and requires minimal sample preparation, although it primarily yields surface rather than internal structural information [37].

3.7 Transmission electron microscopy

TEM offers superior spatial resolution compared to SEM by transmitting electrons through an ultrathin specimen, allowing visualization of internal structures, crystallinity, and particle dispersion [38]. Despite requiring extensive sample preparation, TEM provides valuable information on morphology, size distribution, and drug-loading characteristics of NPs. High-energy electron beams, however, may alter delicate biological samples [37].

3.8 Energy-dispersive X-ray spectroscopy

EDX, typically coupled with SEM or TEM, is used for elemental analysis and chemical mapping. When the sample is irradiated by an electron beam, inner-shell electrons are displaced, producing characteristic X-rays unique to each element [39]. While primarily

qualitative, peak intensities can approximate relative elemental abundances within a sample [40].

3.9 Brunauer–Emmett–Teller

The BET technique measures the specific surface area of NPs through nitrogen adsorption–desorption isotherms. Based on the BET theory, gas adsorption at cryogenic temperatures allows quantification of surface area and pore volume. The resulting isotherms provide information on adsorption capacity, pore size distribution, and textural properties, which are critical for catalytic and drug-loading applications [41].

3.10 Zeta potential analysis

Zeta potential analysis determines the surface charge and electrostatic stability of NPs in colloidal suspension [42]. The devices employed to assess this potential are referred to as zeta potential analyzers [43]. ZP values serve as indicators of NPs stability, with larger absolute ZP values signifying greater stability of NPs [42].

3.11 Dynamic light scattering

DLS, also known as photon correlation spectroscopy, is a standard method for measuring nanoparticle size distribution in suspension [43]. It analyzes fluctuations in scattered light intensity caused by Brownian motion, and particle size is derived using the Stokes–Einstein equation. The polydispersity index (PDI), ranging from 0 (monodisperse) to 1 (highly heterogeneous), provides information on population uniformity [44].

3.12 Vibrating-sample magnetometry

VSM quantifies the magnetic properties of NPs according to Faraday's law of induction. In this technique, a sample vibrates within a uniform magnetic field, generating an induced current proportional to its magnetic moment. VSM is especially useful for characterizing magnetic NPs employed in hyperthermia, imaging, and magnetically targeted drug delivery [45].

3.13 Standardization and reporting guidelines for nanoparticle characterization

To improve the reproducibility of nanoscience-based publications intended for biomedical applications, Caruso and co-workers have advocated implementing a reporting checklist, Minimum Information Reporting in Bio-Nano Experimental Literature (MIRIBEL), as a prerequisite for publication. The MIRIBEL checklist encompasses items such as material characterization (including synthesis, composition, size, shape, dimensions, size dispersity, and aggregation), biological characterization (cell seeding details, cell characterization, and passage), and experimental protocol details (including culture dimensions, administered dose, method of administration, and delivered dose) [46]. Expert feedback from the nanomedicine community, while endorsing the original objectives of the MIRIBEL checklist, highlighted the need for a more specifically tailored and continually refined checklist aligned with the intended application of nanomedicines [47]. Besides the checklist, gathering precise and valid data on the characterization of nanomedicines using standardized procedures is essential for a more accurate comprehension and/or forecasting of the safety and therapeutic/diagnostic efficacies of nanomedicine products. In summary, while providing minimal information about the type

and outcomes of characterization is crucial, it is insufficient to ensure the repeatability and reliability of nanomedicine data. Numerous characterization techniques, including DLS and zeta potential tests, are significantly influenced by experimental settings and sample preparation specifics. Consequently, presenting a measurement of physicochemical properties (e.g., size via DLS) without specifying data acquisition particulars (e.g., for DLS: medium type, particle concentration, cuvette type or size, laser wavelength, filtration conditions, and data representation: number count versus raw intensity) may lead to inconsistencies among laboratories regarding identical nanoparticles. For instance, it was demonstrated that results from two widely utilized methods for nanoparticle sizing (i.e., DLS and differential centrifugal sedimentation) for identical nanoparticles obtained by various laboratories were markedly disparate [48].

4 Classification of nanocarriers of drugs

Nanocarriers are engineered materials designed to improve the pharmacological and therapeutic performance of drugs by enhancing solubility, stability, circulation time, and site-specific delivery. They are broadly classified into organic, inorganic, and hybrid nanocarriers, depending on their core composition. As illustrated in (Fig. 4), a wide range of nanomaterials including liposomes, polymers, metallic NPs, viral NPs, and

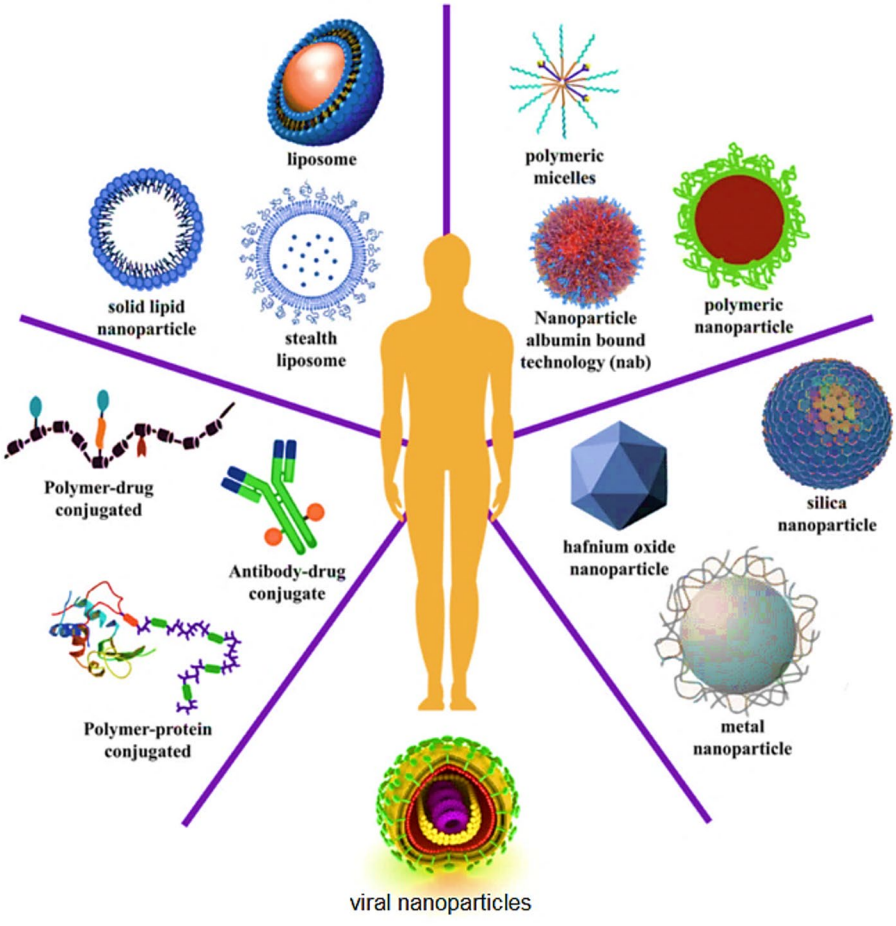

Fig. 4 Various nanocarriers used for drug targeted therapy [62]

conjugate systems have been developed for drug targeted therapy, forming the cornerstone of modern nanomedicine [61].

4.1 Organic carriers

Organic nanocarriers, composed mainly of natural or synthetic polymers and lipids, are the most widely adopted systems in drug delivery. Their popularity stems from high biocompatibility, biodegradability, and extensive tunability in size, surface properties, drug encapsulation, and release behavior.

4.1.1 Lipid based nanoparticles

Lipid-based NPs formulations can be categorized according to their composition and physicochemical properties into three main groups: liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).

4.1.1.1 Liposomes Liposomes are small, spherical vesicles composed of phospholipid bilayers surrounding an aqueous core, which allows them to encapsulate both hydrophilic and hydrophobic therapeutic agents [63]. Liposomes have shown great potential for delivering drugs like doxorubicin, paclitaxel, and genetic material, improving both treatment effectiveness and drug absorption [64]. In 2023, researchers developed liposomes modified with the neurofilament-derived peptide, NFL-TBS.40–63, designed to traverse the blood–brain barrier (BBB) and precisely target glioblastoma cells. This NFL peptide not only facilitated the traversal of the BBB but also enhanced liposome uptake into glioblastoma cells [65]. Early liposomal formulations offered advantages but were quickly removed from systemic circulation. The mononuclear phagocyte system (MPS), especially in the liver and spleen, identifies and absorbs them. To overcome this limitation, researchers used surface modification with polyethylene glycol (PEG). This process, called PEGylation, improved liposome stability and extended their circulation time. PEGylation coats liposomes with hydrophilic polymer. This polymeric layer forms a steric barrier around nanoparticles, which reduces protein adsorption. and minimizing macrophage-mediated clearance [66]. This "stealth" feature significantly extends the plasma half-life of liposomes. It also increases the chances of tumor formation by passive targeting, such as the EPR effect. PEGylated liposomes now play a central role in nanomedicine. Clinically approved formulations use this approach to boost therapeutic effects while reducing toxicity. Despite their benefits, research shows PEGylated liposomes can trigger immune responses in some cases. The Accelerated Blood Clearance (ABC) phenomenon is well known and occurs with repeated use of PEGylated liposomes [67]. In this situation, the immune system develops anti-PEG antibodies that recognize PEG chains on the liposome. This leads to faster opsonization and greater macrophage phagocytosis at later doses. Circulation duration drops, and therapeutic effects can weaken in further treatment cycles.

Another clinically relevant concern associated with PEGylated liposomes is Complement Activation-Related Pseudoallergy (CARPA), a hypersensitivity reaction resulting from activation of the complement system following intravenous administration. CARPA can cause infusion-related reactions, including cardiac discomfort, skin flushing, and short-term changes in blood pressure [68]. These reactions are usually managed but highlight the need to check immunological safety during preclinical and clinical

development. Awareness of these immune limits has led to new surface modification methods for liposomes. Zwitterionic polymers have attracted attention due to their highly hydrated surfaces. These surfaces block nonspecific protein adsorption and can reduce immune activation. Biomimetic nanoparticle coatings are also promising. Liposomes can be coated with natural cell membranes or biomimetic materials to enhance immune evasion and improve circulation stability [69].

4.1.1.2 Solid lipid nanoparticles SLNs are nanoscale carriers consisting of a phospholipid exterior, a stabilizing agent, and water as the dispersive medium [70]. The lipid content may include substances like triglycerides, fatty acids, waxes, steroids, or polyethylene glycol -modified lipids [71]. Unlike liposomes, SLNs have a structure similar to micelles, with the drug being enclosed in a solid, oil-based core rather than in water. A good example is SLNs loaded with mitoxantrone, which demonstrated lower toxicity and improved drug absorption [72]. SLNs loaded with gemcitabine were evaluated in patient-derived primary pancreatic cancer cell lines (PPCL-46) and the MiaPaCa-2 pancreatic cancer cell line. The study demonstrated that SLNs can administer gemcitabine to pancreatic cancer cells more efficiently than gemcitabine alone, indicating that SLNs may represent a promising novel strategy for treating pancreatic cancer [73]. In another study, researchers synthesized SLNs conjugated to transferrin to deliver tamoxifen citrate for breast cancer therapy. The improved targeting capacity of tamoxifen citrate towards MCF-7 breast cancer cells demonstrated the potential efficacy of SLNs in breast cancer treatment [74]. Studies involving SLNs carrying doxorubicin and idarubicin have shown promising effects in drug-resistant leukemia cells (P388/ADR) and mouse models of leukemia [75].

4.1.1.3 Nanostructured lipid carriers Nanostructured Lipid Carriers are the second generation of lipid NPs, designed to address issues in SLNs such as limited drug-loading capacity, crystal changes, lipid solidification, and drug loss during storage [76]. NLCs combine solid and liquid lipids, surfactants, and sometimes co-surfactants and counterions. The mixture forms a solid lipid matrix within a liquid lipid layer [77]. Adding liquid lipids makes the matrix less ordered, thereby boosting drug-loading capacity and preventing leakage [78]. A recent study encapsulated the anticancer drug harmaline in NLCs coated with folate-chitosan (FCH), forming FCH-NLCs, to assess their impact on MCF-7 human breast cancer cells. The spherical FCH-NLCs measured 153 nm in diameter and significantly reduced the viability of MCF-7 cells by increasing the expression of genes responsible for programmed cell death (apoptosis). Additionally, FCH-NLCs selectively targeted cancerous (neoplastic) cells, likely through interactions with folate receptors, suggesting their potential as a targeted therapy [79]. In another study, researchers optimized NLCs containing the drugs metformin and thymoquinone with a size of 78.99 nm and high drug entrapment efficiencies (90% for metformin, 91% for thymoquinone), demonstrated greater efficacy in eliminating breast cancer cells. Table 2 demonstrates different studies on lipid-based NPs.

4.1.2 Polymeric nanoparticles

Polymeric Nanoparticles (PNPs) are nanoscale colloidal structures made from long-chain molecules built by linking different types of monomers together [90]. Drugs can

Table 2 Applications of lipid-based NPs in cancer therapy

Lipid-based nanoparticle	Applications	Refs.
Liposomes	Phase III trial of HER2-targeted liposomal doxorubicin hydrochloride (MM-302) for breast cancer.	[80]
	Phase III trials of thermally sensitive liposomal doxorubicin (ThermoDox) for breast cancer.	[81]
	Evaluation of TfR-targeted liposomes (Tf-PEG-liposomes) in a mouse model of colon cancer.	[82]
	Investigation of liposomes functionalized with the neurofilament-derived peptide, NFL-TBS.40–63, for targeted delivery to glioblastoma cells across the BBB.	[83]
	Phase I trial of siRNA targeting EPHA2 with liposomes (siRNA-EPHA2-DOPC) for advanced neoplasm.	[84]
	Evaluation of paclitaxel liposomes targeting the folate receptor (FR) in cancer therapy.	[85]
	Phase III trial of liposomal paclitaxel (EndoTAG-1) for breast cancer.	[86]
	Attachment of anti-CD22 monoclonal antibodies to PEGylated liposomes loaded with doxorubicin (DOX) for enhanced drug accumulation in non-Hodgkin's lymphoma tumors.	[87]
Solid lipid nanoparticles	Development of arginine-glycine-aspartic (RGD) tripeptide-modified SLNs for targeted delivery of doxorubicin for breast cancer treatment.	[88]
	Evaluation of SLNs loaded with gemcitabine on patient-derived primary pancreatic cancer cell lines (PPCL-46) and MiaPaCa-2 pancreatic cancer cell lines.	[73]
	Development of transferrin-conjugated SLNs for targeted delivery of tamoxifen citrate for breast cancer treatment.	[74]
Nanostructured lipid carriers	Optimization of NLCs loaded with metformin and thymoquinone for breast cancer therapy.	[89]
	Evaluation of folate-chitosan-coated nanostructured lipid carriers (FCH-NLCs) encapsulating harmaline for targeted breast cancer therapy.	[79]

either be enclosed within these particles (forming nanospheres or nanocapsules) or attached to their surface, allowing for controlled and targeted release at the desired site [91]. Initial iterations of PNPs employed non-biodegradable substances such as polyacrylamide, polymethylmethacrylate (PMMA), and polystyrene [92]. However, these substances induced toxicity owing to their gradual degradation and buildup within the body. Currently, biodegradable polymers such polylactic acid, chitosan, alginate, and albumin are favored for their enhanced drug delivery and safety profiles [93]. Studies have also shown that covering PNPs with surfactants like polysorbates can boost their interaction with BBB cells, enhancing drug transport to the brain [94]. For example, indomethacin-loaded nanocapsules significantly reduced tumor size and extended survival in rats with glioma [95]. With over ten polymer-based anticancer formulations currently in clinical trials which include paclitaxel poliglumex (Xyotax), PEG-camptothecin (Prothecan), modified dextran-camptothecin (DE 310), HPMA copolymer-DACH-platinate (AP5346), HPMA copolymer-platinate (AP 5280), HPMA copolymer-paclitaxel (PNU166945), and HPMA copolymer-doxorubicin galactosamine (PK2) [96].

4.1.3 Polymer micelles

Polymer micelles are nano-sized structures formed through the self-assembly of block copolymers, held together by non-covalent interactions [97]. These micelles typically have a core shell structure, where the inner core traps hydrophobic drugs and the outer shell interact with water. Important features of polymer micelles include critical micelle concentration, aggregation number, shape, and size, each influenced by the structure of the polymer blocks. Micelles with lower critical micelle concentration are more stable and better at dissolving drugs in aqueous environments [98]. Their advantages in drug

delivery systems include high drug loading ability, enhanced stability in biological fluids, slower drug release, greater drug buildup at the disease site, and ease of surface modification. Notable examples of polymer micelle-based drugs such as NK911 and NK105, which deliver doxorubicin and paclitaxel, respectively [99].

4.1.4 Dendrimers

Dendrimers are spherical macromolecules made from polymers with a highly branched, tree-like structure. This branching pattern is a key feature that gives them their unique properties. Their synthesis typically begins with an ammonia core reacting with acrylic acid to form a "tri-acid" intermediate, which then reacts with ethylenediamine to form a "triamine." This process continues through repeated steps, producing larger molecules such as "hexa-acid" and "hexa-amine," leading to what is called Generation 1 (G1) dendrimers [100]. Most dendrimers range in size from 1 to 10 nm, though some can grow as large as 15 nm [101]. Their well-defined shape, specific molecular weight, flexible surface chemistry, and good bioavailability make them suitable for delivering nucleic acids. Commonly used dendrimers include poly-amidoamine (PAMAM), PEG, poly propylenimine (PPI), and triethanolamine (TEA) types [102]. PAMAM dendrimers were first explored to overcome multidrug resistance. Studies using DNA-loaded PAMAM dendrimers have shown they can significantly slow tumor growth in epithelial cancer models, outperforming conventional chemotherapy in animal studies [103].

4.1.5 Polymersomes

Polymersomes are vesicle-like structures formed from amphiphilic copolymers that are arranged into a bilayer when placed in water. In the case of three-block copolymers, they can form vesicles with a triple-layered structure. Compared to liposomes, which have phospholipid membranes, polymersomes show lower cell penetration, especially when the hydrophobic part of the copolymer is longer. This feature, however, allows better control over the rate of drug release. Polymersomes also offer improved mechanical and biological stability over liposomes. This is due to reduced interaction with cellular and immune system components, helping preserve the drug inside for longer periods [104].

4.1.6 Extracellular vesicles

Extracellular vesicles (EVs) are a heterogeneous group of membrane encapsulated vesicles released by cells into the extracellular space. They play a crucial role in intercellular communication by transporting bioactive molecules, including proteins, lipids, and nucleic acids [105]. They are generally classified based on their size, biogenesis, and content as summarized in Table 3 [106]. The classification of EVs includes exosomes, microvesicles, apoptotic bodies, and emerging categories such as large oncosomes,

Table 3 Classification of vesicles based on size, biogenesis, and markers

Extracellular vesicles	Size (nm)	Biogenesis	Markers
Exosome	30–150	Endosomal route	CD9, CD63, CD81, Alix, TSG101, HSP70, HSP90β, flotillins
Microvesicles	100–1000	Budding of plasma membrane	Selectins, ARF6, CD40, cytoskeletal protein, heat shock proteins, integrins, flotillins
Apoptotic Bodies	1000–5000	Separation of plasma membrane from the cytoskeleton	Histones, HSP60, GRP78, proteomic profile similar cell lysate

ectosomes, migrasomes, exomeres, and arrestin domain-containing protein 1-mediated microvesicles [107]. Among these, exosomes combined with NPs are widely applied in drug delivery due to their surface components, which closely resemble those of their parent cells. This allows them to avoid immune detection and enter cancer cells efficiently. A well-known example is exosomes carrying doxorubicin (exoDOX), which have been successfully used for breast cancer treatment and shows stronger cancer-killing effects and reduced heart toxicity compared to traditional doxorubicin therapy [108]. EVs play a crucial role in promoting tumor progression by reprogramming immune cells, thereby aiding immune evasion and enhancing cancer cell migration and proliferation. They also facilitate metastasis by helping circulating tumor cells (CTCs) adhere to distant tissues. The mechanism of action of EVs in tumor metastasis involves several key steps that help cancer cells spread, survive, and thrive at secondary sites. These steps include the formation and release of EVs by tumor cells, their interaction with recipient cells, and the functional changes they induce to promote metastasis [109]. EVs released from primary tumors travel to distant organs and modify the local environment, creating a "pre-metastatic niche" that is favorable to incoming tumor cells [110]. This includes changes in the extracellular matrix (ECM), inflammation, immune cell recruitment, and angiogenesis (new blood vessel formation) to support tumor growth. EVs carry pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), as well as miRNAs, such as miR-126 and miR-210, which have been implicated in enhancing endothelial cell function and angiogenesis [111]. They also promote the formation of new blood vessels that supply nutrients and oxygen to growing tumors and provide a route for cancer cells to enter the bloodstream and disseminate to other parts of the body.

4.1.7 Nanoemulsions

Nanoemulsions are small droplets of oil dispersed in water, with sizes typically between 10 and 1000 nm. They exist in three main forms: (1) oil-in-water, (2) water-in-oil, and (3) bi-continuous systems. Modified Nanoemulsions, especially those with specialized membrane coatings, have been widely explored. For example, Nanoemulsions carrying spirulina and paclitaxel have shown improved anticancer activity by influencing immune responses through the TLR4/NF-κB signaling pathway [112]. Another example is a Nanoemulsions containing rapamycin, bevacizumab, and temozolomide, used in treating advanced melanoma [113]. Compared to liposomes, Nanoemulsions offer distinct advantages, including better transparency, improved stability, and good biodegradability. However, there are technical barriers to their clinical use. Producing Nanoemulsions often require high temperatures, strong pressure, and costly equipment like high-pressure homogenizers and microfluidizers [114].

4.1.8 Cyclodextrin nanosponges

Cyclodextrin Nanosponges are small, porous structures made using cyclodextrins cyclic sugars with a water-repelling inner cavity and a water-attracting outer surface. These molecules help improve the drug-carrying ability of NPs by acting as stabilizers. The sponge-like network provides more surface area and allows for better drug encapsulation [115]. For example, β-cyclodextrin Nanosponges loaded with paclitaxel have shown strong anticancer effects in MCF-7 breast cancer cells. Likewise, camptothecin

has demonstrated improved water solubility and chemical stability when combined with cyclodextrin-based Nanosponges [116].

4.1.9 Viral nanoparticles

Viral Nanoparticles (VNPs) are biologically derived nanocarriers engineered from non-replicating or genetically modified viruses such as adenovirus, bacteriophage, or cowpea mosaic virus. Their highly ordered capsid structures and ability to encapsulate nucleic acids or drugs make them efficient for gene delivery and tumor-targeted therapy. Plant viral nanoparticles (PVNPs) are a promising platform for producing cancer vaccines due to their structural characteristics and ability to elicit an immune response. The plant viruses used to construct PVNPs are carefully selected because each virus has unique structural characteristics lending itself to diverse therapeutic uses [117]. PVNPs can be engineered to carry various payloads, including chemotherapeutic compounds and imaging agents. By adding specific ligands on their surface, the tumor-targeting capability of these NPs can be improved, therefore increasing the effectiveness of cancer treatment while reducing side effects on healthy tissues [118]. One advantage of PVNPs is that they are produced in whole plants or in plant cell suspension cultures, which are free of animal pathogens and toxins, rendering them safe for administration to humans and other animals. The ability of glycan moieties on plant-derived glycoproteins to elicit allergic responses in patients has necessitated investigations into the safety profile of plant-derived biologics [119]. A study tested plant-produced H5N1 virus-like particles (VLPs), a subset of VNPs, in preclinical and phase I clinical trials and found that they were safe, well-tolerated, and didn't induce allergic reactions in inoculated humans [120]. A quadrivalent VLP-based vaccine (QVLP) containing influenza A and B VLPs was found to be safe, immunogenic, and effective in phase I/II, phase I, and phase III clinical trials performed in humans [121]. The approval of these products by the relevant regulatory authorities represents a breakthrough in regulatory agencies' acceptance of plant-derived biologics and their production systems. Most human clinical trials using plant-expressed virus-like particle systems to date have not reported any severe adverse effects. It must be noted that each plant-derived biologic is unique and needs to be assessed individually [119].

4.2 Inorganic nanocarriers

Inorganic nanocarriers are small particles made of various materials, including metals, metal oxides, magnetic NPs, silica NPs, graphene oxide, and carbon nanotubes. They are widely studied for their magnetic, optical, and heat-responsive properties, which make them useful for targeted therapy and biomedical imaging.

4.2.1 Carbon-based nanomaterials

Carbon-Based Nanomaterials (CNMs) are attractive carriers for drugs, genes, and proteins due to their large surface area, high drug-loading ability, and strong interaction with hydrophobic molecules through π–π interaction. These nanomaterials possess distinctive optical characteristics, as their graphitic structure facilitates robust absorption in the near-infrared spectrum, specifically within the ranges of 750–1000 nm and 1000–1700 nm. This makes them useful in cancer photothermal therapy, deep-tissue fluorescence, and photoacoustic imaging [122]. CNMs are known for their good

biocompatibility, low immune response, and flexible surface chemistry, which make them ideal for forming targeted, low-toxicity drug delivery systems with high therapeutic potential [123]. They also contain edge defects and active sites that can promote catalytic and redox reactions, allowing controlled release of drugs in response to stimuli in the tumor microenvironment (TME). Moreover, CNMs can influence several cancer-related biological processes, including tumor spread, inflammation, low oxygen levels, abnormal metabolism, and new blood vessel growth, making them valuable tools for TME-focused cancer therapies [124]. CNMs exist in several forms, including graphene, carbon nanotubes, fullerenes, carbon nanohorns, and graphyne. Despite being composed of carbon, they vary in form, architecture, and purpose. Graphene, a flat 2D sheet of sp^2-hybridized carbon atoms, is well known for its strength, electrical properties, and drug-loading efficiency. It can be further divided into: (1) single-layer graphene, (2) graphene oxide (GO), (3) reduced graphene oxide (rGO), and (4) multi-layer graphene. Among these, GO and rGO are widely explored for targeting low-oxygen regions and abnormal blood vessels in tumors [125, 126]. In breast cancer models, GO loaded with doxorubicin has shown superior anticancer performance compared to the free drug [127].

4.2.2 Metallic nanoparticles

Metallic NPs are widely studied for use in biological imaging and targeted drug delivery due to their exceptional optical, magnetic, and heat-generating (photothermal) properties. Common types include gold (Au), silver (Ag), iron (Fe), and copper (Cu) NPs. Au NPs are especially useful for delivering drugs inside cells, as their size and surface can be precisely adjusted [128]. They have significant interaction with visible light, enabling researchers to track their mobility within cells. Gold-on-silica nanoshells conjugated with anti-HER2 antibodies have been engineered to selectively target HER2-positive breast cancer cells [129]. AuNPs can be used to deliver chemotherapeutics and si RNA simultaneously. AuNPs loaded with doxorubicin and Bcl-2 siRNA (Dox-Bcl2-AuNPs) were evaluated for antitumor efficacy on TNBC cells. It is estimated that the global market for biomedically applied magnetic particles will reach US $87.7 million by 2025 and will increase by ~10% annually. The following iron oxide nanoparticles have been approved by the U.S. Food and Drug Administration (FDA) for clinical use: Feraheme® for iron deficiency; Combidex® (U.S.) and Sinerem® (Europe) as a magnetic resonance imaging (MRI) agent; Nanotherm® (MagForce) for cancer treatment; and Lumirem® as an oral gastrointestinal tract imaging agent [130]. Fe NPs can also be integrated with other nanoplatforms to enable their theranostic applications. With this aim, a monodisperse mesoporous silica-coated multifunctional Fe NPs nanoplatform (DOX@MMSN-SS-PEI-cit) was designed to diagnose and treat cancer [131].

4.2.3 Metal–organic frameworks

Metal–Organic Frameworks (MOFs) are promising for several applications, including drug loading and controlled release, due to their unusually high surface area and substantial pore size [132]. Nonetheless, MOFs must be reduced to nanoscale dimensions (NMOFs) to function as drug carriers within blood arteries. The appeal of NMOFs stems from their suitability for biological and pharmaceutical applications, enabling the controlled release of intravenously administered medicines. In comparison to traditional porous materials, NMOFs provide advantages such as the capacity to encapsulate

substantial quantities of pharmaceuticals, along with their customizable composition and architecture [133]. Due to their adaptability, serve as potential platforms for drug delivery and molecular imaging, either independently or inside a unified system [134]. *Zhao et al.* developed innovative MOF-based theranostic core-shell composites, featuring a UiO-66 MOF shell surrounding a Fe_3O_4 core, which enables concurrent drug administration and magnetic resonance imaging [135]. Studies with doxorubicin demonstrated a significant drug-loading capacity and prolonged drug release, establishing Fe_3O_4@-UiO-66 as an exceptional drug delivery vehicle.

4.2.4 Magnetic nanoparticles

They are composed of metals or metal oxides and are often coated with organic materials like polymers or fatty acids to improve their stability and compatibility with the body [136]. Superparamagnetic iron oxide nanoparticles (SPIONs) linked with LHRH have shown promising results in detecting and targeting breast cancer cells [137]. They are mostly utilized in magnetic resonance imaging (MRI) and targeted medicine delivery. In addition to imaging, magnetic NPs are also applied in magnetic hyperthermia, where heat is generated to destroy cancer cells [138]. Magnetic drug delivery technique employs an external magnetic field to direct drug-loaded NPs to a targeted location within the body. They can be modified with pharmaceuticals and subsequently administered into the bloodstream. By externally generating a magnetic field, the NPs can be guided to the targeted site, such as a tumor [139]. This method facilitates more accurate drug administration, decreasing systemic exposure and mitigating negative effects [140]. Magnetic NPs can be utilized in cancer therapy to directly administer chemotherapy agents to tumors, thereby enhancing drug concentration at the tumor location and minimizing damage to healthy tissues which was summarized in Table 4. This method can improve therapeutic effectiveness while reducing side effects [141]. Moreover, magnetic drug delivery can be employed in targeted therapy for various diseases, including neurological disorders, where NPs containing neuroactive drugs can be directed to specific brain regions using externally applied magnetic fields, facilitating more precise treatment and potentially diminishing systemic side effects [142].

4.2.5 Silica nanoparticles

Although silica is a common component in natural materials, its role in biological applications has only recently gained attention. Silica NPs are often used for gene delivery by modifying their surface with amino-silane compounds [167]. Silica NPs functionalized with N-(6-aminohexyl)-3-aminopropyl-trimethoxysilane demonstrate enhanced gene transfer efficiency in Cos-1 cells with minimal toxicity and are already available for commercial purchase [168]. Mesoporous silica nanoparticles (MSNs) are considered excellent drug carriers because of their favorable pharmacokinetics. Using MSNs as drug carriers significantly improved the solubility of paclitaxel and camptothecin, which ultimately increased their cytotoxicity by 4.3-fold for paclitaxel against HepG2 cells and ~ 86% for camptothecin against Capan-1 human pancreatic adenocarcinoma cells [169]. An antibody-targeted and redox-responsive doxorubicin-loaded MSN-based drug delivery system (DOX@MSNs-CAIX) was designed by conjugating anti-carbonic anhydrase IX antibody (CAIX) on the MSNs surface via disulfide linkages [170]. It was reported

Table 4 Magnetic NPs for the targeted delivery of chemotherapeutic drugs

Carrier, drug	Cancer	Targeting	Size (nm)	LC	LE	Refs.
Fe_3O_4/Gly, MTX	Breast	Passive	46.82 ± 5.03	4.2%	–	[143]
Fe_3O_4/BSA, MTX	Breast	Passive	105.7 ± 3.81	3.5%	–	[144]
Fe_3O_4/ PHBV, MTX	Colorectal	Passive	90	6.79 ± 0.01%	84%	[145]
Fe_3O_4/Cat/Ciclo, MTX	Osteosarcoma	Passive	20–80	8.92%	89.27%	[146]
Fe_3O_4/DPA/PEG/HA, MTX	Lung	Active, HA	103	42.94%	88.11%	[147]
Fe_3O_4/FRab, MTX	Cervical	Active, FR ab	50–100	–	90.62%	[148]
Fe_3O_4/Cur-LDH/PDO, Cur	Liver	Passive	179.4 ± 29.8	38%	–	[149]
Fe_3O_4/C-VB-PEGMA, Cur	Liver	Active, VB	10.3 ± 1.3	25%	67.7%	[150]
Fe_3O_4/BSA, Cur	Liver	Active, FA	60.21 ± 12.32	5%	–	[151]
Fe_3O_4/GQD, Cur	Breast, osteosarcoma	Active, FA	34.3	–	–	[152]
Fe_3O_4/BNN/PEG, DOX	Liver	Magnetic	151–216	19 ± 0.54%	83 ± 0.33%	[153]
Achiral nanorobot, DOX	Breast, liver	Magnetic, macrophages	40,000	–	45%	[154]
Mesoporous Fe_2O_3–Au, DOX	Lung	Magnetic	100	–	–	[155]
Fe_3O_4/chitosan aerogel, DOX	Osteosarcoma	Magnetic	–	40%	–	[156]
Fe_3O_4/CMCS/ALS, DOX	Breast	Magnetic	90–170	48.68%	86.23%	[157]
Fe_3O_4/Nylon/DOX	Lung	Magnetic	28 ± 4	73.2%	–	[158]
Fe_3O_4/SiO_2-AP-DNA, DOX	Breast	Magnetic, enzymatic	70	–	–	[159]
Fe_3O_4/SiO_2-CS-FA, DOX	Cervical	Magnetic, active, FA	100	–	15%	[160]
Fe_3O_4 /HT/TA, DOX	Colorectal	Magnetic	70	8.17%	51%	[161]
Fe_3O_4/FA, DOX	Colorectal	Magnetic, active, FA	10	7.15%	95%	[162]
Fe_2O_3/ChitoPEG, DOX	Colorectal	Magnetic	148.9	–	–	[163]
Lipo/SPION/ICG/cRGD, DOX	Fibrosarcoma	Magnetic, active, cRGD	166 ± 42	-	47.5%	[164]
MNC/PDO, CIS	Cervical, breast	Magnetic	90–100	0.067%	–	[165]
Fe_3O_4/Ma/C, OXA	Colon	Magnetic	34 ± 10	40%	–	[166]

that colorectal cancer cells effectively took up camptothecin-loaded mesoporous silica NPs, demonstrating their therapeutic potential [171].

4.2.6 Calcium phosphate nanoparticles

Calcium phosphate NPs are known for being biocompatible, biodegradable, and safe, with minimal adverse effects. Due to these characteristics, they are employed to provide a range of medicinal substances, including insulin, growth hormones, antibiotics, and contraceptives. They are also effective carriers for genetic materials such as plasmid DNA and oligonucleotides [172]. Calcium phosphate NPs have been successfully combined with both viral and non-viral systems to enhance gene delivery into cells. A liposomal formulation containing calcium and glycerol, known as a nanolipoplex, has shown lower toxicity and improved gene transfer efficiency [173].

4.3 Hybrid nanoparticles

Hybrid nanocarriers are multifunctional NMs that integrate both organic and inorganic materials to create platforms with synergistic therapeutic, diagnostic, and

physicochemical properties [174]. By combining the high biocompatibility and versatility of organic carriers with the stability, magnetic, or optical features of inorganic components, these nanocarriers exhibit superior performance in terms of drug encapsulation, targeted delivery, and imaging. Their hybrid structure also enables the incorporation of biological molecules such as antibodies, proteins, and peptides, allowing precise targeting of diseased tissues and controlled release of therapeutic agents [175]. This class includes antibody drug conjugates, polymer–protein conjugates, composite nanocarriers, and stimuli-responsive systems.

4.3.1 Antibody–drug conjugates

Antibody–Drug Conjugates (ADCs) are hybrid nanotherapeutics that link monoclonal antibodies to cytotoxic drugs via stable chemical linkers, combining the target specificity of immunotherapy with the potency of chemotherapy [176]. The antibody component selectively binds to antigens expressed on the surface of cancer cells, facilitating receptor mediated endocytosis of the conjugate. Once internalized, the linker often designed to be cleaved under acidic or enzymatic conditions releases the active drug into the tumor cell, leading to localized cytotoxicity while minimizing systemic side effects. ADCs are composed of three essential elements: a monoclonal antibody, a cytotoxic payload and a cleavable linker that ensures stability in circulation but releases the drug intracellularly [177]. Approved ADCs such as trastuzumab emtansine (T-DM1) for HER2-positive breast cancer and brentuximab vedotin for Hodgkin lymphoma [178]. New-generation ADCs are being developed using biodegradable polymers or nanoparticle-assisted designs to improve stability, drug-loading efficiency, and tumor penetration, representing one of the most promising strategies for targeted cancer therapy [179].

4.3.2 Polymer–protein conjugates

Polymer–Protein Conjugates (PPCs) are biohybrid nanocarriers in which therapeutic proteins, peptides, or enzymes are covalently linked to hydrophilic polymers to improve their pharmacokinetic and pharmacodynamic properties [180]. The conjugation process enhances solubility, prolongs circulation time, and protects the protein from enzymatic degradation or immune recognition. PEG is the most commonly used polymer, giving rise to clinically approved PEG–interferon and PEG–adenosine deaminase formulations [181]. In cancer therapy, PPCs help maintain therapeutic protein levels in plasma and enhance tumor accumulation through the EPR effect. Modern PPCs often incorporate biodegradable or stimuli-responsive polymers that allow controlled release of the therapeutic payload in response to tumor-specific microenvironmental cues such as low pH, elevated redox potential, or enzymatic activity [182]. The tunable nature of these conjugates offers significant advantages in optimizing drug half-life, minimizing immunogenicity, and improving site-specific drug delivery.

4.3.3 Composite nanocarriers

Composite nanocarriers combine the structural and functional benefits of both organic and inorganic materials, producing versatile systems capable of simultaneous therapy and imaging [183]. These nanocarriers typically consist of inorganic cores such as Au, silica, or magnetic NPs coated or embedded within organic matrices like lipids, polymers, or surfactants. The inorganic component provides structural rigidity, magnetic

or optical responsiveness, and improved drug-loading capacity, while the organic shell enhances biocompatibility and stability in biological environments. Composite nanocarriers can be synthesized using sol–gel, intercalation, co-blending, or self-assembly techniques [184]. Au–lipid hybrids have been used for combined photothermal and chemotherapeutic therapy, silica–polymer systems allow sustained multi-drug release, and magnetic polymer composites like SPION–PEG or SPION–chitosan enable MRI visualization along with magnetically guided chemotherapy [185]. The ability to integrate multiple therapeutic and diagnostic functions within one nanoplatform makes organic–inorganic composites powerful tools in cancer theranostics [186].

5 Clinical outcomes and translational barriers of nanoparticle therapies

In recent years, several studies have proposed the use of nanocarriers as a novel approach for improved drug delivery. Table 5 shows some anticancer nanomedicines approved for clinical use, while Table 6 summarized some Nanomedicines in clinical trials for cancer treatment [187].

6 Experimental models relevant to humans

Humanized mice, engrafted with patient-derived immune cells or tumor fragments, better replicate cytokine signalling, macrophage behaviour, and nanoparticle distribution than conventional hosts [200]. Ex vivo models such as patient-derived organoids, tumor-on-a-chip platforms, and precision-cut tissue slices maintain realistic tissue architecture and mechanical properties. These models allow full assessment of nanoparticle penetration and release and help identify immunogenic or toxic features earlier [201].

7 Patient selection informed by biomarkers

Evaluating target receptor expressions (such as PSMA, HER2, or the folate receptor) or identifying tumor microenvironmental features suitable for EPR-based delivery can improve response rates in early clinical trials. This approach has shown better results in trials using targeted micelles and liposomes. It also generates crucial pharmacodynamic data to refine nanoparticle design [202].

8 Artificial intelligence (AI) and machine learning

Predictive models developed using extensive datasets now associate nanoparticle attributes, including size, shape, stiffness, and ligand density, with critical outcomes such as circulation duration, tumor absorption, and endosomal release. Generative algorithms can propose optimized designs before synthesis commences. At the clinical level, AI-driven adaptive trial platforms are used to adjust doses based on real-time pharmacokinetics, imaging biomarkers, and toxicity indicators, facilitating earlier detection of efficacy [203]. The success of these inventions will rely on sustained interdisciplinary collaboration. Timely engagement of academic researchers, manufacturing experts, and regulatory bodies is crucial to ensure that nanoparticle design conforms to practical production and approval criteria [204]. Multidisciplinary advisory groups and adaptable regulatory frameworks that permit protocol modifications based on interim or real-world data may expedite advancement [205]. Transparent communication among stakeholders from the design process onwards will be essential for bridging knowledge gaps and preventing costly delays. By integrating human-relevant modelling,

Table 5 Anticancer nanomedicines approved for clinical use for cancer treatment

Pharmaceutical nanocarrier	Product name	Approved year	Active substance	Indication	Key clinical benefit vs. standard of care	Refs.
PEGylated liposomes	Zolsketil®	2022 (EMA)	Doxorubicin	Breast cancer, ovarian cancer, multiple myeloma, and Kaposi's sarcoma	Reduced cardiotoxicity and prolonged circulation compared with conventional doxorubicin	[188]
Dual-drug liposomal encapsulation	Vyxeos®	2017 (FDA)	Daunorubicin and cytarabine	Acute myeloid leukemia	Fixed synergistic drug ratio improves overall survival in high-risk AML	[189]
PEGylated liposomal	ONIVYDE®	2015 (FDA)	Irinotecan	Metastatic adenocarcinoma of the pancreas	Improved overall survival and drug exposure compared with conventional irinotecan	[190]
Non-PEGylated liposome Doxorubicin (NPLD)	Myocet®	2000(EMEA)	Doxorubicin	Metastatic breast cancer	Reduced cardiotoxicity relative to conventional doxorubicin	[191]
Polymeric micelle	Nanoxel ®	2006 (India)	Docetaxel	Breast and ovarian cancers, AIDS-related Kaposi's sarcoma and NSCLC	Eliminates toxic solvents (e.g., polysorbate 80) and improves tolerability	[192]
Polymeric micelle-bound paclitaxel	Genexol-PM®	2007 (Korea)	Paclitaxel	Metastatic breast cancer, metastatic adenocarcinoma of the pancreas, non-small cell lung cancer (NSCLC)	Higher maximum tolerated dose and improved tumor response without Cremophor EL	[193]
Radio enhancer nanosized product	Hensify (NBTXR3)	2019 (EMA)	Radiotherapy	Soft tissue sarcoma	Enhances radiotherapy efficacy by amplifying local radiation dose in tumors	[194]
Polymeric NPs	Eligard ®	2002 (FDA)	Leuprolide acetate	Prostate cancer	Sustained drug release enabling long-acting hormone therapy	[195]
Albumin-bound paclitaxel	Abraxane ®	2005 (FDA, EMA)	Paclitaxel	Various cancers including metastatic and pancreatic cancers	Solvent-free formulation improves delivery and response rate compared with conventional paclitaxel	[196]
SPIONs coated with amino silane	NanoTherm ®	2013(EMA) 2018 (FDA)	Fe_2O_3 NPs	Various types of cancer, including glioblastoma, prostate, and pancreatic cancers	Enables localized magnetic hyperthermia for targeted tumor destruction	[197]

Table 6 Nanomedicines in clinical trials for cancer treatment

Name	Composition	Application	Clinical trial
ThermoDox	Thermosensitive liposome loaded with doxorubicin	Localized unresectable recurrent and metastatic cancers, including breast cancer, bone metastasis, pancreatic cancer and liver cancer	NCT00093444, Phase I, Completed (2004)
			NCT00346229, Phase I, Terminated (2006)
			NCT00441376, Phase I, Completed (2007)
			NCT00617981, Phase III, Completed (2008)
			NCT00826085, Phase I/II, Completed (2013)
			NCT01464593, Phase II, Terminated (2012)
			NCT01640847, Phase II, Withdrawn (2012)
			NCT02112656, Phase III, Completed (2014)
			NCT02181075, Phase I, Completed (2014)
			NCT02536183, Phase I, Terminated (2016)
			NCT02850419, Phase II, Withdrawn (2017)
			NCT03749850, Phase I, Unknown status (2021)
			NCT04791228, Phase II, Withdrawn (2021)
			NCT04852367, Phase I, Withdrawn (2021)
CPX-1	Liposomal irinotecan and floxuridine	Advanced colorectal cancer	NCT00361842, Phase II, Completed (2006)
CALAA-01	Transferrin-receptor-targeted polymeric nanoparticle loaded with siRNA	Solid tumors refractory to standard-of-care therapies	NCT00689065, Phase I, Terminated (2008)
AuroShell	Nanoparticle made of a silica core and a gold shell	Photothermal ablation of different solid tumors	NCT00848042, Completed (2008)
			NCT01679470, Terminated (2012)
			NCT02680535, Completed (2016)
			NCT04240639, Active not recruiting (2020)

Despite strong preclinical results, numerous nanoparticle systems have difficulty demonstrating equivalent efficacy in clinical settings, particularly during Phase II and Phase III trials. These failures highlight several interrelated challenges that consistently obstruct clinical translation, including model constraints, biological variability, and regulatory barriers. In addition to biological barriers, technical and manufacturing obstacles further impede clinical translation. Enhancing nanoparticle manufacturing while ensuring quality and reproducibility is intricate. Subtle alterations in synthesis, such as agitation rate or solvent formulation, can influence particle dimensions, drug concentration, and surface characteristics, thereby affecting performance [198]. These challenges are particularly evident in complicated hybrid or multifunctional nanoparticles, which may necessitate elaborate assembly procedures and specialized materials. These challenges explain why only a limited number of formulations, particularly Doxil and Abraxane, have been approved [199]. Consequently, contemporary treatment techniques emphasize "intelligent" carriers that integrate tumor-specific targeting with regulated, stimulus-responsive release. Examples include the prostate-specific membrane antigen (PSMA)-targeted polymeric nanoparticle BIND-014 and the thermosensitive liposome ThermoDox. To mitigate the shortcomings of current systems, three synergistic approaches may be employed:

biomarker-informed enrolment, AI-driven optimization, and collaborative regulatory approaches, the domain of cancer nanomedicine may begin to address its existing limitations. These collaborative efforts possess the capacity to transform robust preclinical results into safe, effective, and personalized cancer treatments.

9 Mechanisms of action of nanoparticles

NPs induce apoptosis in cancer cells by a series of mechanisms; reactive oxygen species (ROS)-mediated apoptosis being the most studied among them. Up and down-regulation of proteins, immunological interventions, inhibition of transcription, site-specific

cytotoxicity, etc. are other mechanisms of action of nanoparticles in apoptosis induction in cancer cells, (Fig. 5).

9.1 Generation of ROS

ROS-mediated apoptosis is one of the most studied mechanisms of NPs-induced cytotoxicity. While moderate ROS promotes cell survival, proliferation, invasion, and metastasis, excessive ROS acts as a strong pro-apoptotic signal, inducing cell cycle arrest, apoptosis, and necrosis [207]. NPs, due to their high surface reactivity, generate excessive ROS more effectively than bulk materials, leading to oxidative damage of DNA, proteins, and lipids, followed by cytotoxicity [208]. For example, polysaccharide-enclosed Ag NPs produced significant ROS, triggering cell death mainly through autophagy and extended apoptosis [209]. Mitochondria-targeted NPs generate ROS that inhibit ATP synthesis, while silica carbon NPs coated with lipid membranes inhibited multidrug-resistant tumor growth without systemic toxicity via the same mechanism [210].

9.2 Regulation of apoptosis-related proteins

Under oxidative or exogenous stress, NPs regulate apoptosis-related proteins to remodel metabolic and signaling pathways, impacting cell cycle progression, proliferation, and tumor suppression [211]. CuO-NPs down-regulate anti-apoptotic proteins Bcl_2 and Bcl_{xL}, inducing programmed cell death in HT-29 cells [212]. Se NPs at low concentrations (5 μg/mL) modulate unfolded protein response (UPR) pathways and significantly increase expression of ER-resident selenoproteins, glutathione peroxidases, and thioredoxin reductases, while selectively regulating pro-apoptotic proteins via Cx43 hemichannels [213]. Ag NPs enhance γ-H2AX expression in MCF-7 cells, leading to cell death after Ag ion release [214]. Au NPs conjugates selectively inhibit CDK4, induce G1 arrest, block NF-κB nuclear translocation, and down-regulate MAPK phosphorylation (p42/44, p38), reversing chemoresistance in breast and pancreatic cancer models [215].

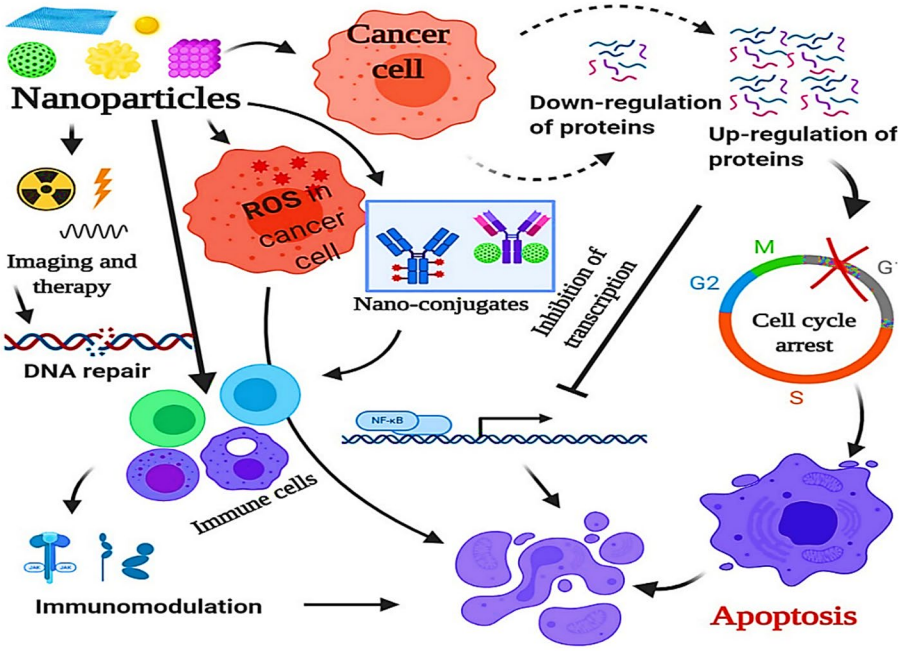

Fig. 5 Mechanisms of cell death in cancer induced by nanoparticles [206]

9.3 Radiation therapy enhancement

Conventional radiotherapy is limited by non-specific damage and rapid clearance of radioisotopes. NPs with radioactive cores or high atomic number elements act as radiosensitizers, prolonging tumor retention via EPR and locally amplifying radiation effects through photoelectrons, and secondary radiation [216]. Upconversion nanoparticles coupled to yttrium-90 (90Y) enabled background-free imaging and localized radiation with reduced side effects [217]. Radioactive Pd-Au NPs showed prolonged retention and dose-dependent tumor growth inhibition in prostate cancer via DNA strand breaks. Bismuth-based nanoparticles (Bi_2S_3, PVP-coated) enhanced X-ray therapy in breast cancer by altering membrane permeability and damaging genomic DNA, offering longer circulation half-life and higher CT contrast than iodine-based agents [218].

9.4 Phototherapy

Phototherapy uses light or electromagnetic radiation to generate heat or reactive species that induce apoptosis [219]. NPs act as photosensitizers with strong near-infrared absorption, converting light into thermal energy or ROS, releasing immunogenic molecules/antigens, and enhancing combined radiotherapy effects. Fe_3O_4 NPs produce heat in alternating magnetic fields, selectively killing fast-dividing cancer cells [220]. Magnetic nanoparticle–anti-αvβ6 antibody conjugates killed 85% of VB6 oral cancer cells after 10-min exposure [221]. Au NPs generate localized hyperthermia for in vivo phototherapy [222]. Au@ZIF-8 nanozymes catalyzed H_2O_2 decomposition to relieve hypoxia and induced tumor toxicity when loaded with Ce6 [223].

9.5 Triggering immunological reactions

NPs enhance host immunity by exposing tumor antigens and modulating the immunosuppressive tumor microenvironment [224]. Au and Ag NPs induce cytokine release in THP-1, NCI-H460, and HL-60 cells, promoting balanced Th1/Th2 responses via ROS, complement activation, and humoral/cellular immunity supporting their use as vaccine adjuvants [225]. Nanoparticle-encapsulated dual therapeutics (e.g., ppp dsRNA) elevate Th1 cytokines, $CD8^+$ T cells, and M1 macrophages, leading to significant tumor growth inhibition [226]. Their physicochemical properties also enable antibody production/inhibition, making them valuable for melanoma diagnosis and treatment [227].

9.6 Site-specific cytotoxicity

NPs enable precise, localized drug release and intracellular delivery of DNA, mRNA, siRNA, and proteins, achieving site-specific cytotoxicity with reduced systemic side effects, improved pharmacokinetics, and enhanced EPR [228]. Hyaluronic acid-based NPs selectively target CD44-positive tumor cells [229]. Folate-receptor-mediated titanium phosphate nanoparticles exhibit high drug loading, enhanced uptake, and real-time therapeutic monitoring [58]. Zinc oxide (ZnO) NPs exploit anionic phospholipid-rich cancer cell membranes for selective Zn^{2+} overload and ROS induction; conjugation with Fe_3O_4 further increases cytotoxicity via combined selectivity and magnetism [230]. Anti-HER2 antibody-conjugated cationic SLNs demonstrate highly specific cytotoxicity in HER2-overexpressing BT-474 and MCF-7 breast cancer lines [231].

9.7 Gene therapy for cancer cell growth inhibition

NPs regulate expression of cancer-associated genes, suppressing tumor growth and inducing antitumor effects [232]. In A549 lung cancer cells, Fe_3O_4 NPs modulated multiple oncogenic genes like *STAT3*, *FGFRL1*, *HNRNPL*, *BCL2L1*, *ATF3*, *RAB5C*, *ANG*, *EIF3I*, *NKIRAS2*, *PIAS4*, *RRAS*, *NUCKS1*, *AKT1*, *SRC*, *PCBP2*, *EIF2C2*, *HRAS*, *CDC34*, *NFKB2*, *EIF4G1*, *EIF5A*. Many of which serve as molecular markers of cancer progression. This gene-level interference disrupts survival pathways and holds significant promise for targeted gene therapy applications.

10 Tumor targeting by nanoparticles

Effective cancer therapy requires drug or gene delivery strategies that selectively accumulate in tumor cells while minimizing damage to healthy tissues. Nanoparticles must overcome multiple biological barriers and interact intimately with the tumor microenvironment, making targeted delivery essential. These targeting approaches are broadly classified into passive and active targeting.

10.1 Passive targeting

Passive targeting has become an effective approach to enhance the efficacy of cancer treatment. This technique exploits the pathophysiological characteristics of solid tumors to achieve selective accumulation of nanocarriers, primarily through the EPR effect, as shown in (Fig. 6) [233]. The EPR effect transpires when tumor tissues exhibit inadequate lymphatic drainage and permeable vasculature, facilitating the preferential accumulation of nanoscale particles in the tumor tissue by passive diffusion and retention. This results in the selective accumulation of nanocarriers in tumor tissues, while reducing their distribution in healthy tissues [234]. In contrast to traditional chemotherapy, the targeted accumulation of nanocarriers in tumor tissues enhances therapeutic efficacy and diminishes toxicity. Nanocarriers for passive targeting offer numerous advantages compared to conventional treatment. Initially, the targeted accumulation of nanocarriers in tumor tissues enhances medication efficacy and lowers toxicity relative to traditional chemotherapy. Secondly, nanocarriers can encapsulate both hydrophilic and hydrophobic

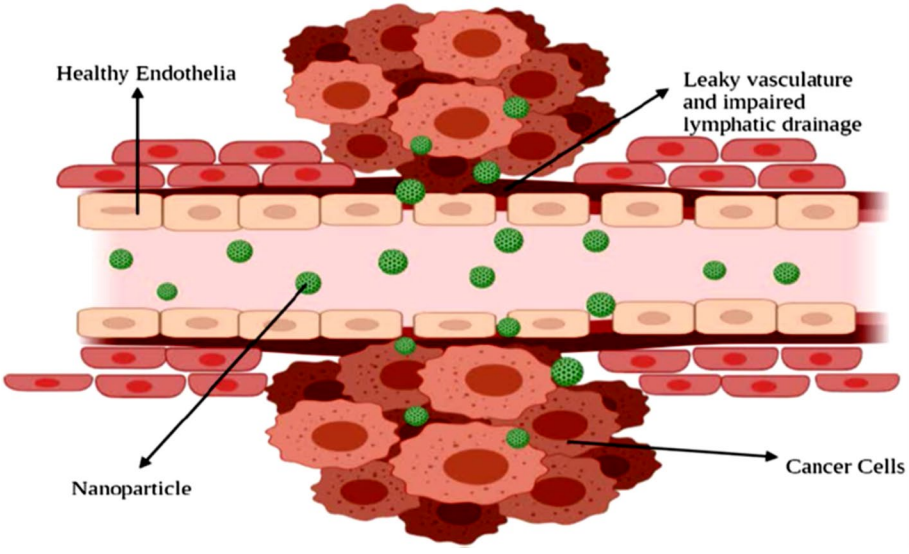

Fig. 6 Passive cellular targeting [237]

pharmaceuticals, facilitating the concurrent administration of numerous medicines with varying modes of action, thus augmenting the efficacy of cancer therapy. Thirdly, nanocarriers can protect the therapeutic payload from breakdown and elimination, leading to prolonged drug presence in tumor tissue [235].

While the traditional EPR-based design philosophy has led to the clinical success of some formulations, it fails to deliver Ehrlich's "magic bullet" nanomedicine that selectively targets tumors across a wide range of cancer phenotypes. Alternative drug delivery strategies that do not require an EPR-sensitive tumor phenotype have gained interest in recent years as disillusionment with the EPR effect rises. EPR-adaptive delivery modifies tumor accessibility to improve agent delivery and therapeutic impact [236]. This principle may still partially explain the delivery efficacy of some agents, but EPR-adaptive strategies can be applied to a wider range of clinical targets, including those previously inaccessible to traditional EPR-based strategies. These solutions avoid the drawbacks of conventional nanomedicine delivery by reducing their reliance on the EPR effect.

EPR-adaptive delivery improves nanomedicine biodistribution via chemical and physical methods. Chemical mediators directly modify tumor vasculature, stroma, and cancer cells to increase tumor access. Bradykinin, prostaglandins, and nitrous oxide cause inflammation to restore tumor blood flow and inflow, increasing drug permeability [238]. Vascular normalization, which restores convoluted, inadequate tumor vasculature with modest anti-angiogenic therapy, improves nanomedicine delivery and therapeutic outcomes [239]. Collagenase and hyaluronidase lower tumor interstitial fluid pressure, while direct apoptosis in cancer and stromal cells reduces microvasculature pressure, thereby improving agent penetration [240]. Losartan, an angiotensin II receptor antagonist, decompresses tumor arteries, enhances tumor perfusion, and reduces collagen formation, enhancing drug accumulation. A Phase II clinical trial of 49 locally advanced pancreatic cancer patients showed improved margin-negative resection rates and prolonged survival with FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irontecan) as neoadjuvant therapy [241]. These chemical methods offer the potential to improve the therapeutic benefits of nanomedicine while maintaining the clinical workflow of combination therapy. Physical techniques represent the other arm of the EPR-adaptive delivery strategy. These involve the use of external stimuli to modify a delivery site either prior to or concurrent with nanomedicine delivery. This includes radiation, ultrasound, hyperthermia, and photodynamic therapy which are summarized in Table 7 [242].

10.2 Active targeting

Active targeting is an extensively studied nanotechnology strategy for cancer therapy. It involves attaching specialized ligands such as peptides, antibodies, or aptamers to the nanoparticle surface to enable selective recognition of receptors overexpressed on cancer cells. Upon ligand receptor binding, nanoparticles undergo receptor-mediated endocytosis, delivering their therapeutic payload (e.g., chemotherapeutic drugs) directly into target cells with high efficiency, (Fig. 7). A key distinction must be made between tissue-level tumor accumulation and cellular-level uptake [243]. Tumor accumulation is mainly governed by biodistribution, vascular transport, and passive extravasation mechanisms. Active targeting ligands generally do not substantially increase the total amount of nanoparticles reaching the tumor. Their principal contribution lies in enhancing binding affinity. They promote receptor-mediated internalization and improve intracellular

Table 7 Summary of physical strategies for EPR-adaptive delivery

Technique	Physiological effect	Strengths	Weaknesses
Radiation	Decreased intratumoral and interstitial fluid pressure, reduced perfusion, alteration of ECM and vessel growth	Established therapeutic benefit, fits clinical workflow, high penetration depth, utilizes existing clinical resources	Radiation dose and fractionation schedule must be optimized for different tumor types to prevent delivery impairment, damage to surrounding tissue
Ultrasound	Transient disruption of endothelium increases vascular permeability	High penetration depth, non-invasive, localized, minimal damage to surrounding tissue, amenable to repeated treatments, can use existing clinically approved microbubbles	Some strategies require image guidance; some techniques are not compatible with current clinical ultrasound systems
Hyperthermia	Vasodilation, increased vessel permeability	Versatile modes of delivery, potentially non-invasive, localized, exploitable side-effect of other external stimuli	Delivery resistance after repeat sessions, size limitations on eligible sensitizing agents
Photodynamic therapy	Damage to vessels causes transient vascular leakiness	Co-registration of photosensitizers and applied light gives high specificity to area of illumination, potentially non-invasive	Low penetration depth of light necessitates superficial targets or invasive light delivery probes, delay required for photosensitizer build-up before light administration extends clinical burden

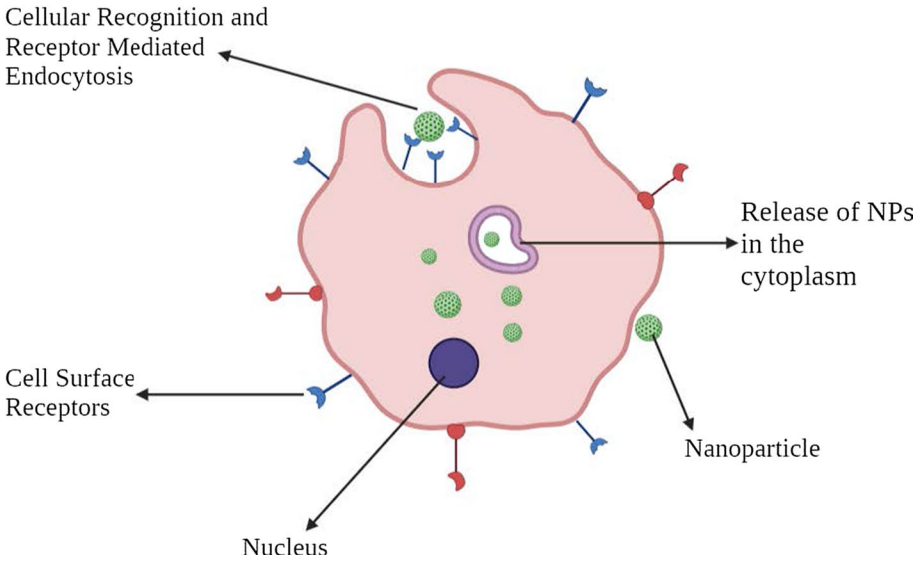

Fig. 7 Active cellular targeting [237]

retention once nanoparticles have extravasated into the tumor microenvironment. The core mechanism relies on the specific recognition of nanoparticle-bound ligands by cell-surface receptors. This recognition triggers endocytosis and efficient intracellular delivery [244]. Commonly exploited receptors include transferrin receptor, folate receptor, glycoprotein receptors, and epidermal growth factor receptor (EGFR). Among these, the transferrin receptor is particularly attractive due to its high expression in many solid tumors and minimal presence in normal tissues. For instance, transferrin-modified PEG–phosphatidylethanolamine nanoparticles have demonstrated markedly enhanced receptor-mediated uptake in A2780 ovarian cancer cells [245]. The multivalent presentation of ligands on nanoparticles further strengthens binding avidity. However, targeting

efficiency strongly depends on nanoparticle physicochemical properties. These include size, shape, ligand density, surface chemistry, and the route of administration [246].

11 Challenges and limitations

Developing nano-therapeutics with high efficacy and tumor-site accumulation rather than normal cells should be the main focus of researchers. The composite nature of NPs makes their toxicity difficult to assess. There is no validated model for assessing nano-bio interactions, especially nano-immuno interactions. Other factors hindering approval are reproducibility and transparency [247]. Additionally, higher cost and complexity restrict translation success.

11.1 Translational and preclinical-to-clinical gap

The journey from drug manufacturing to approval is very complex and time-consuming. Advancements in instrumentation and characterization methods are necessary for successful drug development. The choice of drug selection with a combinatorial regimen for the specific disease and targeted population should also be considered. Biological barriers can disrupt targeted delivery, permeability, penetration, endo/lysosomal escape, intracellular processing and trafficking, and metastasis [248].

11.2 Manufacturing and scalability issues

Lab-scale production of drugs is easier to achieve. However, large-scale manufacturing is challenging due to limited advanced experimental set-ups and insufficient scale-up information. Scalability and batch-to-batch reproducibility present two significant barriers to the advancement of nanomedicines with novel architectures and compositions. Many promising leads are often based on nanomaterials prepared in batches of tens of milligrams, but there are far fewer reports of multigram syntheses of nanomaterials prepared with low (< 5%) size polydispersity. Multigram quantities of nanomaterials are necessary to perform quality preclinical evaluations for in vivo toxicological studies and ADME profiling, prior to filing for IND status, so batch-to-batch variations must be tightly controlled to meet safety standards [249]. Adverse effects may occur due to difficulties during scale-up and challenges in reproducing the preparation process.

11.3 Regulatory and ethical aspects

Developed nanomedicines are generally approved by FDA and EMA. The lack of standard operating procedures for evaluating nanomedicines makes the process more difficult. Checking the drugs for any changes during each phase of clinical trials is crucial for safety and biocompatibility. Well-defined characteristics and the drug's reproducibility are also essential for initiating clinical trials. Chemistry, manufacturing, and control (CMC) challenges also limit progress, requiring attention to material quality, synthetic efficiency, contamination, process automation, and cost-effectiveness [250].

11.4 Biological and delivery barriers

To improve drug delivery, several steps must be considered. These include internalization, circulation, penetration into the tumor microenvironment, binding to the target, and destruction of tumor cells. It is necessary to understand the relationship between NPs' physicochemical properties and their biological responses. In recent years,

researchers have also focused on computer algorithms for achieving proper drug delivery. Opportunities and challenges are two sides of a coin. Clinical trial failures and post-marketing withdrawals of certain nanomedicines due to inadequate efficacy or emerging safety issues exemplify these limitations and underscore the need for clearer, nanomedicine-specific regulatory criteria. More clinical trials are needed to confirm the findings of preclinical and in vitro studies [251]. These trials can help develop a better understanding of how NPs interact with cells and the effects they have.

11.5 Administration route limitations and emerging concerns

The main routes of administration for anticancer drugs are oral, intravenous, and subcutaneous. Newer methods include inhalation, rectal, and pulmonary delivery. However, these approaches are limited by the high toxicity caused by drug deposition and high therapeutic potency. Massive drug doses are needed because of drug loss in the pulmonary tract. In rectal delivery, low absorption is a significant problem. Recently, mitochondria-based targeting has shown great promise in cancer therapy due to the mitochondria's role in tumor progression [252]. Difficulties in clinical trials and biosafety concerns have arisen due to the NPs' positive charge, which can be toxic to normal cells. Another study mentioned that liposomal formulations lose activity over time when exposed to blood proteins. The main drawback of carbon-based nanomaterials is the difficulty in standardization due to their non-uniform nature. Some tumors are difficult to identify due to their small size. Thus, diagnostic techniques must be improved.

11.6 Clinically unsuccessful nanomedicines

These persistent translational challenges are vividly illustrated by several nanomedicines that showed strong preclinical promise but ultimately failed in clinical development. For instance, BIND-014, a PSMA-targeted polymeric nanoparticle loaded with docetaxel, advanced through Phase I/II trials but failed in Phase II for non-small cell lung cancer and metastatic castration-resistant prostate cancer, primarily due to insufficient improvement in efficacy compared to free docetaxel despite targeted design [253]. Similarly, ThermoDox®, a thermosensitive liposomal doxorubicin formulation, did not meet its primary progression-free survival endpoint in Phase III trials for hepatocellular carcinoma, highlighting limitations in controlled release and tumor accumulation under clinical conditions [254]. CALAA-01, a transferrin-targeted polymeric nanoparticle delivering siRNA against ribonucleotide reductase, was terminated early in Phase I due to toxicity concerns and lack of sustained therapeutic benefit [255]. These cases underscore the critical gaps in translating preclinical advantages such as targeted delivery and reduced toxicity into meaningful clinical outcomes, often due to interpatient heterogeneity, inadequate tumor penetration, or unexpected biological interactions. Addressing these through more robust patient stratification, standardized nanotoxicology protocols, and realistic modeling of human tumor physiology remains essential for future success.

12 Future perspectives

Utilization of NPs in cancer immunotherapy may be promising. They can enhance immune system activation for more effective anticancer responses. NPs tailored for tumor antigen delivery to APCs and lymphocytes can carry immunomodulatory chemicals. Engineered NPs deliver TAAs, adjuvants, or immune checkpoint inhibitors to

boost immune response and slow cancer growth. Combining CRISPR/Cas9 with different delivery technologies might help reprogrammed immune cells, such as T and NK cells, by genome editing to recognize and eliminate cancerous cells [256, 257]. Gene editing also affects immune cell activity, enabling them to resist immunosuppressive signals and fight cancer more effectively. Personalized medicine is changing cancer treatment by emphasizing patient-specific needs and therapeutic responses. The discovery of unique tumor biomarkers in genomic and proteomic analyses enables personalized medicine. These vaccines target specific tumor characteristics. As a result, they improve drug specificity and accelerate the immune cells' ability to eradicate tumors. Studies will continue to explore their ability to elicit strong immune responses. Circulating tumor DNA (ctDNA) analysis reveals genetic changes or shifts in tumor burden. This can help monitor treatment responses in real time and suggest adaptive therapy. Clinicians can improve treatment plans using genomic data. Early detection of resistance mutations can lead to switching to more effective anticancer drugs or adjusting drug dosages as tumors evolve. Nanomedicine design, formulation, and treatment efficacy prediction now rely more on AI and ML. AI-driven computer models analyze large datasets to predict nanoparticle behavior and increase drug loading. They also help tailor nanoparticle surfaces for tumor targeting. AI-based algorithms can identify nanoparticle compositions that improve pharmacokinetics, biodistribution, systemic toxicity, and TME drug accumulation. AI-assisted imaging and diagnostics also help evaluate drug efficacy in real time [258]. Future drug delivery systems will offer multifunctional capabilities for both therapy and diagnosis. Smart nanocarriers can allow on-demand drug release and improve tumor penetration. They reduce systemic toxicity and boost efficacy by targeting cancer cells and sparing healthy tissues. This targeting can respond to tumor cues like pH, redox gradients, hypoxia, or enzyme activity [259]. Liposome–polymer conjugates and MOFs help drug loading and enable stimuli-responsive release. MOFs also enhance biocompatibility and improve therapy by co-delivering drugs with distinct mechanisms of action. Therefore, MOFs may enhance cancer treatment in the future.

13 Conclusion

Nanoparticles have revolutionized cancer therapy, offering versatile platforms for targeted drug delivery, improved pharmacokinetics, and integrated theranostics. This includes the development of various synthesis strategies, characterization techniques, and classifications of nanocarriers. Organic carriers excel in biocompatibility and controlled release. Inorganic and hybrid systems offer advantages in imaging, hyperthermia, and multifunctionality. Together, these systems exploit tumor-specific pathophysiology to improve therapeutic indices. Clinical successes, such as liposomal doxorubicin and albumin-bound paclitaxel, highlight nanomedicine's promise. However, challenges such as interpatient EPR heterogeneity, long-term toxicity, manufacturing scalability, and regulatory complexity remain. These challenges underline the gap between preclinical innovation and broad clinical adoption. Addressing them requires standardization, advanced computational modeling, and interdisciplinary collaboration. Looking ahead, integrating AI for predictive design, CRISPR-enabled immunomodulation, and smart, stimuli-responsive nanocarriers may transform precision oncology. These approaches aim to enhance patient outcomes by minimizing off-target effects and overcoming resistance.

Sustained research must focus on translational rigor to fully realize nanotechnology's clinical potential in cancer therapy.

Author contributions
Yosri A. Fahim: Conceptualization, writing original draft, review and editing, Supervision. Ibrahim W. Hasani: Data curation, Writing original draft, review and editing. Samer Kabba: Data curation, Writing original draft, review and editing. All authors have read and agreed to the final version of the manuscript.

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