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Targeted nanodelivery systems for personalized cancer therapy

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Abstract

Conventional cancer therapies such as chemotherapy face challenges such as poor tumor targeting, systemic toxicity, and drug resistance. Nanotechnology offers solutions through advanced drug delivery systems that preferentially accumulate in tumors while avoiding healthy tissues. Recent innovations have enabled the optimization of engineered nanocarriers for extended circulation and tumor localization via both passive and active targeting mechanisms. Passive accumulation exploits the leaky vasculature of tumors, whereas active strategies use ligands to selectively bind cancer cell receptors. Multifunctional nanoparticles also allow the combination of imaging, multiple therapeutic modalities and on-demand drug release within a single platform. Overall, precisely tailored nanotherapeutics that leverage unique pathophysiological traits of malignancies provide opportunities to overcome the limitations of traditional treatment regimens. This emerging field promises more effective and personalized nanomedicine approaches to detect and treat cancer.

The key aspects highlighted in this review include the biological barriers associated with nanoparticles, rational design principles to optimize nanocarrier pharmacokinetics and tumor uptake, passive and active targeting strategies, multifunctionality, and reversal of multidrug resistance.

Key words: nanotherapy; drug delivery; cancer targeting; tumor microenvironment; personalized medicine.

Introduction

Cancer remains one of the leading causes of death worldwide, prompting intense research into more effective and tailored therapeutic approaches. Conventional cancer treatments such as chemical treatment have limited selectivity, resulting in poor bioavailability at tumor sites and systemic toxicity [1, 2]. The emerging field of nanomedicine offers promising solutions through advanced nanoengineering and nanodelivery systems. Recent innovations in nanotechnology have enabled the development of nanoscale platforms that can preferentially accumulate in tumors while avoiding healthy tissues. By leveraging the unique pathophysiological traits of malignancies, nanotherapeutics provide opportunities to overcome the limitations of traditional chemotherapy.

Recent advances in nanotechnology have led to the engineering of diverse nanoplatforms that can preferentially accumulate in tumor tissues while reducing exposure to healthy cells. This tumor-targeting ability is achieved by leveraging unique pathophysiological traits of malignancies. For example, tumors typically have leaky vasculature and impaired lymphatic drainage, allowing nanocarriers of certain sizes to selectively extravasate from blood vessels and penetrate into the tumor microenvironment. This phenomenon is known as the EPR effect [3]. NPs ranging from 10-100 nm in diameter have been shown to effectively exploit the EPR effect for passive tumor targeting after intravenous administration [4].

Additionally, the tumor microenvironment has abnormal physicochemical properties, such as an acidic pH and high reducing capacity [5]. pH- or redox-responsive nanocarriers can be designed to release their drug payload specifically when exposed to these intracellular tumor conditions [6]. Active targeting strategies further enhance selectivity by functionalizing the nanoparticle surface with targeting ligands [7]. These ligands bind to receptors or antigens that are overexpressed on cancer cells compared to those on normal tissues [8]. Some examples include folate receptors, transferrin receptors and lectins [9]. This molecular recognition guides nanotherapeutics directly to cancer cells while avoiding healthy cells lacking these biomarkers [10].

Overall, nanotechnology provides multiple opportunities to overcome the nonselective biodistribution and severe side effects associated with conventional chemotherapies. Engineering nanocarriers that leverage unique aspects of tumor pathophysiology enables more personalized and precise drug delivery. Both passive and active targeting mechanisms significantly improve nanoparticle accumulation in tumors compared to normal tissues [11]. This approach promises to increase treatment efficacy while reducing systemic toxicity. By developing nanotherapeutics customized to cancer traits at the molecular level, nanomedicine provides promising opportunities for advancing cancer treatment [12].

This review discusses the progress and promise of nanobased targeting strategies for cancer therapy.

Nanobased targeting strategies for cancer therapy

First-generation chemotherapeutics are distributed nonspecifically throughout the body, leading to only a small fraction of the administered dose being localized in the tumor [13]. NPs in the size range of 10–100 nm can exploit leaky tumor vasculature to accumulate passively via the EPR effect [14]. Liposomes, polymers, dendrimers, micelles and other nanocarriers have been optimized for extended circulation and tumor localization based on their size, charge and surface chemistry [15]. Ligand-mediated active targeting further improves nanoparticle uptake in cancer cells by facilitating the molecular recognition of overexpressed receptors [16]. Examples of these agents include transferrin, folate and aptamers, which are biomarkers that are upregulated in malignancies [17]. Compared with conventional chemotherapies, combined passive and active strategies enable more precise and personalized delivery.

Another major obstacle addressed by nanocarriers is the poor aqueous solubility of hydrophobic drugs such as paclitaxel [18]. One successful example of protein NPs already used in clinical practice is albumin-bound paclitaxel NPs, which are sold under the name Abraxane [19]. This drug was obtained by high-pressure homogenization of the drug and a bovine albumin solution, resulting in NPs approximately 130 nm in size that can be easily administered intravenously. As shown, Abraxane production can be easily scaled up to industrial levels without loss of stability or therapeutic activity [20]. Therefore, methods such as simple pressure homogenization used in Abraxane represent a promising strategy for the development of other albumin-based formulations. Nevertheless, there is still a need to optimize advanced protein nanostructures for pharmacokinetic properties and drug release profiles.

Encapsulation of drugs with poor solubility in nanoplatforms or conjugation with nanoparticle matrices improves their solubility and enables parenteral administration [21]. Moreover, encapsulation increases the stability of therapeutic drugs, protecting them against enzymatic degradation and the influence of unfavourable pH conditions or ionic forces present in the body [2].

Multifunctionality is another key advantage of NPs. Theranostic nanosystems integrate imaging agents, diagnostic modules, and triggered drug release mechanisms to provide real-time monitoring of therapy [22]. Stimulus-responsive strategies trigger precise drug release within the tumor microenvironment in response to conditions such as acidic pH or elevated oxidative stress levels. Such precise spatiotemporal control over nanobased delivery has the potential to substantially improve patient outcomes through more targeted therapy while reducing adverse effects. For example, polymeric micelles were engineered to stabilize drug cargo at physiological pH while allowing stimulus-mediated release under acidic tumor microenvironment conditions. In vitro and in vivo studies have demonstrated that these micelles exhibit desirable effects, including intracellular pH-responsive drug release, infiltration into tumor tissue, and potent antitumour efficacy with minimal toxicity [23].

Biological barriers that NPs can help overcome

The human body contains several defensive barriers that impede the delivery of therapeutics to target sites. NPs have shown promise in overcoming these obstacles [24].

Intracellular delivery

The cell membrane acts as a selectively permeable barrier, limiting the uptake of exogenous materials such as therapeutic nucleic acids, proteins, and drug molecules into cells. Overcoming this delivery challenge is crucial for medical applications relying on bioactive intracellular agents. Cationic nanocarriers can facilitate intracellular access through electrostatic association with negatively charged biomacromolecules such as DNA, coupled with cell entry via endocytosis and membrane destabilization.

For example, cationic lipids and polymers have been extensively utilized to enhance the intracellular delivery of nucleotide therapeutics. A recent study demonstrated that aptamer-functionalized NPs effectively deliver PD-L1 siRNA to triple-negative breast cancer cells, resulting in almost complete suppression of PD-L1 expression within 90 minutes of treatment [25]. The NPs also displayed minimal systemic toxicity in vivo. Similarly, lipid-based NPs

can effectively bind lapatinib and anti-survivin siRNA for HER2+ breast cancer treatment, potentially enhancing their anticancer activity [26].

Other biomolecular therapeutics have also benefited from cationic nanocarrier-mediated delivery approaches. Recently, Lipid NPs were shown to efficiently deliver gene-editing proteins across the intestinal epithelial layer, proving useful for potential oral drug delivery [27].

Likewise, cationic micelles with shielding polymers can reduce cytotoxicity and maintain cell viability for nonviral gene delivery, offering high potential for in vivo applications [28].

Overall, cationic nanosystems have demonstrated significant potential to overcome cell membrane barriers and enable effective intracellular therapeutic delivery through charge-mediated interactions and endocytic internalization. Careful carrier engineering to optimize physicochemical and biological properties can further improve delivery outcomes in diverse biomedical applications [29].

Delivery across epithelial barriers

Epithelial tissues found in the gastrointestinal tract, lungs, kidneys and other organs form highly selective permeation barriers essential for proper physiological functioning. Tight junctions between adjacent epithelial cells strongly limit the passive transport of exogenous substances due to their extreme impermeability [30]. Orally administered drugs face additional obstacles, including enzymatic degradation in the stomach and poor intestinal solubility. Nanoparticle carriers can overcome several of these delivery challenges to enhance therapeutic uptake across mucosae.

NPs can encapsulate labile drugs, protecting them from harsh conditions in the gastrointestinal environment [31]. The nanoparticle surface can also be functionalized with tight junction modulators to transiently breach paracellular pathways [32]. Alternatively, nanoparticle size (~100 nm) and surface properties may be tailored to promote cell-mediated active transport via transcytosis [33]. Through such mechanisms, NPs increase therapeutic absorption by the intestinal epithelium following oral delivery.

Similarly, for pulmonary delivery, NPs preserve sensitive biomolecular components from airway clearance mechanisms and affiliated enzymes. Cationic NPs strongly interact with negatively charged lung epithelia, triggering caveolae/clathrin-mediated endocytosis and transcellular migration [34]. As such, NPs significantly intensify the transport efficacy of respiratory therapeutics compared with free drugs. Appropriately engineered NPs thus

promote delivery across diverse epithelial barriers, advancing oral, nasal and inhalational pharmacotherapy.

Delivery within the tumor microenvironment

Tumor biology limits therapeutic efficacy through multiple mechanisms. Angiogenesis spurs chaotic blood vessel development, impairing drug perfusion. The resulting high interstitial fluid pressure further impedes nanoparticle penetration into the tumor core [35]. Hypoxic and acidic tumor zones resist both chemo- and radiotherapy due to diminished mechanisms of cell death [36]. Overcoming these complex transport and physiological barriers constitutes a major goal in drug delivery science.

The enhanced permeability and retention (EPR) effect provides one strategy to improve tumoritropic nanoparticle delivery. Aberrant capillary fenestrations permit tumor nanoparticle accumulation, a phenomenon further enhanced by the absence of functional lymphatic vessels [37]. However, deeper tumor penetration necessitates additional targeting and stimulus responsiveness [38]. Multistage NPs undergo stepwise size alteration to migrate through narrow tumor labyrinths. For example, protonation in acidic hypoxic regions triggers polymer expansion, facilitating the release of inner drug payloads [39]. Overall, nanovehicles enable modular solutions to meet the challenges presented by the hostile tumor microenvironment.

Delivery to target immune cells

However, targeting NPs to specific subsets of immune cells is difficult but necessary for modulating immunity. NPs with functional groups activating immune cells in lymph nodes have been designed [40]. Additionally, antibody-coated NPs recognize antigens on the surface of target cells. For example, polymer NPs coated with antibodies directed against CD40, DEC-205 and CD11c receptors on dendritic cells showed increased antigen uptake and the ability to stimulate T cells compared to NPs without such targeting [41]. Similarly, lipid NPs with fragments of antibodies against T-cell antigens allowed for selective labelling and stimulation of these cells after administration to the body [42].

Recently, approaches have focused on delivering NPs to dendritic cells, which are key antigen-presenting cells. For example, manose-modified NPs show increased uptake by dendritic cells via receptor-dependent endocytosis [43]. Lipid-calcium-phosphate NPs coated with single-chain antibodies also achieve selective targeting of dendritic cells in lymph nodes

[44]. This leads to localized delivery of antigens and adjuvants, stimulating strong cytotoxic T-cell responses.

Thus, NPs can be used to deliver drugs or vaccines through surface groups that recognize antigens on immune cells to enable more precise and effective interactions with specific types of leukocytes. The use of such targeted nanocarriers improves the delivery of therapy to specific effector cells and increases immune responses against target antigens.

In summary, the modular design and tunable properties of NPs make them extremely adaptable delivery vehicles capable of penetrating various biological barriers and accessing hard-to-reach targets.

Figure 1.

Precisely engineered nanocarriers for optimized tumor targeting

The selective delivery of chemotherapeutic agents to tumor tissues while avoiding healthy organs is a major challenge in cancer therapy. Nanocarriers have emerged as a promising solution for optimizing drug accumulation in the tumor area through the enhanced permeation and retention (EPR) effect. This effect allows NPs to selectively extravasate through the abnormal leaky vasculature of the tumor and accumulate there. However, the EPR effect is heterogeneous among patients and tumor types, limiting its reliability for precise drug targeting [45]. Therefore, rationally designing nanocarriers with optimized sizes, shapes, and surface properties is essential for enhancing tumor selectivity.

Size and shape modulation

The size and shape of nanocarriers directly impact their circulation time and penetration through tumor tissues. It has been shown that the nanoparticle size should be approximately 100 nm to benefit from both extended blood circulation times through reduced renal clearance and good tumor penetration [46]. Furthermore, compared with spheres, nonspherical nanocarriers, such as nanorods, have demonstrated enhanced tumor targeting owing to their superior margination toward vessel walls and improved diffusion inside tumor tissues [47].

Surface functionalization

Actively targeted nanocarriers can more precisely deliver their drug payload to cancer cells by exploiting ligand–receptor interactions. Specific receptors tend to be overexpressed on the membranes of cancer cells compared to healthy cells. Thus, decorating nanocarriers with

ligands that bind these receptors allows preferential uptake into tumor tissues via receptor-mediated endocytosis [48].

A variety of ligands, including peptides, antibodies, aptamers and small molecules, have been investigated for the active targeting of nanocarriers [49]. These ligands bind to receptors such as transferrin, folate, epidermal growth factor and interleukin receptors, which are commonly upregulated in cancer cells. Receptor–ligand binding triggers endocytosis of the nanocarrier, directing it into endosomes and lysosomes, where the encapsulated drugs are released. This leads to enhanced intracellular drug accumulation and cytotoxicity in cancer cells [50].

Moreover, since ligand–receptor binding is saturable, drug uptake can be optimized by tuning the density of ligands on the nanocarrier surface. Multivalent nanocarriers with multiple copies of targeting ligands have been shown to augment the targeting specificity and further improve drug delivery [51].

Figure 2.

A combination of passive and active targeting strategies is designed to maximize selectivity through enhanced permeability, optimized particle geometry, and specific cancer cell recognition. Tailoring NPs by leveraging cancer pathophysiology and molecular profiles significantly improves specificity compared to untargeted vehicles and conventional chemotherapies [52]. These advances have brought the field closer to realizing truly targeted nanotherapeutics.

Multifunctional nanosystems for cancer therapy

Multifunctional nanosystems are promising platforms for cancer diagnosis and therapy. They combine multiple functions, such as the detection of cancer cells, drug delivery, photodynamic therapy and gene therapy [53]. NPs are modified with appropriate ligands to target their action on cancer cells and elements of the tumor microenvironment [54].

One example is gold NPs coated with folic acid and monoclonal antibodies directed against the HER2 receptor [55]. This allows these nanosystems to selectively bind to breast cancer cells and subsequently release the drugs they contain [56]. Additionally, gold NPs generate heat under infrared radiation, causing hyperthermia and leading to the destruction of cancer cells [57]. Therefore, these NPs have two functions — they deliver drugs and induce hyperthermia.

Another type of promising nanocarrier is mesoporous silica NPs, which, in addition to drug delivery, can be surface modified to obtain additional diagnostic functionalities. For example, by introducing iron oxide nuclei into the structure of these carriers, these NPs gain superparamagnetic properties that enable their use as contrast agents in magnetic resonance imaging [58].

Moreover, the surface of silica NPs can be modified with fluorescent probes whose signal depends on the local pH. Owing to this approach, these nanosystems can be used not only for monitoring drug release but also for imaging the tumor microenvironment and assessing therapeutic response [59].

A separate class of promising nanocarriers for theranostic applications in oncology is made up of superparamagnetic iron oxide NPs (SPIONs). The magnetic core allows precise monitoring of biodistribution via magnetic resonance imaging methods. Moreover, through appropriate surface modification, SPIONs can selectively deliver drugs to cancer cells and tumors [60]. These properties make superparamagnetic iron nanostructures attractive, multifunctional therapeutic and diagnostic platforms [61].

Here are some additional examples of multifunctional nanosystems used in cancer theranostics:

Cancer theranostics are currently using increasingly advanced nanoparticle systems that combine the possibilities of cancer diagnostics and therapy [62]. The main advantage of these materials is the integration of many functions in one nanostructure, which allows for the achievement of a synergistic effect and increased effectiveness of treatment [63].

One example of such systems is graphene NPs coated with platinum compounds and the fluorescent label nigrosin [64]. They can simultaneously detect cancer cells via fluorescence and destroy them by local tissue heating with graphene and platinum [65, 66].

Another type of multifunctional nanocarrier consists of mesoporous silica NPs with anticancer substances trapped in the pores [67]. They release drugs gradually and directly into cancer cells [68]. Additionally, by adapting the surface of these NPs, they can be actively targeted to cancer tumors [69].

Another solution is to modify liposomes with hyaluronic acid, which facilitates their accumulation in tumors [70]. In addition to chemical drugs, these liposomes may contain contrast agents that enable magnetic resonance imaging [71]. This allows real-time monitoring of the distribution of liposomes containing the drug into the tumor.

The possibilities of cancer theranostics are also expanded by polymer NPs with specific surface ligands that direct them to cancer cells [72]. They can deliver interfering RNA

molecules directly to these cells, enabling the silencing of selected genes involved in the progression of the disease [73].

In turn, after entering the cell, lipid NPs with recombinant fusion proteins release the embedded genetic material [74]. This process facilitates cancer gene therapy by providing factors that regulate gene expression or DNA editing complexes [75].

The integration of various diagnostic and treatment methods within single NPs significantly increases the effectiveness of oncological therapies [76]. Importantly, the properties of these nanosystems can be precisely tailored individually to the patient's profile, enabling a personalized approach to therapy [77]. Multifunctional nanotheranostics create new perspectives in cancer therapy.

Figure 3.

Reversing multidrug resistance

Multidrug resistance (MDR) is the main cause of chemotherapeutic failure in cancer patients. The process involves the ability of cancer cells to actively remove various anticancer drugs from inside the cell, which significantly reduces their concentration and effectiveness [78]. However, there are several promising strategies for reversing MDR resistance in cancer cells.

Due to their unique physicochemical properties, NPs are a promising platform for drug delivery and overcoming MDR resistance in cancer cells [79]. They can be functionalized by adding appropriate ligands recognized by receptors on cancer cells to their surface [80]. This leads to active uptake of NPs from the circulation and targeted transport to the tumor [81].

Moreover, the electrical charge and hydrophobicity of NPs can be masked by the addition of biopolymer or PEG coatings. This prevents their detection and removal by ABC transport pumps [82]. ABC transporters are proteins located in the cell membrane that use energy from ATP to actively transport various substrates across the membrane to the outside of the cell [83]. The family of ABC transporters includes P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein (MRP) [84]. They are produced in excess in the membranes of cancer cells. They capture anticancer drugs from inside the cell and actively remove them from the cell [85]. This leads to a decrease in the intracellular concentration of these drugs, preventing them from achieving a therapeutic effect [86]. ABC transporters are therefore responsible for the development of MDR through the pumping out of

chemotherapeutic drugs from cancer cells [87]. Their inhibition or bypass via NPs is a promising strategy for overcoming cancer resistance during treatment [88].

Another strategy is gene therapy, which involves introducing specific genes into cancer cells to combat MDR resistance [89]. The main challenge is the efficient and selective transfer of genetic material to cancer cells [90]. NPs provide an ideal carrier platform in this case [91]. They provide genes encoding enzymes that metabolize drugs, increasing their intracellular concentration, or genes that inhibit apoptosis [92]. This restores the sensitivity of cancer cells to treatment and reverses multidrug resistance by modulating key signalling pathways [93].

Another method is photodynamic cancer therapy (PDT), which involves the activation of a photosensitizer using light of a specific wavelength, which leads to the production of reactive oxygen species that destroy cancer cells. The main obstacle is the low solubility and nonselective distribution of photosensitizers in the body [94,95]. NPs can increase the effectiveness of PDT in several ways.

First, photosensitizers are immobilized, and their solubility is increased. Photosensitizing molecules often have low solubility in water, which makes them difficult to use. The use of polymers (PLGA) or lipid nanocarriers allows for increased solubility, improved release kinetics and modified distribution routes of these compounds from the bloodstream to tissues [96].

Another mechanism is to target PDT by functionalizing the surface of NPs with ligands recognized by receptors overexpressed on cancer cells, such as transferrin or folic acid. This leads to the selective uptake of nanocarriers from the circulation, mainly to the target tissue, reducing systemic toxicity [97].

NPs can also help photosensitizers overcome MDR mechanisms and accumulate in cancer cells by masking their charge or hydrophobicity, which prevents them from being pumped out by transport systems [98].

Conclusions

The presented literature review indicates that precisely targeted drug delivery systems using nanotechnology are a promising therapeutic strategy for cancer treatment, allowing us to overcome the limitations of conventional cytotoxic chemotherapy.

The developed nanotherapeutics can selectively accumulate in cancer tumors through enhanced permeability and retention (EPR) and functionalization of the surface of nanocarriers with ligands recognizing receptors overexpressed on cancer cells. This results in improved bioavailability of drugs at the target site while minimizing systemic toxicity.

Additionally, remarkable progress has been made in designing nanoplatforms that exploit unique features of cancer pathophysiology for targeted transport of therapeutics. Both passive and active targeting strategies significantly improve nanoparticle accumulation in tumors compared to normal tissues.

The combined approaches further enhance selectivity through optimized particle geometry, surface functionalization, and cancer cell recognition. These advances have brought us closer to developing truly personalized nanomedicine.

Additionally, reversible modulation of multidrug resistance in tumors using precisely designed therapeutic nanocarriers allows us to overcome the key limitations of conventional chemotherapy. This enables high concentrations of intracellular therapeutics to be achieved. Thus, owing to the precise adaptation of the structure to the specificity of the tumor microenvironment, nanotherapeutics can bypass the barriers that prevent the effectiveness of typical cytostatics.

Perspectives

In the future, continued innovations in nanocarrier designs and targeting mechanisms promise more precise spatiotemporal control over drug release in the tumor microenvironment. Stimulus-responsive and theranostic strategies also enable real-time monitoring of nanobased therapies. Such integrated diagnostic and therapeutic functions within multifunctional NPs will be crucial to improving patient outcomes. Importantly, the modular and tunable properties of these nanosystems enable continuous improvement to maximize treatment personalization on the basis of cancer molecular profiles.

Given the rapid progression of anticancer nanomedicine, even more sophisticated and patient-tailored therapeutic methods based on precise drug delivery nanosystems are expected in the near future.

Conflict of interest

The authors have no relevant financial or nonfinancial interests to disclose.

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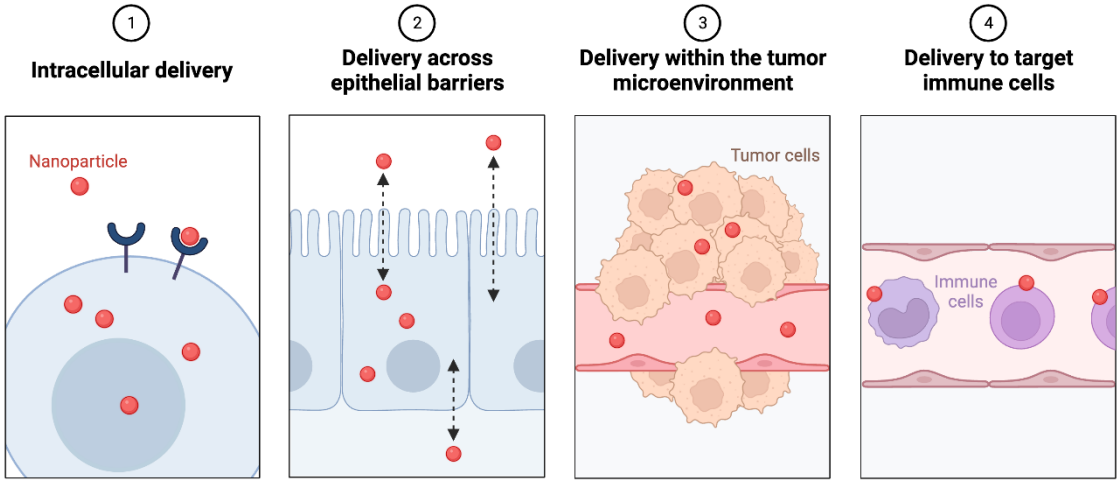
Figure 1. Biological barriers that nanoparticles can help overcome


1
Intracellular delivery
Nanoparticle
2
Delivery across epithelial barriers
3
Delivery within the tumor microenvironment
Tumor cells
4
Delivery to target immune cells
Immune cells

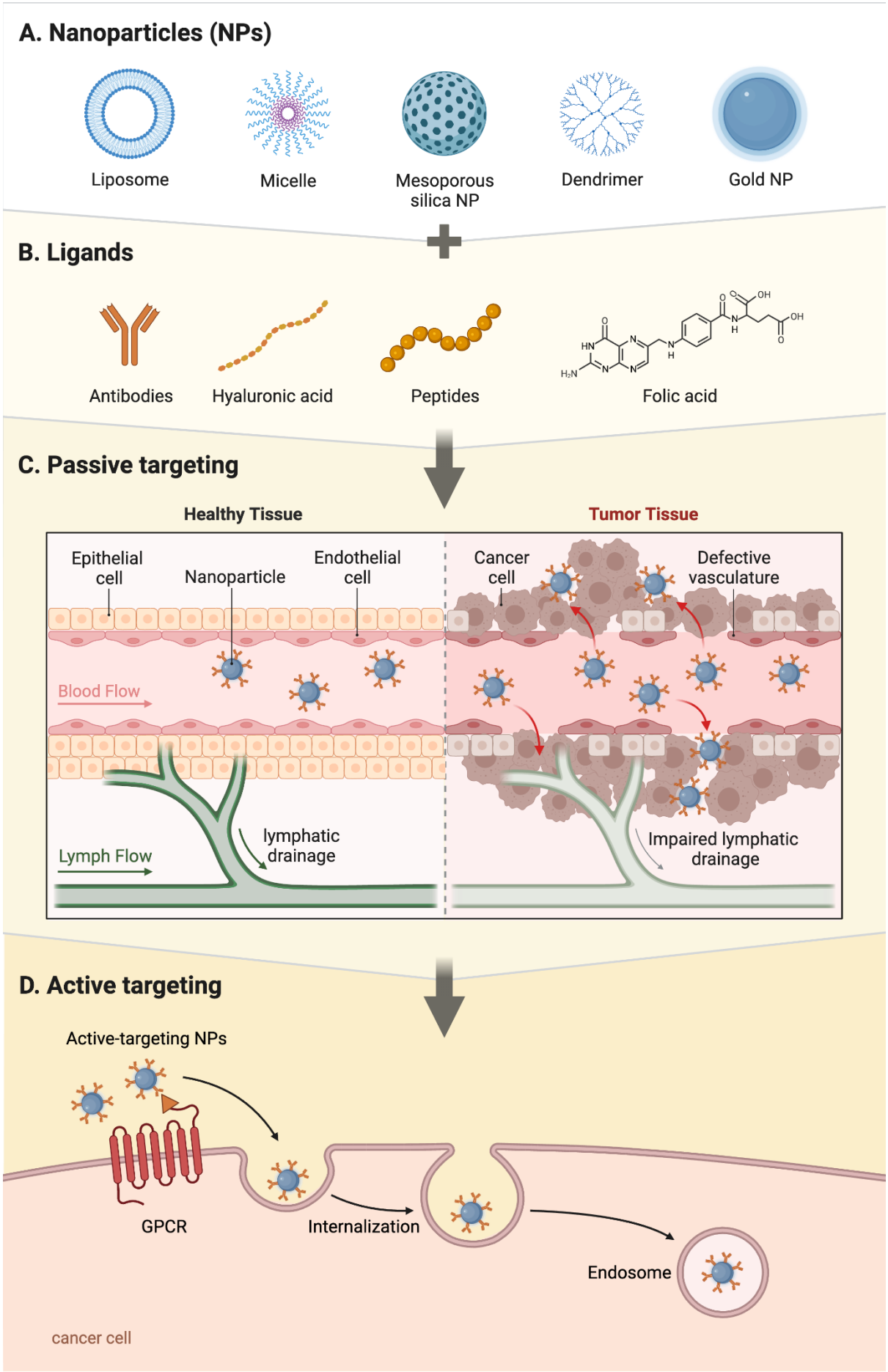

A. Nanoparticles (NPs)
Liposome
Micelle
Mesoporous silica NP
Dendrimer
Gold NP
B. Ligands
Antibodies
Hyaluronic acid
Peptides
Folic acid
C. Passive targeting
Healthy Tissue
Tumor Tissue
Epithelial cell
Nanoparticle
Endothelial cell
Cancer cell
Defective vasculature
Blood Flow
Lymph Flow
lymphatic drainage
Impaired lymphatic drainage
D. Active targeting
Active-targeting NPs
GPCR
Internalization
Endosome
cancer cell

Figure 2. active and passive targeting of nanoparticles to cancer cells. **A.** Nanoparticles (NPs) — NPs are shown as small, rounded objects that can transport drugs or other therapeutic agents; **B.** Ligands — ligands are shown as small molecules attached to the nanoparticle surface that can recognize and bind to receptors on cancer cell surfaces; **C.** Passive targeting — NPs accumulate in the tumor via the enhanced permeability and retention effect. They do not have targeting ligands; **D.** Active targeting — NPs have ligands on their surface that selectively bind to receptors on cancer cells. This leads to enhanced nanoparticle accumulation in the tumor

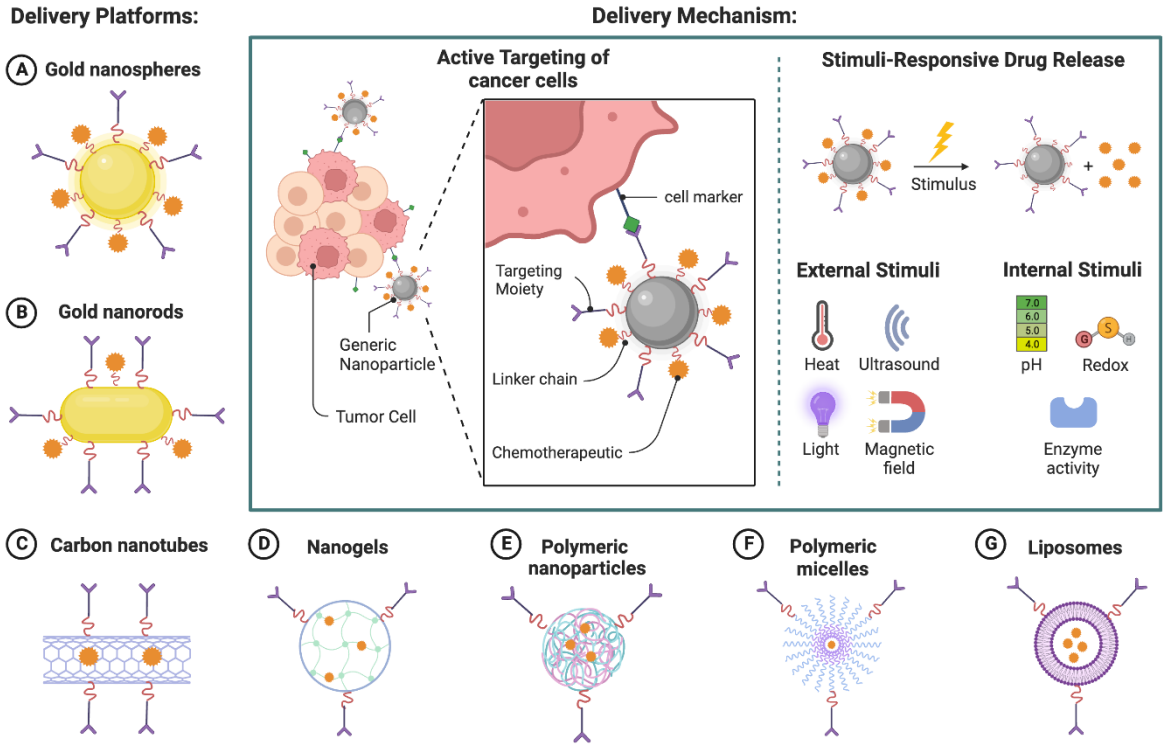


Figure 3. Nanoparticle-mediated targeted drug delivery to cancer cells