



In vivo Fate of Targeted Drug Delivery Carriers

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Abstract: This review aimed to systematically investigate the intracellular and subcellular fate of various types of targeting carriers. Upon entering the body via intravenous injection or other routes, a targeting carrier that can deliver therapeutic agents initiates their journey. If administered intravenously, the carrier initially faces challenges presented by the blood circulation before reaching specific tissues and interacting with cells within the tissue. At the subcellular level, the carrier undergoes processes, such as drug release, degradation, and metabolism, through specific pathways. While studies on the fate of 13 types of carriers have been relatively conclusive, these studies are incomplete and lack a comprehensive analysis. Furthermore, there are still carriers whose fate remains unclear, underscoring the need for continuous research. This study highlights the importance of comprehending the in vivo and intracellular fate of targeting carriers and provides valuable insights into the operational mechanisms of different carriers within the body. By doing so, researchers can effectively select appropriate carriers and enhance the successful clinical translation of new formulations.

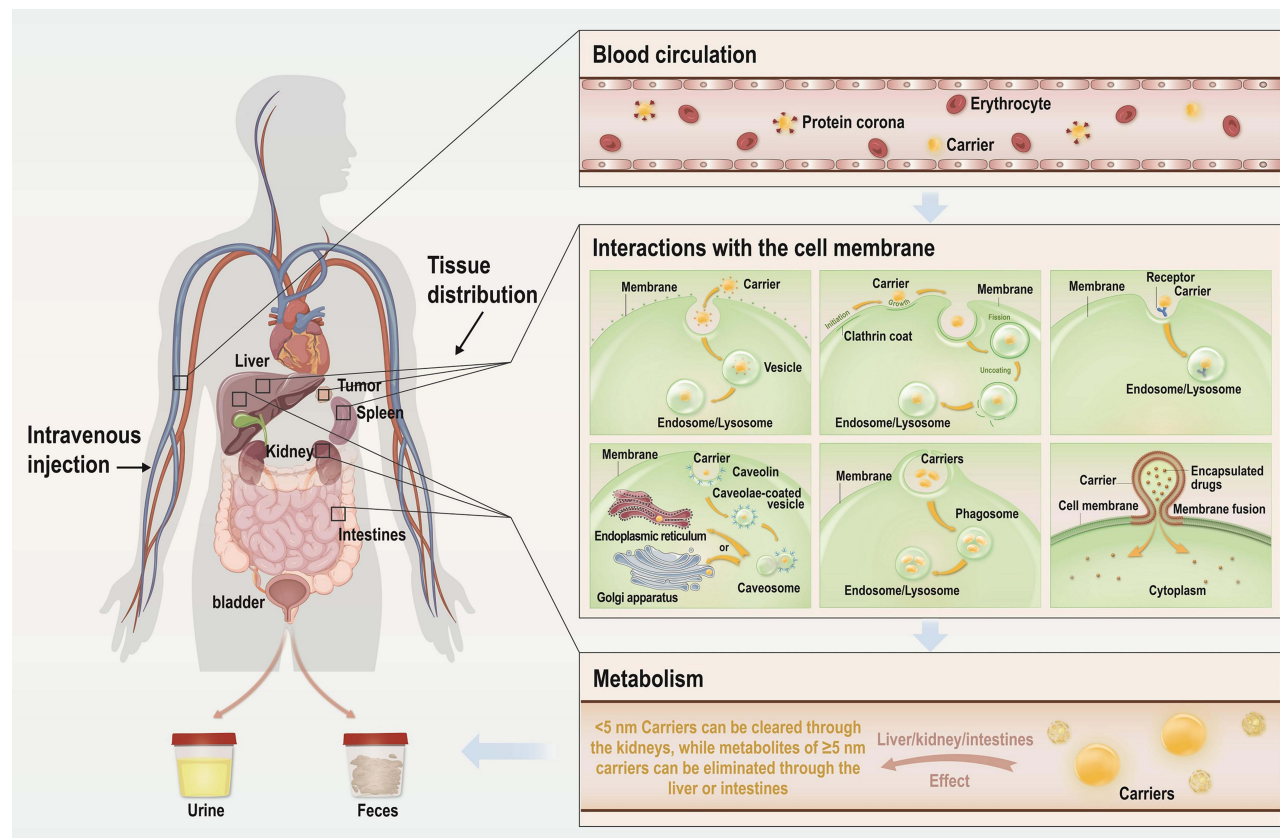
Plain language summary: Nowadays, scientists are actively researching nanocarrier drugs. After administration via injection or other methods, these drugs experience in the body and reach the target treatment site to relieve or cure symptoms. As research progresses, scientists are gaining more insights into the behavior of nanocarrier drugs in the body, which is useful in developing safer and more effective drugs. Historically, research has focused primarily on the drug itself. However, it is important to understand that the carrier that delivers and protects the drug (often described as the drug sitting in a “car” or under an “umbrella”) plays an essential role in the drug’s therapeutic effect. This paper aims to highlight the importance of the carrier’s role, which is vital for developing new drugs and advancing basic research.

Keywords: drug carriers, targeted delivery, in vivo fate, subcellular fate

Introduction

Over the past 70 years, significant advancements have been made in drug delivery technology. A crucial development in modern pharmacy is the invention and implementation of carrier-based drug delivery systems, specifically those using nanometer-sized particles. These carriers offer several advantages over traditional drug delivery systems, effectively addressing various challenges in disease treatment.^{1,2} Nanocarriers are vehicles for drugs, acting as a protective shield within the body. They shield drugs from degradation in the physiological environment throughout the pre-release process, prolonging the drug’s half-life and enabling targeted delivery. Targeted delivery drug carriers, including liposomes, lipid-based nanoparticles, protein-based nanoparticles, polymer nanoparticles, and inorganic nanoparticles, can deliver drugs to designated sites, enhancing drug efficacy, improving drug bioavailability, minimizing damage to normal tissues and cells, and reducing side effects.^{1,3} Traditional systemic drug delivery methods have

Graphical Abstract



several limitations, such as low drug-specific bioavailability, inadequate drug concentration at the target site, and significant adverse effects. As a response to these challenges, targeted therapies have emerged.^{3,4} Moreover, the invention and advancement of targeted delivery drug carriers hold great significance in treating diseases that require precise drug release, such as cancer. The aforementioned targeted delivery drug carriers encompass various types that have gained considerable attention and research, including nanogels, micro/nanomotors, microbubbles, polysaccharide, biomimetic nanoparticles, extracellular vesicles, yeast, and viral vectors.^{5–10} With continuous advancements in passive targeting, active targeting, and other targeting methods, the diversity of targeted delivery drug carriers continues to expand.

Many delivery carriers with targeting capabilities have been mentioned; however, how many nanocarriers have made it to market? We have compiled a table of the nanocarriers approved by the Food and Drug Administration (FDA) (Table 1), including those with “Prescription” and “Discontinued” status. Of these, four of the liposome-based drugs have a “Discontinued” status; only one of the micelle-based drugs was approved but is now also with a “Discontinued” status, and one of the iron oxide nanoparticles-based drugs has a “Discontinued” status. The FDA has approved 13 nanocarriers, six of which are with a “discontinued” status. The discontinuation of a marketed drug is complex and includes (1) problems with the safety, efficacy, or controllable quality of the drugs; (2) emergence of new, more efficacious, decrease in the market share; (3) owing to the control by the relevant departments, the supply of raw materials is difficult because of the environmental pollution, hindering the production; (4) low end-demand and small market share of the disease cured by the drugs; (5) increase in costs of production. In addition to production, market, policy, and other external factors, the efficacy and safety of the drug need extra attention. In the field of nanomedicines, a small proportion of the research focuses on

Table I Summary of FDA-Approved Nanocarrier Drugs to Date (Grouped by Nanocarrier Type, Including Discontinued Nanocarrier Drugs)^a

Carriers	Marketing States	Drug Name	Active Ingredients	Approval Date	Company	Route
Liposomes	Prescription	DOXIL (LIPOSOMAL)	DOXORUBICIN HYDROCHLORIDE	1995	BAXTER HLTHCARE CORP	INJECTION
		ABELCET	AMPHOTERICIN B	1995	LEADIANT BIOSCI INC	INJECTION
		AMBISOME	AMPHOTERICIN B	1997	ASTELLAS	INJECTION
		VISUDYNE	VERTEPORFIN	2000	VALEANT LUXEMBOURG	INJECTION
		EXPAREL	BUPIVACAINE	2011	PACIRA PHARMS INC	INJECTION
		ONIVYDE	IRINOTECAN HYDROCHLORIDE	2015	IPSEN	INTRAVENOUS
	Discontinued^b	VYXEOS	CYTARABINE/ DAUNORUBICIN	2017	CELATOR PHARMS	INTRAVENOUS
		DAUNOXOME	DAUNORUBICIN CITRATE	1996	GALEN (UK)	INJECTION
		DEPOCYT	CYTARABINE	1999	PACIRA PHARMS INC	INJECTION
		DEPODUR	MORPHINE SULFATE	2004	PACIRA PHARMS INC	EPIDURAL
Micelles	Discontinued^b	MARQIBO KIT	VINCRISTINE SULFATE	2012	ACROTECH	INTRAVENOUS
		ESTRASORB	ESTRADIOL HEMIHYDRATE	2003	EXELTIS USA INC	TOPICAL
Albumin carriers	Prescription	ABRAXANE	PACLITAXEL	2005	BRISTOL-MYERS	INTRAVENOUS
Microspheres	Prescription	ZILRETTA	TRIAMCINOLONE ACETONIDE	2017	PACIRA PHARMS INC	INTRA- ARTICULAR
Iron oxide nanoparticles	Prescription	FERAHEME	FERUMOXYTOL	2009	COVIS	INTRAVENOUS
	Discontinued^b	FERIDEX I.V.	FERUMOXIDES	1996	AMAG PHARMS INC	INJECTION

Notes: ^aThe above information comes from the official FDA website (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>). ^b"Discontinued" has been bolded to make it more visible.

using nanocarriers to deliver drugs. In the field of nanocarrier delivery, researchers focus more on the nature of the loaded drug than the nature of the blank nanocarriers. Additionally, there is a tendency to overly concentrate on the design of the nanocarriers themselves. Most pharmaceutical researchers design the carrier in a very subtle way and modify it to have several great properties, expecting them to work effectively in delivering drugs *in vivo*. However, the designed carrier may not function as intended once in the body.

When developing nanocarriers, formulation design and subsequent pharmacological experiments are usually performed by different teams, which poses a major problem as front-end pharmaceutical researchers, although having theoretical knowledge and insights into carrier design, often lack a thorough understanding of the carrier's *in vivo* fate and mechanisms compared to pharmacologists. The process of bringing a nanocarrier to market requires a substantial investment in terms of money, human resources, or material resources. If the drug has poor clinical effects or safety issues, it can result in significant losses owing to the need for rework or abandonment. Therefore, in the early stage of nanocarrier design, we should consider the clinical impact, which requires researchers to have sufficient knowledge about the *in vivo* fate of nanocarriers.

Therefore, pharmacy workers and others involved in nanocarrier research should first study the fate of the carriers *in vivo*, increase the investment in the study of the fate of the blank carriers *in vivo*, and firmly grasp the fate of the carrier *in vivo*. By doing so, the success rate of pharmacological experiments and clinical translation can also be improved, benefiting patients by providing drugs for their conditions promptly.

The above was also our intention while conducting this study, which aimed to provide an overview of the in vivo fate of delivery carriers with targeting capabilities that have been reported. We aimed to compare the subject matter of this study with other studies on similar topics about drug delivery carriers (Table 2).

In conclusion, this article aimed to summarize the in vivo fate mechanisms of 13 major classes of targeted drug delivery carriers that have undergone some research progress. Specifically, this compilation elaborates on their major tissue distribution upon entry into the body, blood circulation time, interaction mechanisms with cell membranes, intracellular transport methods, escape capabilities, degradation and excretion pathways, and potential toxicity. Despite the existence of undefined aspects in the in vivo fate mechanism of the targeted delivery drug carriers summarized in this article, this study can provide valuable references for researchers in selecting targeted drug delivery carriers and gaining a preliminary understanding of their in vivo distribution.

Types of Targeted Drug Delivery Carriers

Presently, various carriers are used for targeted drug delivery. We broadly categorized the delivery carriers with targeting capabilities reported into 13 major categories (Figure 1). We organized their common carriers (We listed the specific carrier categories commonly used, and analyzed these commonly used carriers. The commonly used carrier categories was not listed because they are not generalized designations, belonging to a specific class of carriers, and are subsequently used directly in the analysis), meaning, property, role, the types of drugs that can be transported and their main fields of application, and created a table (Table 3).

Biodistribution

Small molecule drugs are often quickly eliminated by the kidneys upon entering the bloodstream, potentially reducing their efficacy. However, when drugs are loaded into carriers, their circulation half-life is prolonged, leading to enhanced accumulation at the targeted site and promoting therapeutic efficacy. Various targeted drug delivery carriers exhibit unique biological distributions, and the following section discusses three main aspects of the distribution for each carrier.

Targeting

Targeted drug delivery is a promising research approach for treating diseases such as cancer, aiming to deliver therapeutic drugs precisely to the affected site and minimize damage to healthy tissue. This approach improves drug efficacy while reducing side effects.³

Table 2 Theme Comparison of This Review Article with Other Review Articles on Similar Topics (with Examples of Typical Articles)

Review Article	Core Content	Whether or Not The Focus is on Depicting in Vivo Fate	Number of Carriers	Type of Carriers	Examples
This review article	The in vivo fate of 13 major classes of targeted drug delivery carriers	Yes^b	13 major classes^b	Targeted drug delivery carriers^b	N/A ^a
Other review articles similar to the topic of this one	The in vivo fate of a drug delivery carrier	Yes^b	One	Drug delivery carriers	[11]
	A review of one or more targeted drug delivery carriers	No	≥1 (<number of this articles)	Targeted drug delivery carriers^b	[2,3]
	A review of one or more carriers for the treatment of a particular disease or for a particular route of administration	No	≥1 (<number of this articles)	Drug delivery carriers	[12,13]

Notes: ^a“N/A” means “not applicable”. ^bBolded is to highlight.

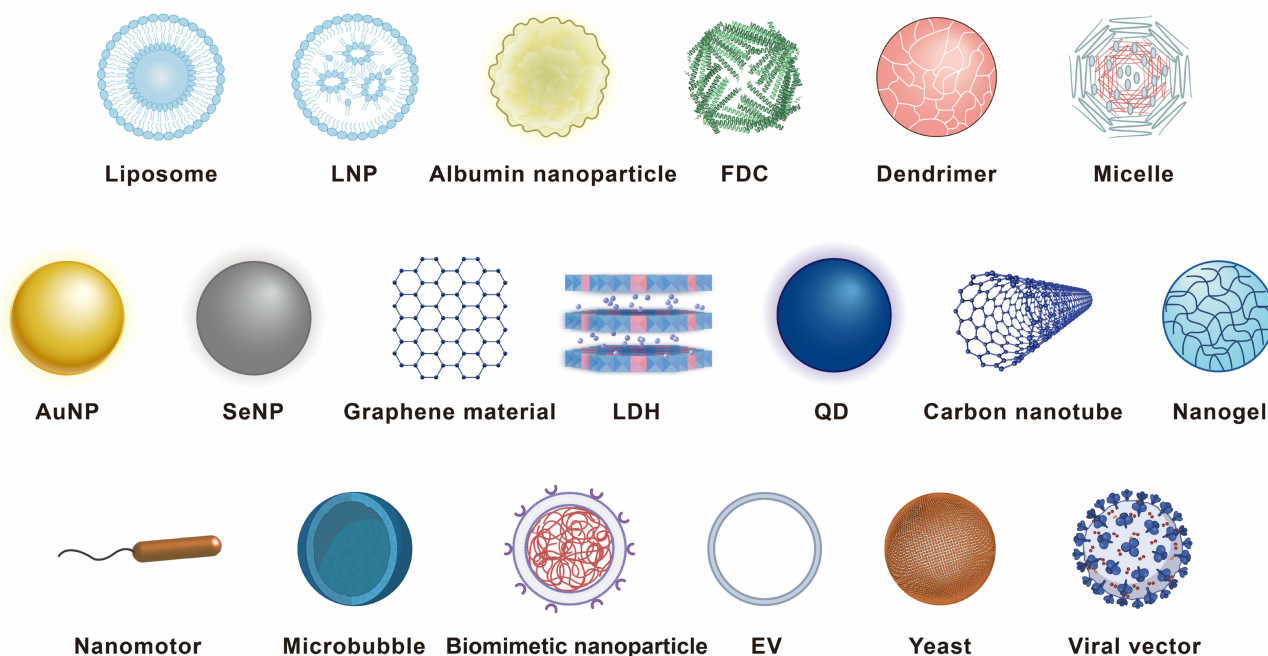


Figure 1 Schematic diagram of targeted drug delivery carriers.

Targeted drug delivery can be achieved through three main strategies: 1) passive targeting, primarily based on the carrier's size, and Enhanced Permeability and Retention (EPR) effect. The EPR effect refers to high permeability and prolonged retention of substances <200 nm in solid tumors. The lack of vascular support tissue, poor structural integrity, and large inter-endothelial cell gaps in tumors allow carriers <200 nm to easily penetrate the vascular wall and enter tumor gaps. Furthermore, tumors lack lymphatic vessels, preventing the carried drugs from being drained and enabling long-term accumulation.^{59–61} 2) Active targeting mode: addition of targeting ligands. Targeting ligands are substances with a high affinity for the target site, including folate, transferrin, peptides, antibodies, aptamers, and oligosaccharides. These ligands bind to specific receptors over-expressed in the lesion tissue, facilitating targeted drug delivery.^{61,62} 3) Physicochemical targeting mode: using physical and chemical methods to enable targeted formulations to exert their therapeutic effects in specific locations. The carriers prepared via this method are stimulus-sensitive carriers, which undergo rapid changes when exposed to external stimuli (such as light, magnetic fields, high temperature, ultrasound) or special target site environments (such as enzyme overexpression, low pH), releasing the drugs they carry and achieving accurate drug release at the target site.^{63,64}

Passive Targeting

Carriers based on passive targeting patterns are liposomes,⁶⁵ lipid nanoparticles (LNPs),⁶⁶ albumin carriers,⁶⁷ follicular dendritic cell (FDC),⁵⁹ dendrimers,²⁴ micelles/ polymeric micelles (PMs),^{68,69} gold nanoparticles (AuNPs),³⁷ nanogels,⁷⁰ microbubbles,⁷¹ angelica sinensis polysaccharide (ASP),⁴³ extracellular vesicles (EVs),⁷² adeno-associated viral (AAV) vectors.⁷³ Carriers that target specific sites without adding ligands belong to the passive targeting strategy. The targeting mechanism of passive targeting carriers is as follows.

Liposomes, Dendrimers, and LNPs

Carriers with a diameter <200 nm, such as liposomes and dendrimers, are easily passively targeted to tumors because the endothelial walls of healthy tissues are tightly connected, preventing the carriers from entering. In contrast, tumors have larger inter-endothelial gaps and more porous capillaries, resulting in higher permeability. The amount of carriers taken up by tumors can be >100 times higher than that of healthy tissues.^{24,59,74,75}

Table 3 Summary of a Brief Description of the 13 Major Classes of Targeted Drug Delivery Carriers

Types of Targeted Drug Delivery Carriers	Common Carriers	Meaning	Drugs Capable of Transport	Property	Role	Main Fields of Application ^b	References
Liposomes	N/A ^a	Nano-sized vesicles with a phospholipid bilayer structure	Hydrophilic or hydrophobic	Flexible synthesis capabilities	Improving drug delivery efficiency and treatment efficacy	Cancer treatment, bacterial infections, fungal diseases	[14–17]
Lipid-based nanoparticles (LNPs)	N/A ^a	Lipid shells around the inner core	Small molecule drugs and nucleic acids	Controllable composition, high payload capacity	Overcome the multiple biological barriers	RNA-based therapy	[14,18–20]
Protein-based nanoparticles	Albumin carriers ^c , Ferritin drug carrier (FDC)	Nanoparticles derived from proteins	Non-specific	Easily surface modification, controlled particle size	Protect drugs from enzyme degradation and kidney clearance, improve drug stability and activity	Lung delivery, cancer treatment	[21–23]
Polymer nanoparticles	Dendrimers, micelles	Particles synthesized from polymers	Poorly soluble drugs	Controlled release	Protect drugs, improve drug bioavailability and therapeutic activity	Cancer treatment	[24–28]
Inorganic nanoparticles	Au nanoparticles (AuNPs), selenium nanoparticles (SeNPs), graphene materials, layered double hydroxides (LDHs), quantum dots (QDs), carbon nanotubes	Particles with dimensions on the nanoscale that are composed of inorganic materials	Non-specific	Different properties depending on inorganic material and structure	Protect drugs from degradation and leakage in physiological environments	Tumor drug delivery, gene transfer, photothermal therapy, biomedical imaging	[29–32]
Nanogels	N/A ^a	Three-dimensional water-based multifunctional carriers formed through molecular cross-linking	Non-specific	High stability, loading capacity, stimulus sensitivity	Withstand shear forces and serum proteins in the blood	Neurodegenerative diseases, brain tumors, epilepsy, ischemic attacks treatment, gene therapy	[33–36]

Micro/nanomotors	N/A ^a	Self-propelled micro-engines	Non-specific	High-speed movement, automatic propulsion, penetration of complex cell environments	Transport cargo to target sites using fuel as a driving force	Responsive drug release, deep tissue penetration, cancer treatment	[37–39]
Microbubbles	N/A ^a	Small bubbles coated with magnetic or drug-containing nanoparticles	Non-specific	Echogenic properties	Release drugs in the body upon ultrasound activation	Cardiovascular diseases, inflammation, cancer treatment	[40–42]
Polysaccharide	Angelica sinensis polysaccharide (ASP), chitosan	Natural macromolecular polymers composed of multiple monosaccharides linked together through linear or branched glycosidic bonds	Non-specific	Renewability, ease of modification	Improve the water solubility, stability, and permeability of drugs, promote drug absorption, and cross the biological barrier	Immunology, tumor therapy, inflammation, hyperglycemia	[43–48]
Biomimetic nanoparticles	Nanoparticles enveloped in platelet membranes or red blood cells (RBCs)	Nanoparticles enveloped in membranes derived from various sources	NPs	Biomimetic properties	Evade the immune system and accumulate efficiently at lesion sites	Immunology, tumor therapy	[44,49,50]
Extracellular vesicles (EVs)	Exosomes	Membrane-bound particles derived from cells	Non-specific	Circulatory stability, endogenous	Improve the stability and efficiency of the drug, reduce the frequency of the drug	Gene therapy, cardiovascular treatment	[51–54]
Yeast	N/A ^a	A shell with a porous surface and a hollow interior	Nucleic acid compounds, insoluble small molecule drugs	A short growth cycle, high speed, low production cost	Facilitates simple gene replacement or mutation	Genetic analysis, inflammation, tumor therapy, vaccinology	[9,55]
Viral vectors	Adeno-associated viral (AAV) vectors, adenoviral (Ad) vectors, lentiviral vectors	Viruses that have been artificially modified to lose their pathogenicity and carry exogenous genes	Genes	High transduction efficiency, ability to maintain stable expression	Help to transfect the genes, trigger robust cellular and humoral immune responses	Gene therapy, cancer treatment, immunological disorders, and other severe diseases	[10,56–58]

Notes: ^a“N/A” means “not applicable”. ^bThis application is investigative studies. ^c“Albumin carriers” mean albumin nanoparticles, not albumin-coupled drugs.

LNPs can bind with apolipoprotein E (ApoE) in plasma to form ApoE-bound lipoproteins, which are mainly cleared by the liver, allowing LNPs to reach the liver preferentially for liver targeting. This method is commonly used to deliver RNA to the liver using cationic or ionizable LNPs. The presence of ionizable lipids and intentional short acyl chain PEG lipids enhance the ability of LNPs to deliver RNA compared to liposomes. Liver targeting is insufficient for treatment, as specific cell targeting is often necessary. Therefore, Kim et al modified the overall size of LNPs by adjusting the polyethylene glycol (PEG) content, specifically targeting hepatocytes.⁷⁶ Lipid nanoparticles (LNPs) can be modified to selectively target specific cell types. They offer the benefits of delivering mRNA with high transfection efficiency, high expression levels, and good stability, making them crucial carriers for mRNA vaccine development.⁷⁷

Albumin Carriers and FDC

Albumin carriers can specifically bind to cell surface albumin receptor (gp60), which binds to intracellular caveolin-1, leading to membrane invagination and the formation of caveolae. Caveolae can transport albumin carriers to tumors, making carriers bind to secreted protein acidic and rich in cysteine protein overexpressed in tumors, thereby targeting the albumin carriers to the tumor.⁷⁸ The tumor-targeting effect of ferritin is ten times greater than that of the EPR effect. Ferritin does not require surface modification as it naturally targets tumors through its specific affinity for transferrin receptor 1 (TfR1), which is overexpressed in malignant tumors. Ferritin is the optimal size of 12 nm for inducing the EPR effect caused by disrupting the blood and lymphatic systems in tumors.⁷⁹

AuNPs, Nanogels, and ASP

AuNPs, after being injected into the body, can accumulate in inflammatory and tumor sites through the enhanced permeability and EPR effect to achieve passive targeting.³⁷

Nanogels also accumulate at the site of lesions through the enhanced permeability and EPR effect to achieve passive targeting. However, the targeting capabilities of these nanogels are low; therefore, current nanogels are mostly designed as active targeting agents by adding ligands and other methods.⁷⁰

ASP has a high affinity for the asialoglycoprotein receptor that is highly expressed in the liver, allowing for liver targeting.⁴³

EVs, Yeast, and AAV Vectors

EVs can cross physiological barriers and target tissues through their surface protein markers.⁸⁰ However, some problems are encountered in the targeting design of EVs because of the complex composition and naturally highly heterogeneous of EVs, which influence the therapeutic effect.⁸¹

The mechanism of specific targeting of phagocytes by yeast carriers is unique. The β -glucan in the yeast cell wall can specifically bind to pattern recognition receptors on phagocytes, thereby targeting phagocytic cells.⁵⁵

AAV vectors, such as AAV8, target the liver, and AAV1 and AAV5 target cells in the central nervous system.⁷³

Active Targeting

Carriers based on active targeting patterns are biomimetic nanoparticles and carriers modified with folate, transferrin protein, peptides, antibodies, aptamers, hyaluronic acid (HA), PEG, and oligosaccharides.^{49,62,82}

Folate, transferrin protein, peptides, antibodies, aptamers, HA, and oligosaccharides can bind with specific receptors overexpressed in lesions, allowing carriers to target lesion sites. For example, folate receptor (FR) and TfR in tumors are responsible for the uptake of folate and iron, respectively. Tumors need a large amount of folic acid and iron during rapid proliferation. Folate and transferrin can bind to FR and TfR expressed at high levels in cancer cells with high affinity, mediating carriers modified with folate or transferrin to target tumor tissues, respectively.^{83,84} HA can bind to CD44 receptors that are significantly expressed in cancer cells, targeting carriers modified with HA to cancer cells.⁸⁵

The emerging targeting strategy is to load drugs for precisely targeted delivery by using vesicles from disease cells or some cell membranes that contain receptors on their surface that bind specifically to cells at the site of the disease as carriers. For example, Yon et al⁸⁶ developed a bio-compatible tumor cell-derived extracellular vesicle biomimetic porous silicon nanoparticle as a drug carrier for targeted cancer therapy (Figure 2). This carrier exhibits enhanced tumor accumulation and penetration into the deep tumor. The developmental idea of using biomimetic extracellular vesicle nanoparticles derived from tumors as drug carriers for targeted chemotherapy in cancer is a proof-of-concept and provides new design ideas for researchers developing targeted delivery drug carriers.

Yan et al⁸⁷ prepared a penetrating macrophage-based nanoformulation (MZ@PNM)-encapsulating hydrogel (MZ@PNM@GCP) that responded to the periodontitis microenvironment. The loaded nanoparticles (MZ@PNM) could specifically target porphyromonas gingivalis, a key mediator of periodontitis, through their Toll-like receptor 2/1 mimicking membrane on macrophages. Subsequently, the macrophage membrane fused with the bacterial outer membrane, and the cationic nanoparticles within MZ@PNM disrupted the bacterial structure and released metronidazole in the bacterial cytoplasm (Figure 3).

Physicochemical Targeting

When the physicochemical target carriers are exposed to external stimulation or are in a target site environment, they will rapidly change and release their loaded drug to achieve the effect of precise drug release at the target site. For example, thermo-sensitive liposomes, photo-sensitive liposomes, ultrasound-guided carriers, and pH-sensitive carriers are all based on this design.⁸² Thermo-sensitive liposomes are sensitive to temperature, photo-sensitive liposomes are sensitive to light, and ultrasound-guided carriers are guided by ultrasound, all of which are precisely delivered to target sites under external stimulation. The mechanism of pH-sensitive carrier release is that in different pH environments inside the body, pH-sensitive carriers are sensitive to the pH of a specific environment and undergo structural or other changes, thereby releasing the loaded drugs in that location, achieving precise drug release. Generally, there are two types of pH-sensitive carriers. One type is polymers containing ionizable functional groups, which protonate owing to pH changes, resulting in changes in hydrophilic–hydrophobic balance and changes in structure or solubility. The other type has acid-labile bonds; therefore, they are cleaved in acidic environments, leading to changes in carrier structure and drug release.⁸⁸ For example, the pH of plasma, the tumor microenvironment, and the pH of lysosomes and nuclei are neutral (6.5–7.0) and acidic (4.5–5.5), respectively. Therefore, carriers sensitive to an environment with a pH of 6.5–7.0 can release drugs precisely in tumor environments, achieving tumor targeting.^{89,90}

Moreover, carriers with dual sensitivity can be combined to achieve dual targeting control, such as thermo-sensitive magnetic liposomes, which are thermally sensitive and magnetically guided, making them more suitable for the special properties of the lesion location.⁸²

In addition to carriers with inherent targeting properties, other carriers mostly need to be modified on the surface to have targeting properties to cells and tissues. Researchers have also discovered some materials that are very suitable for developing targeted carriers, such as selenium nanoparticles (SeNPs),⁹¹ graphene and its composite materials,⁹² layered double hydroxide (LDHs),⁹³ quantum dots (QDs),⁹⁴ chitosan,⁹⁵ adenovirus vectors,⁹⁶ and lentiviral vectors.⁹⁷

Different targeted drug delivery carriers have different targeting mechanisms, and selecting targeting carriers can be based on the site and characteristics of the disease to be treated. For example, we can choose a carrier that can specifically bind to the lesion or passively target the lesion, or we can modify a carrier with better performance to make it actively target the lesion. Furthermore, a responsive targeting vector can be designed to target some focal sites with special environments. If the microenvironment of a focal site has a low pH, a targeting vector sensitive to low pH can be designed so that it is released at that site but not in a normal pH environment. Precisely targeted carriers for release can also be achieved by designing carriers externally controlled or stimulated by delivering the carrier through control or stimulation such as light, heat, temperature, and magnetic field.

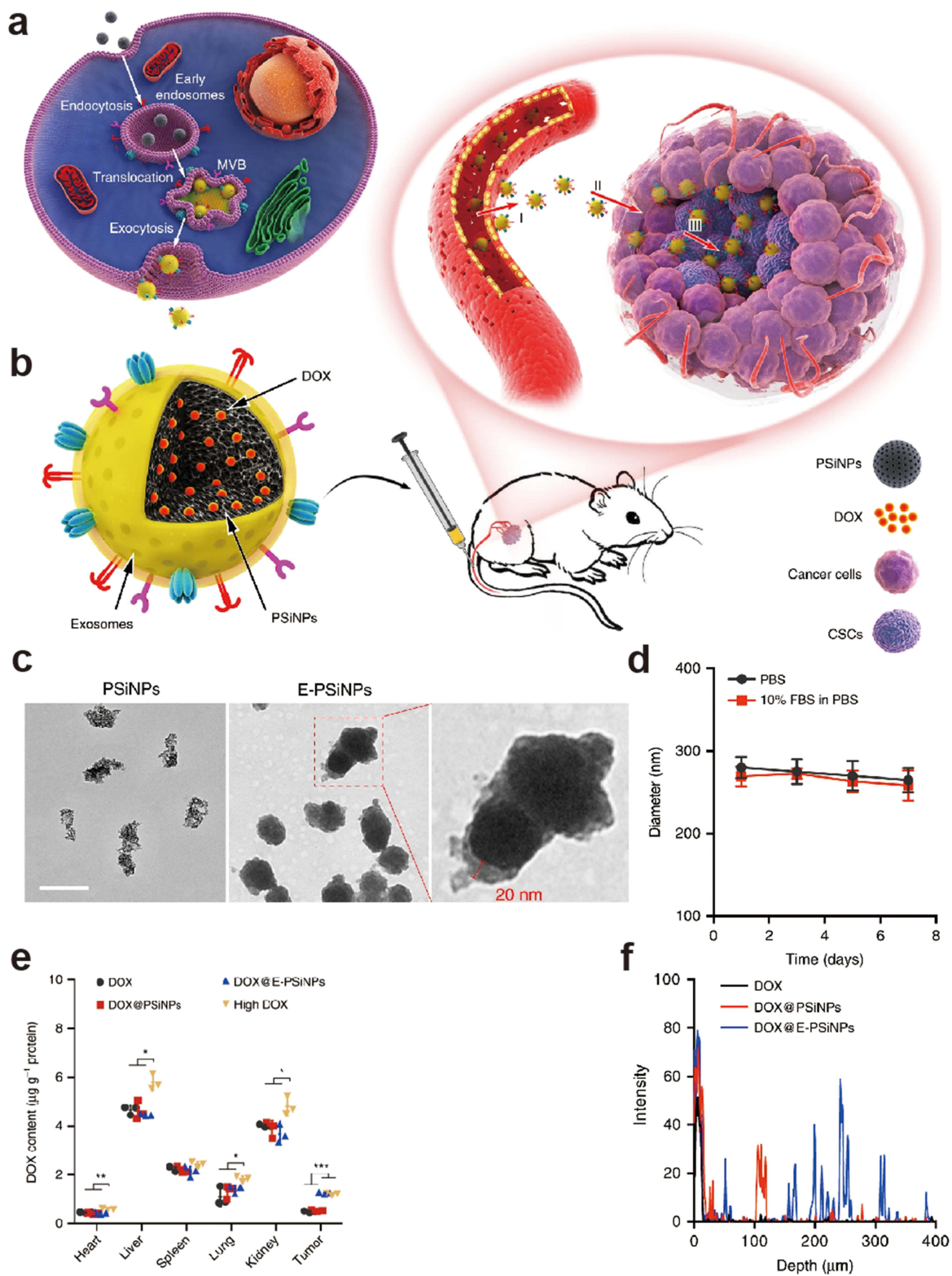


Figure 2 (a and b) Schematic diagram of E-PSiNPs as drug carriers for targeted cancer chemotherapy. (c) Transmission electron microscope images of PSiNPs and E-PSiNPs. (d) Hydrodynamic diameter of E-PSiNPs incubating in phosphate-buffered saline with or without 10% fetal bovine serum for different intervals. (e) DOX content in tumor tissues and major organs of H22 tumor-bearing mice 24 h after intravenous injection. (f) Penetration of DOX@PSiNPs or DOX@E-PSiNPs into tumor parenchyma. Reprinted from Yong T, Zhang X, Bie N, et al. Tumor exosome-based nanoparticles are efficient drug carriers for chemotherapy. *Nat Commun.* 2019;10(1):3838. Creative Commons.⁸⁶

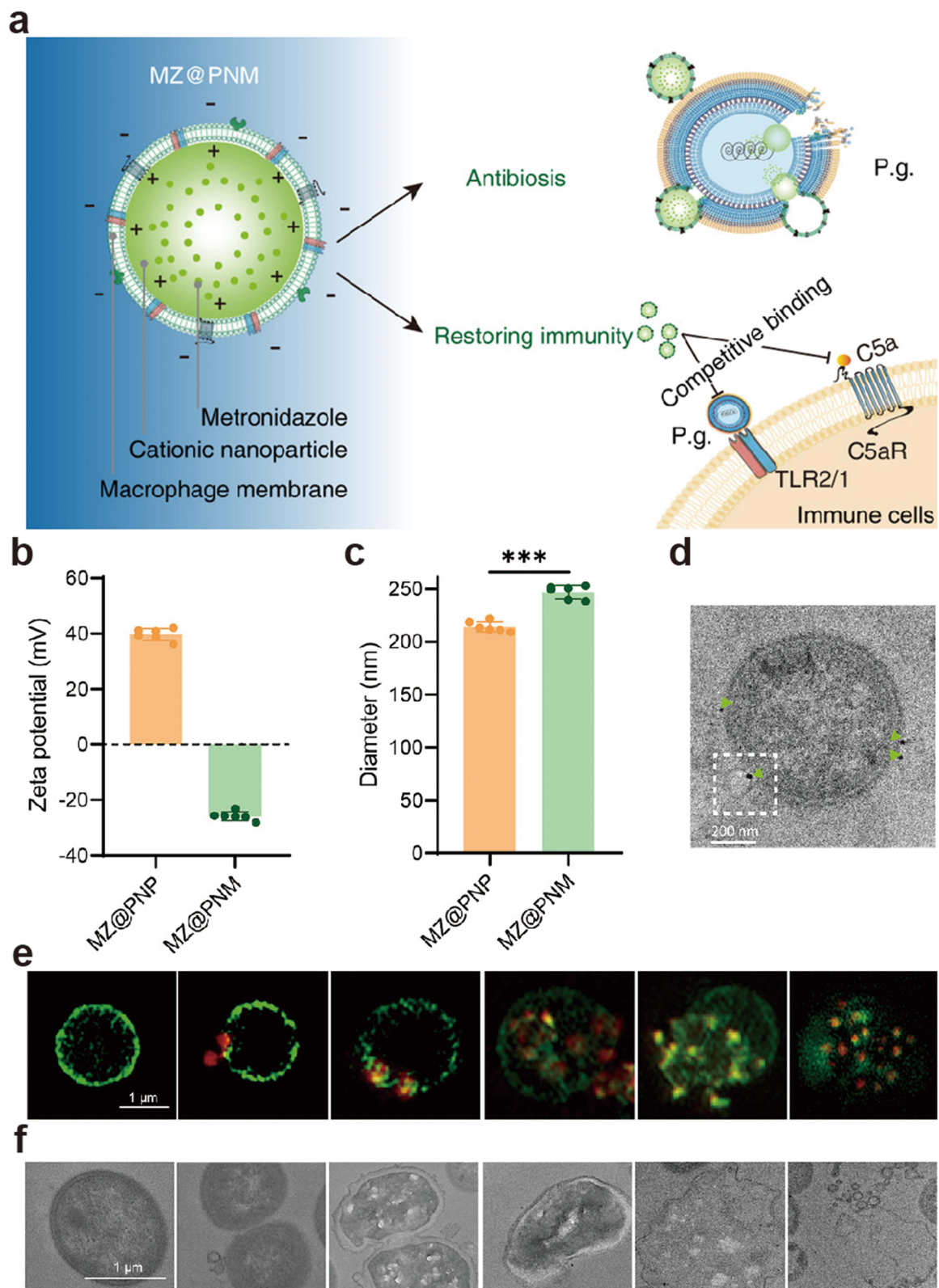


Figure 3 (a) Schematic diagram of the action of MZ@PNM in targeting and killing P.g. (b–c) Zeta potential and diameter characterization of MZ@PNM and MZ@PNP. *** $p < 0.001$. (d) Representative TEM image of the nanomacrophages targeting P.g. (e–f) Representative fluorescence image and TEM images of the destruction of P.g. by MZ@PNM over time. Reprinted from Yan N, Xu J, Liu G, et al. Penetrating Macrophage-Based Nanoformulation for Periodontitis Treatment. *ACS Nano*. 2022;16(11):18253–18265. Copyright © 2022, American Chemical Society.⁸⁷ P.g., Porphyromonas gingivalis; TEM, Transmission electron microscope.

Major Tissue Distribution

Generally, carriers with a diameter <5 nm are easily cleared from the circulation, while carriers >50 nm accumulate non-specifically in the liver, which has fenestrations with a length of 50–100 nm. Carriers with a diameter >200 nm accumulate in the spleen, which has fenestrations with a length of 200–500 nm.^{2,98,99} However, the specific distribution of particles with diameters ranging from 20–150 nm is also influenced by their charge and shape. For example, among particles of this size, those shaped like cylinders or discs are more likely to distribute to the liver and spleen.⁹⁸ Below is a summary of the major tissue distribution of various carriers.

Liposomes, LNPs, and Graphene Materials

Conventional liposomes and LNPs, which are carriers composed of lipids, are recognized and taken up by the reticuloendothelial system (RES) after intravenous injection, with most accumulating in the liver and spleen (RES organs), and after oral administration, they are hydrolyzed in the gastrointestinal tract, with only a few remaining carriers able to circulate to the target site.^{11,14,63} After LNPs are administered through the intramuscular route, they first accumulate in the muscle tissues, then enter the systemic circulation through the lymphatic system and the blood circulatory system, part of which will be taken up by the RES organs such as the liver, and the remaining will reach the corresponding target site to deliver mRNA according to the design.¹⁰⁰

Graphene and graphene oxide are mainly distributed in the liver after entering the body and are taken up by the RES.¹⁰¹

EVs

EVs entering the body are primarily accumulated in the liver, followed by the spleen, gastrointestinal tract, and lungs, although the actual distribution of EVs from different cells and in different amounts may vary.¹⁰² For example, ginger-derived extracellular vesicles remain in the gastrointestinal tract for a long time after oral administration, while grape fruit-derived extracellular vesicles mainly accumulate in the lungs and brain after nasal administration.^{103–105} Additionally, exosomes accumulate most in the liver, followed by the spleen, gastrointestinal tract, and lungs, although excessive accumulation of exosomes in the liver is relatively low owing to the phagocytic system's uptake threshold.¹⁰⁶

PEG-modified carriers affect carrier distribution in tissues, reducing steric hindrance, forming a barrier to prevent the modulatory effect of serum proteins, reducing phagocytosis by the RES, and protecting the carrier from uptake by the liver.⁶⁴

Blood Circulation Time

When the carriers enter the bloodstream, they will adsorb plasma proteins, such as serum albumin, lipoproteins, complement components, and immunoglobulins, and form a protein corona on its surface. This structure makes the carrier more prone to attaching to specific receptors on the surface of phagocytes for phagocytosis, thereby shortening its circulation time in the bloodstream and affecting its stability and fate in the body. Additionally, the circulation time of the carrier in the bloodstream is also related to its shape. For example, filamentous polymer micelles align with the blood flow owing to their shape, resulting in longer circulation times than spherical polymer micelles.^{98,107} Therefore, different targeted drug delivery carriers have different circulatory times in vivo. The following are discussions on the circulatory time of various carriers in vivo.

Liposomes, LNPs, Dendrimers, and Micelles/PMs

Conventional liposomes are easily eliminated by the RES owing to their easy uptake, resulting in a short circulatory time.⁶³ Newly developed long-circulating liposomes, which combine liposomes with some chemically and biologically inert synthetic polymers, can prolong the circulatory time of drugs in vivo.²

NPs with a diameter of 10–100 nm are not easily engulfed by the RES and generally have longer circulatory times, while larger NPs are easily engulfed by the RES and have shorter circulatory times.² LNPs with a diameter <200 nm are not easily taken up by the RES and are cleared by the RES, resulting in a longer circulatory time.⁹⁹

Conventional dendrimers have a short circulatory time owing to their small volume of 10 nm, which makes them easily cleared *in vivo*.²⁴ Micelles and PMs have a hydrophilic outer shell and are 10–100 nm in diameter, making them not easily taken up and cleared by the RES, resulting in a longer blood circulation time.^{68,108,109}

Albumin Carriers

Endogenous albumin circulates for approximately 19 days because when it enters the endothelial cells, the FcRn receptors in the endothelial cells expel the albumin from the cells via exocytosis, and the albumin returns to the bloodstream through the lymphatic system, resulting in prolonged circulation. However, if albumin is made into albumin nanoparticles or modified into drugs, the circulation time will be reduced to an extent.⁶⁷

AuNPs, Graphene Materials, QDs, Nanogels, and Microbubbles

AuNPs have a short plasma half-life, which is mainly influenced by two substances in the body that affect the carrier's half-life, namely opsonins and dysopsonins. Opsonins (such as complement and immunoglobulin supplements) can promote the rapid engulfment of liposomes via the RES, while dysopsonins (such as serum albumin and lipoprotein) can improve the circulation half-life of liposomes by preventing engulfment.⁷⁴ Opsonins are easily adsorbed onto the surface of AuNPs, promoting the clearance of AuNPs by phagocytes, resulting in a short half-life for AuNPs.⁸⁹ Graphene and graphene oxide are easily cleared from the blood, resulting in a short circulatory time.¹¹⁰ QDs' coating materials have certain immunogenicity, which can easily cause an immune response in the body, leading to the clearance and ineffectiveness of QDs, resulting in a short half-life. However, if low-toxicity materials such as carbon and silicon are used for preparation, their circulation time can be prolonged.¹¹¹

Nanogels with a size of 20–200 nm are not easily engulfed by the RES and have a longer blood circulation time.³³ Using ultrasound-mediated microbubble carriers can significantly prolong their circulation time.⁷¹

Biomimetic Nanoparticles, EVs, and Viral Vectors

Red blood cell membrane coating and platelet membrane encapsulation can reduce the uptake of nanoparticles via the RES and extend their circulation in the bloodstream.^{44,112} EVs have a long circulation time because they are endogenous and are not easily cleared by the immune system.⁷²

Owing to the expression of non-deleted viral genes and ensuing immune responses to the expressed viral proteins, the circulation time of Ad vectors in the bloodstream is relatively short.⁷³ Among them, chimpanzee-derived Ad vectors have the longest circulation time because the level of neutralizing antibodies against them in the body is the lowest.⁵⁶

Moreover, modifying the carriers can also change the circulation time in the bloodstream. For example, coating the carrier surface with PEG to form a PEG-coating can provide a protective barrier to prevent carrier lipolysis when entering the gastrointestinal tract. The ethylene glycol units of PEG coating can form a hydrating layer by tightly binding with water molecules. This hydration layer can prevent protein adsorption and recognition by RES, thereby extending the half-life of drugs and increasing their circulation time.^{11,85,113,114} Modifying the carrier with dextran can also protect it and prolong its circulation in the bloodstream. This benefits the drug accumulation around the target tissue or cells to enhance its effectiveness.¹¹⁵

In addition, nanomotors¹¹⁶ and cell carriers¹¹⁷ can prolong the circulation of drugs in the blood. Since the data obtained from different studies are different, and the circulation time of some carriers is not recorded, it is inaccurate to directly state the long or short circulation time of the carriers, so we have compiled a table on the expected pharmacokinetic parameters and biodistribution of the carriers (Table 4) for the readers' reference.

Fate of Targeted Drug Delivery Carriers at the Site of Lesions

In the previous section, we discussed how targeted drug delivery carriers can distribute to different tissues and organs after entering the human body. Thereafter, carriers face the problem of releasing drugs. Different carriers have different mechanisms for drug release. Some carriers may release drugs at the site of lesions without entering cells, while others may only interact with cell membranes and release drugs into the cytoplasm but not

Table 4 Summary of General PK and Major Tissue Distribution of Different Types of Carriers

Type of Carriers	Major Tissue Distribution	$t_{1/2}$ (h)	AUC _{0-∞} (ng.h/mL)	CL (mL/min)	C _{max} (ng/mL)	T _{max} (h)	References
Liposomes	Liver, spleen	10.628	37,640	5.75	3520	0.5	[118]
LNPs	Liver, spleen	0.72–24	221,400–277,400	Unknown	Unknown	Unknown	[20,119,120]
Albumin carriers	Tumor tissue (rarely distributed in the liver)	17–163	77,700	0.47	1284	Unknown	[118,121,122]
FDC	Tumor tissues	3.95–17.2	6630–9930	Unknown	1060–1700	2.5	[79,123]
Dendrimers	Liver	30.66	6830	0.045	263.89	4	[118,124]
Micelles	Liver	4.33–13.9	2043.2–3790.4	0.0276–0.0504	92.7–1000	Unknown	[118,125–127]
AuNPs	Liver, spleen	6.32	41,240	0.019	Unknown	Unknown	[128]
SeNPs	Liver, spleen	20.06–21.56	66,060–75,140	0.026	Unknown	Unknown	[129]
Graphene materials	Liver	22.4	14,800	Unknown	Unknown	Unknown	[130]
LDHs	Liver, spleen	18.62–26.52	77,150–142,170	0.088–0.092	2070–6330	1.84–2.54	[131]
GQDs	Liver, spleen	5.67–6.57	87,790–112,130	Unknown	13,702–16,302	Unknown	[132]
Nanogels	Liver, spleen	1.06	712,010–808,910	2.5	Unknown	Unknown	[133]
Micro/nanomotors	Target site (nonspherical micro/nanomotors are distributed in the spleen)	0.4–5.6	0.8–8.6	1.752	Unknown	Unknown	[134]
Microbubbles	Target site	2.11–16.83	571.63–1385.75	Unknown	5.2–11.86	0.42–6.4	[135]
ASP	Liver	14.58	8462	0.426	566.3	3.5	[136]
Chitosan	Liver, spleen	1.12–3.18	2,132,800–3,887,000	0.174	Unknown	Unknown	[137]
Biomimetic nanoparticles	Most at the target site, less in the liver and spleen	4.95–8.87	16,020–17,760	0.006	3700–4120	Unknown	[138]
Exosomes	Liver, spleen, gastrointestinal tract, lungs	2.49–13.2	592.2–2575.9	0.0054–0.0154	Unknown	Unknown	[139]
Yeast	Spleen	9.9–10.1	6200–7200	Unknown	360–440	Unknown	[9]
AAV vectors	Skeletal muscle, lung, central nervous system, retina	14.6–18.2	23,250–29,350	Unknown	Unknown	Unknown	[140]
Ad vectors	Unknown	1.5	3700	Unknown	46,000	Unknown	[141]
Lentiviral vectors	Unknown	2.84	84,500	0.004	2210	0.25	[142]

enter the cells. Some carriers can enter cells through certain pathways and be transported at the subcellular level through certain pathways. Some cannot escape the fate of degradation, while others can escape. The following is a discussion of the fate of each carrier at the site of lesions. The carriers discussed in this section are carriers in their complete form that can reach the site of lesions.

Fate of Carriers That Interact with Cell Membranes

There are two main types of interactions between carriers and cell membranes (Figure 4): 1) endocytosis, which refers to transporting extracellular substances into cells through deformation movements of the plasma membrane. This process requires entry into the cell, and carriers that enter cells through endocytic pathways will reach lysosomes or endosomes for degradation. Some carriers will escape after reaching endosomes or lysosomes to avoid degradation; 2) membrane fusion, which refers to the ability of the carrier's membrane to fuse with the cell membrane, allowing the loaded drugs to be directly released into the cytoplasm without entering the cell. Drugs delivered through this process will not enter endosomes or lysosomes and do not need to undergo escape.^{143,144}

Carriers for Cellular Entry by Endocytosis

There are several pathways for endocytosis of targeted drug delivery carriers: (1) adsorptive endocytosis; (2) clathrin-mediated endocytosis; (3) receptor-mediated endocytosis; (4) caveolae-mediated endocytosis; (5) phagocytosis.^{2,143,145} Not all endocytosis pathways were covered. Clathrin-mediated-mediated endocytosis and pinocytosis were not covered. Listed here are only the explicitly documented endocytosis pathways for all targeted delivery carriers summarized in this study.

In general, carriers that enter cells by endocytosis first enter the lysosomes or endosomes. The exception to this is caveolae-mediated endocytosis, in which carriers entering the cell are transported via a non-lysosomal pathway within the cell for reasons explained in detail in the section on caveolae-mediated endocytosis. Lysosomes and endosomes contain more than 60 acidic hydrolases, which are inactive enzymes that become active when drugs enter the lysosomes or endosomes and can degrade the incoming substance. This process occurs at a pH of about 5. The pH in lysosomes and endosomes is about 4.5–5.5, with pH changes occurring

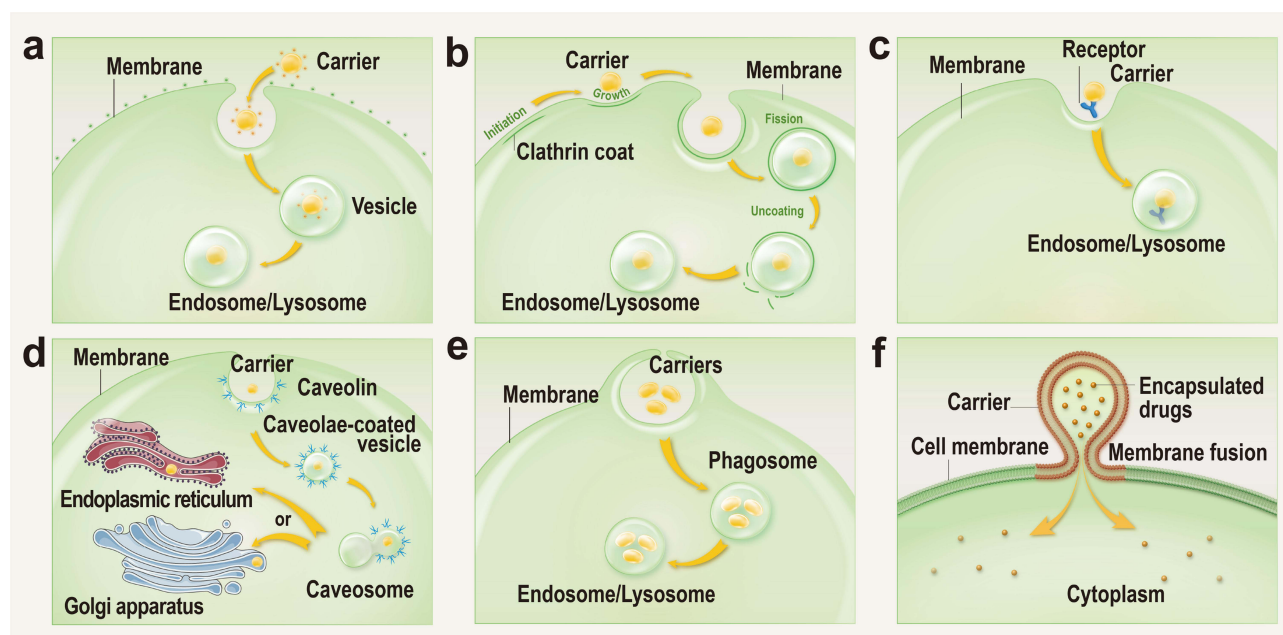


Figure 4 Schematic diagram of mechanisms of endocytosis and membrane fusion. (a) Adsorptive endocytosis. (b) Clathrin-mediated endocytosis. (c) Receptor-mediated endocytosis. (d) Caveolae-mediated endocytosis. (e) Phagocytosis. (f) Membrane fusion.

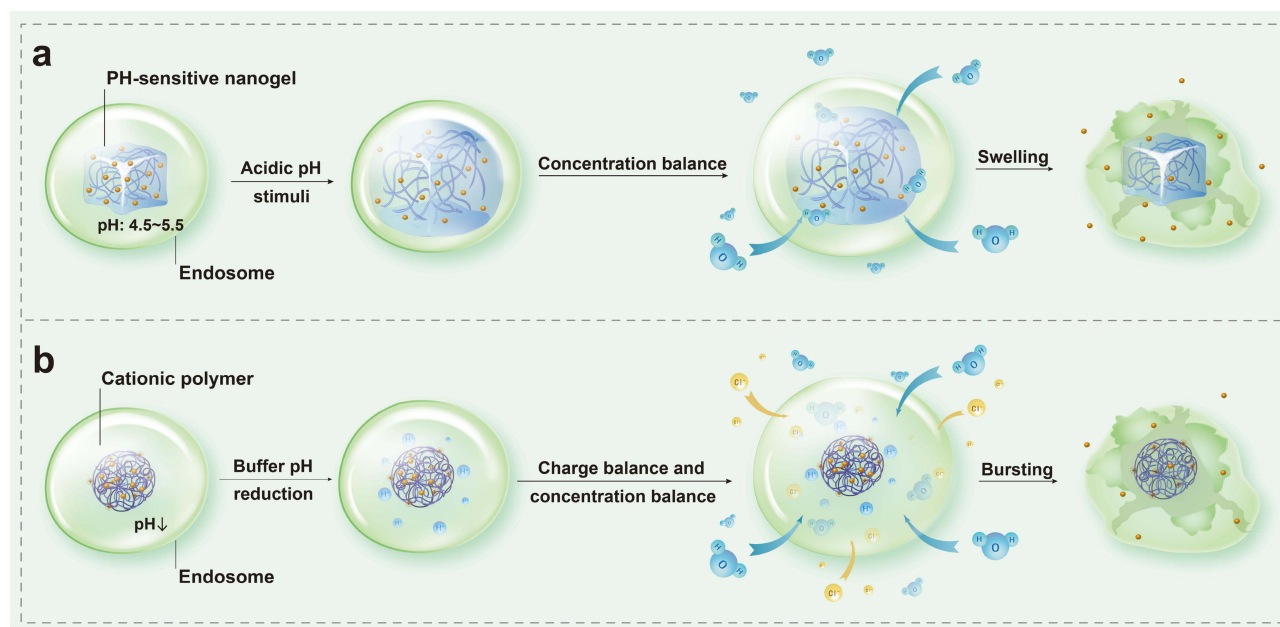


Figure 5 Schematic diagram of the action of the endosomal escape mechanism. (a) Carboxylic acid, phosphoric acid, amino, and other functional groups of pH-sensitive nanogel undergo dissociation in the acidic environment of the endosome. At this point, external water enters the nanogel, causing it to swell, rupture the endosome, and release the enclosed drugs into the surrounding nanogel to achieve endosomal escape. (b) The pH of the endosome decreases between the early and late stages, and cationic polymers can buffer the pH drop of endosomes and trap H^+ after entering endosomes. At this time, to maintain charge balance and concentration balance, Cl^- and water molecules will flow into the endosome in large quantities, causing the endosome to burst, and the drugs and carriers in them are released into the cytoplasm to achieve endosomal escape.

before and after degradation. Therefore, if the carrier is required to transport drugs to the nucleus or the degradation of carriers in lysosomes or endosomes is not desired, carriers with “endosomal/lysosomal escape” properties can be selected, or carriers can be designed to have “endosomal/lysosomal escape” capability.⁷⁵ “Endosomal/lysosomal escape” may not be the only way to prevent carriers from being degraded by endosomes or lysosomes; however, it is currently the most widely used method. There are generally two mechanisms by which nanoparticles can escape the endosome or lysosome upon internalization (Figure 5): (1) Expansion-induced variation, where the nanoparticle carrier dissociates within the endosome/lysosome, causing mechanical strain that leads to rupture of the organelle, thereby releasing the carrier and its cargo into the cytoplasm, followed by cytoplasmic transport of the nanoparticles; (2) Proton sponge effect, where the pH within the endosome/lysosome decreases, allowing cationic polymers within it to capture several protons. To maintain charge and concentration balance, external Cl^- and water molecules flow into the organelle, resulting in increased permeability and eventual rupture of the organelle, thereby releasing the cargo or carrier into the cytoplasm and achieving escape.¹⁴⁶ The following is a classification of various carriers’ cellular uptake, subcellular level transportation, and drug release mechanisms, mainly based on endocytosis.

Cellular Entry Mechanism, Subcellular Level Transport Pathway, and Drug Release Mechanism of Carriers Entering Cells via Adsorptive Endocytosis

Adsorptive endocytosis is a process of cellular uptake of external substances, which are adsorbed onto the cell membrane by interacting with the charge, hydrophobicity or other physicochemical properties of the cell membrane. Subsequently, the cell membrane depresses and wraps around these substances, forming endocytosis vesicles that transport them inside the cell for further processing. It is similar to receptor-mediated endocytosis, but differs in that adsorptive endocytosis is not dependent on specific cell surface receptors.^{147,148} Currently, carriers that enter cells through adsorptive endocytosis are cationic liposomes¹⁴⁷ and chitosan.¹⁴⁹ The mechanisms are as follows.

Cationic liposomes with ionizable lipids can electrostatically bind to the negatively charged cell membrane, enter the cell through adsorptive endocytosis, and become a vesicle engulfed by the cell membrane. Thereafter, it detaches from the cell membrane and enters the cytoplasm. Subsequently, it is transported through the endosome-lysosome pathway in the cell. In the acidic environment of the endosome, cationic liposomes are protonated, allowing them to interact with ionizable lipids in the bilayer of the endosome, forming a non-bilayer hexagonal structure that disrupts the bilayer. This releases the drug in the lipid into the cytoplasm.^{74,147} Additionally, combining cationic liposomes with primary or secondary amines with positive charges can help them escape from lysosomes, thereby protecting drug molecules.⁷⁴

Chitosan with positive charges can adhere to the negatively charged cell membrane surface via electrostatic interaction, enter cells through adsorptive endocytosis, and reach the endosomes. Owing to its positive charge, it can undergo endosomal escape, allowing the release of loaded drugs into the cytoplasm. However, the endosomal escape ability of chitosan is inefficient; therefore, researchers often modify it to enhance this capability.¹⁴⁹

Cellular Entry Mechanism, Subcellular Level Transport Pathway, and Drug Release Mechanism of Carriers Entering Cells via Clathrin-Mediated Endocytosis

The mechanism of clathrin-mediated endocytosis is that when some receptors on the cell membrane surface are bound, the clathrin coat protein in the cytoplasm aggregates on the membrane, and the adaptor protein makes the membrane bend, enclosing the carrier into a clathrin-coated pit. Thereafter, it invaginates and enlarges and finally breaks off, allowing the carrier to be transported into the cell.¹⁴⁴ The carriers that enter cells through clathrin-mediated endocytosis include graphene/graphene oxide,¹⁰¹ LDHs,⁹³ and AAV vectors.^{56,73} The mechanism is as follows:

Positively charged LDHs penetrate the negatively charged cell membrane through clathrin-mediated endocytosis.⁹³ Thereafter, LDHs enter the endosome, where they partially dissolve and release metal ions. Several water molecules in the cytoplasm enter the endosome, causing it to burst. The drug, with some LDHs, is released into the cytoplasm.³⁴ When AAV vectors reach the cell surface, they first bind to sugars (such as sialic acid, lactose, or heparan sulfate) and AAV receptors on the cell surface and enter the cell through clathrin-mediated endocytosis. Thereafter, they reach the endosome and are transported through the late endosome and lysosome compartments. During this process, AAV vectors undergo endosome/lysosome escape. Finally, the genetic material in the carrier is transported to the nucleus and exerts its effect.^{56,73}

Cellular Entry Mechanism, Subcellular Level Transport Pathway, and Drug Release Mechanism of Carriers Entering Cells via Receptor-Mediated Endocytosis

The mechanism of receptor-mediated endocytosis is that when the carrier reaches the cell surface, it specifically binds to receptors on the surface to form a complex. Thereafter, the membrane invaginates to form a coated pit, which detaches from the membrane to form a coated vesicle, taking up the extracellular carrier.¹⁴⁵ The carriers that enter cells through receptor-mediated endocytosis are FDC⁷⁸ and nanogels containing pullulan.³³ The mechanism is as follows.

FDC specifically binds to TfR overexpressed on the surface of tumors and enters cells through TfR-mediated endocytosis. Subsequently, FDC is transported through the endosome-lysosome pathway, where FDC undergoes reversible decomposition and releases the drug in the acidic environment of the endosome and lysosome.^{78,79}

Nanogels containing pullulan can strongly bind to salivary glycoprotein receptors and enter cells through receptor-mediated endocytosis. The mechanism of drug release from nanogels is a phenomenon called the “shape-memory effect.” In the acidic environment of the endosome, the nanogel swells, causing the endosome to rupture. Thereafter, water enters the nanogel, releasing the drug into the cytoplasm. When in the neutral cytoplasm, the nanogel shrinks to its original size, retaining unreleased drugs within the nanogel, waiting for the next release cycle. The process of drug release consists of two mechanisms: “swelling” and “permeation”.^{33,150}

Cellular Entry Mechanism, Subcellular Level Transport Pathway, and Drug Release Mechanism of Carriers Entering Cells via Caveolae-Mediated Endocytosis

The mechanism of caveolae-mediated endocytosis is that the carrier reaches the cell membrane surface, covered by

caveolin, to form a vesicle and enter the cell. This process bypasses lysosomes, avoiding drug degradation.¹⁵¹ Caveolae-mediated endocytosis typically allows particles sized 20–100 nm to enter the cell, with a maximum particle size limit of 200 nm. Particles larger than 200 nm may enter the cell through alternative pathways.^{152,153} Most endocytic processes are energy-dependent. Carriers that enter the cell through these endocytic processes are first transported to lysosomes or endosomes for degradation, destroying the carriers before they can deliver the loaded drugs to the cytoplasm or nucleus. Unless carriers can escape lysosomes/endosomes, it would be better if carriers could directly bypass lysosomes or endosomes. Caveolae-mediated endocytosis is an excellent way to achieve this. Carriers entering the cell via this pathway can bypass the lysosome-endosome pathway of cytoplasmic delivery through membrane insertion and diffusion and reach the cytoplasm directly. It can avoid degradation of carriers and loaded drugs in lysosomes or endosomes and improving drug retention and efficacy. However, the only carriers that enter the cell via caveolae-mediated endocytosis are graphene QDs (GQDs) and carbon nanotubes.^{154,155} GQDs are distributed in the endoplasmic reticulum and nucleus after entering the cell,¹⁵⁵ and how drug release occurs is unclear. The fate of carbon nanotubes after reaching the cytoplasm is still unknown. This field has great development potential, and to avoid carriers degraded by lysosomes or endosomes, carriers can be designed to enter the cell by caveolae-mediated endocytosis.

Zhang et al¹⁵⁶ have successfully designed nanoparticles that enter cells through this pathway. They developed a core-shell nanocarrier coated by cationic albumin (CNC), which can simultaneously deliver miRNA-34a and docetaxel into breast cancer cells for synergistic therapeutic effects. CNCs can effectively protect miRNA-34a from degradation by RNase and serum, and they can also enter the cytoplasm via caveolae-mediated endocytosis, avoiding degradation by endosomes or lysosomes and improving cargo utilization efficiency (Figure 6a–d). While carriers that enter the cell by other endocytosis first undergo lysosomal or endosomal transport pathways at the subcellular level (Figure 6e).¹⁵⁷ Carriers without escape capability are easily degraded in lysosomes or endosomes, and carriers with escape capability have different ways or degrees of lysosomal or endosomal escape according to their respective escape mechanisms (Figure 6f).¹⁵⁸

Cellular Entry Mechanism, Subcellular Level Transport Pathway, and Drug Release Mechanism of Carriers Entering Cells via Clathrin-Mediated Endocytosis and Phagocytosis

In addition to the above carriers, some carriers have multiple mechanisms, generally two.

Phagocytosis refers to the cell engulfing the carrier.¹⁵⁹ LNPs are absorbed by cells through clathrin-mediated endocytosis and phagocytosis. Thereafter, they are transported through the endosome-lysosome pathway in cells.¹¹ During the endocytosis, the positive charges on the cationic LNPs can be neutralized and disrupted by the negative lipids of the cells, leading to the release of the encapsulated drugs.¹⁶⁰

Cellular Entry Mechanism, Subcellular Level Transport Pathway, and Drug Release Mechanism of Other Carriers Entering Cells via Endocytosis

In addition to the carriers discussed above, some *carriers* only enter the cell through endocytosis; however, the specific endocytic pathway is unknown.

Micelles enter the cell through endocytosis and reach the endosomes, where the micelles may degrade into monomers, may also degrade in advanced endosomes, or may escape from endosomes.^{151,161} EVs¹¹² and yeast⁵⁵ enter cells through endocytosis. Ad vectors can enter cells through endocytosis, reach the endosome, and then the viral shell is decomposed. Thereafter, V and VI proteins help the viral genetic material escape from the endosome and enter the cell nucleus through the nuclear envelope.⁵⁶

In addition, nanocarriers containing fusogenic, pH-sensitive, or cationic lipids can escape from the endosome pathway to the cytoplasm.¹⁵¹

Carriers for Interaction with Cell Membranes via Membrane Fusion

The representative vectors that act with the cell membrane through membrane fusion and release the drug into the cytoplasm are lentiviral vectors.⁵⁶ The glycoproteins on the envelope of lentiviral vectors bind to corresponding receptors

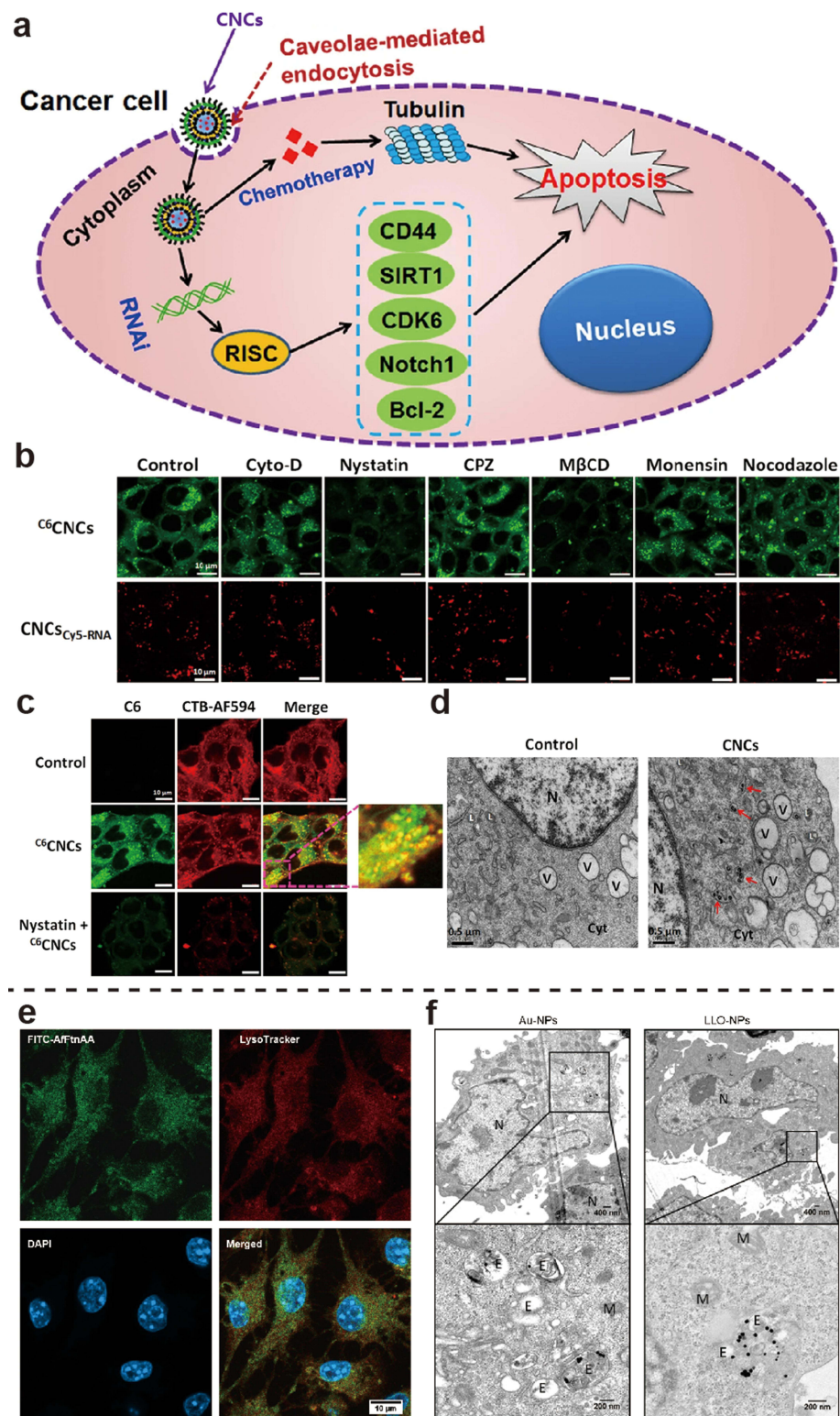


Figure 6 (a) Schematic illustration of CNCs co-delivering DTX and miRNA-34a. (b) Confocal laser scanning microscopy images of intracellular fluorescence of CNCs in 4T1 cells pretreated with various inhibitors. (c) Colocalization of C⁶CNCs with caveolae after incubation in the absence or presence of nystatin. (d) Cytosolic location of the CNCs in 4T1 cells observed using TEM after incubation. Reprinted from Zhang L, Yang X, Lv Y, et al. Cytosolic co-delivery of miRNA-34a and docetaxel with core-shell nanocarriers via caveolae-mediated pathway for the treatment of metastatic breast cancer. *Sci Rep.* 2017;7:46186. Creative Commons.¹⁵⁶ (e) Confocal imaging of 200 nM FITC (green)-conjugated AfFnAA uptake by RAW264.7 cells after 24 h of incubation. Reprinted from Ravishanker S, Nedumarani AM, Gautam A, Ng KW, Czarny B, Lim S. Protein nanoparticle cellular fate and responses in murine macrophages. *NPG Asia Materials.* 2023;15(1):1. Creative Commons.¹⁵⁷ <https://creativecommons.org/licenses/by/4.0/>. (f) TEM images of mouse embryonic fibroblasts incubated with listeriolysin O H311A-NPs. Reprinted from Plaza-Ga I, Manzaneda-González V, Kisovec M, et al pH-triggered endosomal escape of pore-forming Listeriolysin O toxin-coated gold nanoparticles. *J Nanobiotechnology.* 2019;17(1):108. Creative Commons.¹⁵⁸ TEM, Transmission electron microscope; CNC, cationic albumin; DTX, Docetaxel.

on the cell membrane, causing the viral membrane to fuse with the cell membrane and directly release the genetic material inside into the cytoplasm.^{56,162} The spikes on the surface of the viral vector can also help it bind strongly to the cell membrane.¹⁶³ The invasion of genetic information of lentiviral vectors mainly includes two processes: reverse transcription and integration. After the viral shell is removed, viral nucleic acids and protein complexes that enter the cytoplasm are key components for subsequent genetic information to be integrated into chromosomal DNA, often called reverse transcription complex (RTC). Viral RNA is first reverse-transcribed into double-stranded viral DNA in RTC and transported to chromosomal DNA, where it is integrated.¹⁶²

Carriers for Interaction with Cells via Endocytosis and Membrane Fusion

The above describes the mechanisms by which carriers interact with cells through endocytosis and membrane fusion. These carriers belong to either of these mechanisms; however, some carriers may interact with the cell membrane, such as microbubbles, via both mechanisms. There are two main mechanisms by which microbubbles enter cells: 1) they are engulfed by the cell membrane; 2) they enter the cell through membrane fusion, where the phospholipid component of the microvesicle merges with the double-layered phospholipid of the cell membrane, directly delivering the loaded drug into the cytoplasm.⁷¹

Others

The cellular uptake of AuNPs and SeNPs is poor.^{89,91} Micro/nanomotors can quickly internalize into cells and are not prone to be captured and degraded by lysosomes.¹⁶⁴ Targeting ligands influence the pathway of carrier endocytosis by binding specifically to receptors on the cell membrane. When a carrier has a cognate receptor on the target cell or is modified with a ligand that binds to a receptor on the target cell membrane, it enters the cell via receptor-mediated endocytosis. For instance, if a carrier is modified with albumin, it will bind to the albumin receptor on the target cell and enter via caveolae-mediated endocytosis. Similarly, ferritin-modified carriers bind to the TfR1 receptor on tumor cells, allowing entry through receptor-mediated endocytosis. The endocytosis pathway can vary even with the same targeting ligand if different cells are targeted. For example, entry via lipid raft-mediated endocytosis requires the presence of lipid rafts on the cell membrane, with the niche being a specific type of lipid raft.^{78,79}

Fate of Carriers That Do Not Interact with Cell Membranes

Not all carriers can transport drugs into cells. Some carriers may change when they reach the target site and release drugs outside cells, such as neutral liposomes and physicochemical targeting carriers. Neutral liposomes have no significant interaction with cells; therefore, their drug release mainly occurs in the extracellular space. When physicochemical targeting carriers reach the target site, they undergo a certain stimulus from the external environment or are sensitive to the specific environment, and the carrier will change, allowing it to release the loaded drugs. For example, around tumors, rapid anaerobic glycolysis produces excessive protons and carbon dioxide. The tumor lacks a functional lymphatic drainage system, resulting in insufficient oxygen supply and excessive lactate secretion, leading to extracellular acidification (the Warburg effect). Therefore, the extracellular pH around tumors is generally between 6.8 and 7.0, and in some cases, even as low as 5.7. For pH-sensitive carriers that are sensitive to such pH conditions, when they reach the tumor site, their lipids, organic functional groups, or inorganic compounds can easily change shape and release the loaded drugs. Poly (methacrylic acid), N-isopropyl acrylamide, poly (diethylaminoethyl methacrylate), poly (acrylamide), and poly (acrylic acid) are key components of pH-sensitive carriers that respond to pH changes, namely “pH-responsive membrane-desheating type polymers.” Under acidic pH conditions, pH-responsive membrane-desheating type polymers with carboxylic groups are protonated to eliminate electrostatic forces. The hydrophobicity of the polymer increases, and the polymer transforms from a hydrophilic state to a hydrophobic state, enhancing the interaction between the carrier and cell membranes and promoting drug release.⁶³

Clarifying how the carrier interacts with the cell membrane is also significant in the design and selection of carriers. If one does not want the carrier to be degraded by endosomes or lysosomes and to reach the nucleus, one can choose

a carrier that has an endosomal/lysosomal escape capability or one that does not enter the cell via the endosome-lysosome pathway or one that is designed to have that capability.

If the carrier does not enter the cell and releases the drug directly into the cytoplasm, a carrier that interacts with the cell membrane via membrane fusion can be selected. If the carrier and drug is not required to enter the cell but only required to release the drug in the cellular microenvironment, the carrier that does not enter the cell can be selected. In conclusion, before determining the carrier, one should not only consider the carrier's encapsulation rate, drug loading, and other characteristics but also focus on its fate *in vivo*. Usually, pharmacy workers focus on the targeting ability when designing a carrier, which is good but should not be ignored at the subcellular level of transport, which is related to the degradation of the carrier.

Elimination and Safety of Carriers

In the previous section, we discussed the fate of carriers at the site of lesions and how they release drugs. Thereafter, we need to focus on what happens to the carriers after drug release, whether they can be degraded, how they are eliminated from the body, whether they are safe, and whether they are toxic to the body and the specific adverse reactions they cause. The following sections will elaborate on the elimination and safety of carriers.

Once the NPs release the loaded drug, the biomolecules on their surfaces are degraded by cathepsin L. Then, NPs of different compositions undergo different degradation modes. For example, the metabolism of polymer NPs is mainly through the degradation of the polymer backbone. And different particles display different degrees and rates of degradation in the body. Finally, particles with a diameter <5 nm can be rapidly cleared by the kidneys, while metabolites of larger particles are mainly excreted through the liver and bile.^{2,165} However, when NPs escape from lysosomes, they may cause lysosomal damage, leading to oxidative stress, other organelle malfunctions, and the production of reactive oxygen species (ROS).¹⁵¹ ROS refers to chemically reactive chemicals containing oxygen, including peroxide and superoxide, which are harmful to the human body.¹⁶⁶ Therefore, NPs are low-toxicity and can cause genetic and reproductive toxicity, inflammation, oxidative stress, and cell apoptosis, causing damage at the molecular and genetic levels.¹⁰⁹

Liposomes and LNPs

Many studies claim that liposomes have good biodegradability and biocompatibility, and can be converted into new substances by biochemical reactions or by microorganisms such as bacteria, without accumulation in the body or additional toxicity. However, it is important to note that many studies have shown that liposomes can cause complement activation, leading to complement activation-related pseudoallergy (CARPA). This necessitates special attention in the research and development of liposomal drugs, including the addition of several evaluation metrics.^{15,80} LNPs are low-toxicity and biodegradable, mainly reaching the liver and degraded by lysosomal acid lipase to produce lipids, which are metabolized and excreted from the cells and finally from the systemic circulation (50% excreted in urine and feces). The elimination process does not exceed 24 h.^{11,49,99}

Albumin Carriers, FDC, and Dendrimers

Albumin carriers are non-toxic, biodegradable, and non-immunogenic.^{67,78} Albumin carriers are absorbed in the proximal convoluted tubule and degraded into smaller molecular fragments by hydrolases in the tubular cells and enter the bloodstream. The amino acid components of albumin can be used for tissue repair.¹⁶⁷ FDC has low toxicity and is also biodegradable.²

Cationic dendrimers form nanoholes when they interact with negatively charged cell membranes, leading to leakage of cellular contents and eventual cell death. Therefore, cationic dendrimers usually exhibit high cell toxicity, while anionic and neutral dendrimers exhibit low or no toxicity.¹⁶⁸ Dendrimers are excreted through the liver and kidneys.^{169,170}

Inorganic Nanoparticles

Metal-based nanoparticles induce DNA or oxidative damage in normal tissues.¹⁷¹ As reported in many studies, AuNPs can cause some degree of oxidative damage both in vivo and in vitro, with the greatest effects on the liver, spleen, and kidneys; however, the main toxicity and its extent are determined by the properties, formulation, and physicochemical properties of the AuNPs. AuNPs are eliminated from the body in urine and feces.¹⁷² Graphene and graphene oxide are toxic, and graphene oxide can potentially cause cell hemolysis and respiratory toxicity.¹⁵⁵ Graphene and graphene oxide are mainly excreted through the kidney.¹⁷³ LDHs have biodegradability and low cell toxicity.^{29,34} LDHs are excreted through the liver and kidney, namely urine and feces.³⁴ QDs have high toxicity, among which carbon QDs have lower toxicity.¹⁶⁵ The specific degradation of QDs depends on the degradability of the materials they are composed of. For example, Si QDs, composed of silicon material, are degraded into silicic acid and excreted in urine. These types of QDs are safer than traditional QDs.⁹⁴ Large GQDs are non-toxic and are eliminated through the liver after drug release. GQDs administered via subcutaneous or intravenous injection are ultimately excreted in urine, while those administered orally are excreted in feces.¹⁵⁵

Nanogels and Micro/Nanomotors

Nanogels are biodegradable and can degrade into non-toxic, biodegradable products. They may be eliminated through the kidneys; however, undegraded nanogels swell and become too large to pass through the kidneys.^{33,150} Nanogels containing surfactants or monomers can cause some adverse reactions.¹⁵⁰

Chemically powered micro/nanomotors use toxic fuel, which results in significant toxicity, although the toxicity can be reduced by using endogenous substances instead of toxic fuel.¹⁶⁴ Under ideal conditions, micro/nanomotors can be degraded into non-toxic compounds.¹¹⁶ The excretion pathways of micro/nanomotors are still unknown.

Polysaccharide

Polysaccharide are non-toxic or low-toxicity and have good biodegradability.⁸⁵ ASP is non-toxic and have no immunogenicity,⁴³ while dextran is non-toxic.¹¹⁵ Furthermore, HA is non-immunogenic and biodegradable.¹⁷⁴ Chitosan has good biodegradability and is non-toxic, although some studies suggest that it may have a low level of toxicity. However, its toxicity is similar to its molecular weight, which means lower toxicity is related to less molecular weight and vice versa. Administration through the nasal cavity can cause slight nasal leakage, while oral administration can cause minor gastrointestinal side effects such as bloating, diarrhea, and constipation.^{45,175,176} Chitosan is mainly degraded by muramidase and enzymes produced by bacteria in the gastrointestinal tract.¹⁷⁷

EVs and Viral Vectors

EVs have high heterogeneity and complex composition, making accurate in vivo dosage monitoring difficult and safety low.⁸¹ However, exosomes are relatively safe and have no cell toxicity. For example, curcumin-wrapped exosomes are safe and have no toxic effects or immune stimulation.¹⁷⁸

After nuclear escape, AAV vectors undergo proteasome degradation and form other structures.¹⁷⁹ However, for most vectors, drug release into the cytoplasm is sufficient; therefore, even if the vector structure changes after escaping lysosomes/endosomes, as long as it does not affect the drug, escaped vectors can increase drug delivery concentration. However, for viral vectors to be transfected, reaching the cell nucleus is their mission. AAV vector structure changes after nuclear escape, which can disrupt the cargo delivery to the nucleus, leading to reduced transfection efficiency and drug efficacy. Systemic administration of AAV vectors has certain toxicity, causing elevated transaminase levels (the most common adverse reaction), ocular inflammation, and possibly liver toxicity.^{180,181} However, the adverse reactions of AAV vectors are closely related to the dosage. Therefore, dosage control according to demand is necessary.¹⁸¹ Ad vectors have high transduction efficiency and packaging capability; however, they also cause high levels of inflammation and potentially immune toxicity, even leading to

death.¹⁷⁹ However, it should not be overly alarming. Although we emphasize “non-toxic” and “safety” when developing vectors, it is best to choose materials compatible with the body to avoid immune reactions and other adverse reactions that can affect normal bodily function. Nonetheless, while safe and non-toxic vectors are what researchers are seeking, they are necessary for treating diseases. For diseases for which there are currently only chemotherapy treatments with severe side effects or no cure, Ad vectors can be a good choice as their toxicity is lower than that of chemotherapy. Lentiviral vectors do not cause any significant adverse reactions.⁵⁶

Initially, protein replacement therapies alleviated disease symptoms by replacing missing or malfunctioning proteins. These treatments required regular injections or protein supplements, which could be recognized as foreign by the patient’s immune system, potentially triggering an immune response. Subsequently, gene-based therapies emerged, offering long-lasting therapeutic effects by introducing normal genes into the patient’s body. This approach enables the patient’s own cells to produce the required proteins on a long-term or permanent basis, reducing the likelihood of immune rejection and addressing the root cause of the disease without the need for frequent treatments. Gene therapy vectors are classified into non-viral and viral vectors. Viral vectors have become popular in gene therapy research due to their superior properties, such as their natural ability to efficiently infect and deliver genes, their ability to selectively target specific sites, their high specificity, and their potential to enable long-term or permanent gene expression.^{182,183}

Others

As mentioned earlier, vector modifications require clarification of their safety. PEG is non-biodegradable, immunogenic, and can accumulate in the body. Intravenous injection of PEGylated vectors can also cause multiple immune responses.^{143,184} Therefore, when using PEGylated vectors, these points must be considered. Pullulan is biodegradable, non-immunogenic, and relatively safe.³³

When selecting carriers, researchers do not want them to be difficult to metabolize and accumulate in the body, causing invisible toxicity. For carriers that are not easily excreted, researchers often modify the carriers to target excretory organs such as the kidneys; however, this also means that the carriers do not easily accumulate at the target site, which reduces the therapeutic efficacy. Umeda et al have proposed a new strategy that, instead of reducing the accumulation of carriers in the RES, promotes their removal after accumulation. Radionuclide therapy is a new approach to cancer treatment that will replace chemotherapy, which uses the cytotoxicity of radionuclides to kill cancer cells and responds in real-time to the location of the drug in the body. However, because radionuclides are distributed non-specifically, they accumulate in healthy tissues and cause systemic toxicity, and using liposome-loaded radionuclides to help with their targeted delivery in research is common. However, the ability of liposomes to reduce the radionuclide’s non-specific accumulation is not very high. Therefore, Umeda et al¹⁸⁵ discovered a ligand called ethylenedicycysteine, which was modified to load radionuclides in liposomes and increased the ratio of tumor/liver distribution of radionuclides and clearance of the carriers after accumulation with relatively high efficiency (Figure 7).

A point of concern is whether the degradation products of carriers can be reused for the physiological processes of the organism. For example, (1) in the aspect of “membrane production”, the lipids obtained by elimination can be reassembled and used to form the phospholipid bilayer of the cell membranes, which play an important role in the growth, repair, and division of the cell; (2) In “lipoproteins formation”, some lipids and proteins obtained by elimination can be combined to form lipoproteins, which play an important role in the transport of lipids and cholesterol; (3) In “protein synthesis”, the amino acids obtained by elimination are involved in the formation of proteins, which are essential for the structure of cells and organisms, the transport of substances, signaling, catalysis, immunity and so on; (4) In the “source of energy”, carrier upon dissociation produces organic matter such as proteins, carbohydrates, lipids, etc., which can be metabolized and release energy, which is used to maintain the basic activities of the cell and the organism. Therefore, the elimination of drug delivery carriers includes not only how they are eliminated and what their metabolites are but also other aspects, such as the previously described, the elimination products of the carriers have the potential to be involved in the natural processes of the organism, and this is a novel research angle.^{186–188}

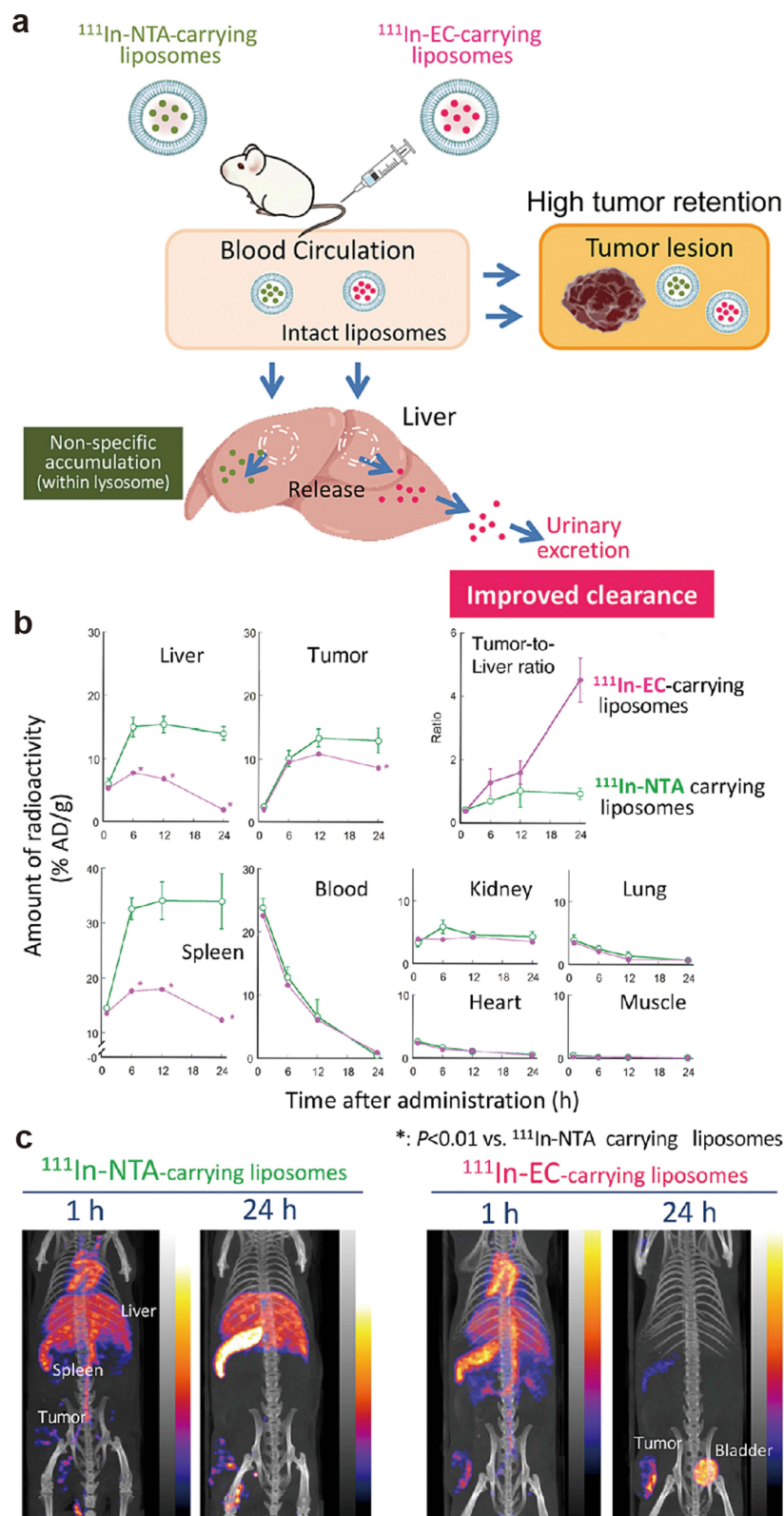


Figure 7 (a) Schematic illustration of the in vivo fate of radiionuclide-carrying liposomes in tumor-bearing mice. (b) Time-dependent uptake, retention, and clearance of ¹¹¹In radioactivity in each organ and tumor. *: $p < 0.01$. (c) In vivo single-photon emission computed tomographs of the two types of ¹¹¹In-carrying liposomes in sarcoma 180-bearing mice. Reprinted from *J Control Release*, volume 361, Umeda IO, Koike Y, Ogata M, et al. New liposome-radiionuclide-chelate combination for tumor targeting and rapid healthy tissue clearance. 847–855, copyright 2023, with permission from Elsevier.¹⁸⁵

Conclusion

We elaborated the process that the fate of drug delivery carriers in the body and subcellular compartments undergo upon entering the body and their toxicity and side effects. The *in vivo* fate of drug delivery carriers specifically includes their targeting specificity, tissue distribution, circulation time, mechanism of action on cell membranes, intracellular transport mode, escape ability, degradation ability, and excretion mechanism. Although detailed articles on the *in vivo* fate of specific types of drug delivery carriers exist, they have only focused on the mechanism of a type of carrier and have not provided an overview of the *in vivo* fate mechanism for various carriers used for targeted delivery. While this article may not be as comprehensive and detailed as the literature, it is suitable for different readers. The advantage of this article lies in its broader coverage and overall nature. Researchers who have identified their research targets can refer to this article to guide their carrier design work. Researchers who have not yet identified the type of carrier to study, researchers from other fields, and even the general public who come across this article can regard it as an introduction to the *in vivo* fate of drug delivery carriers, providing a preliminary and comprehensive understanding of the design and fate of these carriers. As mentioned before, design should not be done for the sake of design. Pharmaceutical workers should have such awareness. Researchers involved in the development of drug delivery carriers should have a framework in mind regarding their *in vivo* processes, which is crucial and worth emphasizing repeatedly. Additionally, the images in this article are concise and lively. If one only looks at the captions and images without reading the text, a visual framework for targeted drug delivery carriers can be formed, adding interest and popularization to the monotonous text. [Table 5](#) provides a clear and concise overview of the framework. Readers can directly refer to the table to understand the *in vivo* process of different targeted drug delivery carriers.

Targeted delivery systems can target diseased sites, enhance the biodistribution of drugs, and minimize harm to normal tissues and cells. These systems are extensively sought after for precise drug release in diseases like cancer. Moreover, targeted delivery systems possess significant potential.

The fate of a carrier *in vivo* is influenced by various factors, including its administration method, particle size, surface charge, surface ligand modification, shape and so on. While this study does not extensively discuss each of these factors, aspects of certain carriers' fate require further research, guiding the efforts of pharmaceutical professionals.

In summary, this study provides an overview of >13 targeted drug delivery carriers that have made significant progress in understanding the mechanisms underlying their *in vivo* fate. This study elaborates on their tissue distribution, circulation time, mechanism of action on cell membranes, intracellular transport mode, escape ability, degradation, excretion, and potential toxicity. By enhancing pharmacological knowledge among researchers, promoting *in vivo* research on targeted drug delivery carriers, and improving the success rate of clinical translation of pharmaceuticals, this study plays a crucial role in advancing the field.

This article highlights several challenges faced by targeted drug delivery carriers. Nanoparticles, for instance, often struggle with inefficient delivery to target sites and require modification to enhance targeting efficiency. Liposomes, dendrimers, and similar carriers have short half-lives *in vivo*, making them prone to rapid clearance or degradation, which complicates treatments needing sustained effective concentrations. Additionally, metal nanoparticles and viral vectors lack sufficient research on biocompatibility and toxicity, raising concerns about their safety in practical applications. Beyond these *in vivo* challenges, the production of cell carriers and other advanced carriers involves high precision, complex processes, and significant costs, limiting their applicability. These examples only scratch the surface; the development of nanocarrier drugs still has a long way to go.

All the literature cited in this study was selected as references only when the following requirements were met: (1) For carriers with more research, the Journal Citation Reports (JCR) partition of the article needs to be in zones 1, 2, or 3, with a score ≥ 3 . (2) For carriers with very little research, articles with JCR partitions in zone 4 were acceptable, with a score ≥ 3 . (3) For articles with lower scores, observing the specific content of the article to determine whether it has the value of being cited was necessary. (4) If there was no score or partition of the article, the quality of the journal and the value of its specific content were considered to determine if it could be used as cited literature. Future studies could focus on enhancing the biocompatibility and safety profiles of drug delivery carriers by exploring novel materials and modification strategies.

Table 5 Summary of the Fate of Various Carriers After Intravenous Injection into the Body

Types of Targeted Drug Delivery Carriers	Targeting	Interaction with Cells	Intracellular Transport Pathway	Endosome/ Lysosomal Escape	Drug Release	Excretion	Degradability	References
Liposomes	Passive targeting. (Thermo-sensitive liposomes, photo-sensitive liposomes, thermo-sensitive magnetic liposomes: physicochemical targeting.)	Neutral liposomes: no interaction; Cationic liposomes: adsorptive endocytosis.	Cationic liposomes: endosome-lysosome pathway.	Cationic liposomes: lysosomal escape.	Neutral liposomes are released into the extracellular space; Cationic liposomes are released into the cytoplasm after interaction with the endosome.	Kidney (urine).	Biodegradable.	[11,70,74,99]
LNPs	Liver targeting.	Clathrin-mediated endocytosis and phagocytosis.	Endosome-lysosome pathway.	No.	The positive charges on the cationic LNPs are neutralized by the negative lipids of the cells, leading to the release of the drugs.	Urine and feces.	Degradable.	[11,65,74,76]
Albumin carriers	Passive targeting and tumor targeting.	Caveolae-mediated endocytosis.	Golgi and ER pathway.	N/A ^a	Trigger release (in the special environment of the lesion, albumin carriers undergo structural changes and release drugs).	Be degraded into smaller molecular fragments by hydrolases in the tubular cells and then enter blood circulation. The amino acid components of albumin are used for tissue repair.	Biodegradable.	[21,78]
FDC	Passive targeting and tumor targeting.	TFR-mediated endocytosis.	Endosome-lysosome pathway.	No.	Drugs are released after endosome /lysosomal acidification.	Liver and kidney.	Biodegradable.	[79,123]
Dendrimers	Passive targeting.	Dendrimers can disrupt or penetrate the cell membrane.	N/A ^a	N/A ^a	N/A ^a	Liver and kidney.	No.	[75,168]
Micelles/PMs	Passive targeting.	Endocytosis.	Endosome-lysosome pathway.	No.	Drugs are released after endosome /lysosomal acidification.	The kidney excretes small-sized PMs.	No.	[25,151,161]

AuNPs	Passive targeting.	Endocytosis.	Endosome-lysosome pathway.	No.	Drugs are released after endosome /lysosomal acidification.	Kidney and intestine (Urine and feces).	No.	[89,158,172]
SeNPs	Suitable for developing targeted carriers.	Endocytosis.	Endosome-lysosome pathway.	No.	Drugs are released after endosome /lysosomal acidification.	Urine and feces.	No.	[89,91]
Graphene/ Graphene oxide	Suitable for developing targeted carriers.	Clathrin-mediated endocytosis.	Lysosome pathway.	No.	Drugs are released after endosome acidification.	Kidney.	No.	[92,155,173]
LDHs	Suitable for developing targeted carriers.	Clathrin-mediated endocytosis.	Endosome pathway.	Endosomal escape.	LDHs dissolve partially and release metal ions, after which a large amount of water molecules enter the endosome, causing it to swell and burst, releasing the medication.	Liver and kidney (Urine and feces).	Biodegradable.	[34,93]
GQDs	Suitable for developing targeted carriers.	Caveolae-mediated endocytosis.	ER pathway.	N/A ^a	Unknown.	Liver.	No.	[154,155]
Nanogels	Passive targeting.	Endocytosis.	Endosome-lysosome pathway.	Can be designed as carriers with escape ability.	Trigger release.	Kidney.	Biodegradable.	[33,150]
Micro/ nanomotors	Targeting.	Penetrate cells.	N/A ^a	N/A ^a	Trigger release.	Unknown.	Degradable.	[116,164]
Microbubbles	Passive targeting.	Endocytosis or membrane fusion.	Lysosome pathway (entering cells by endocytosis).	Unknown.	Trigger release.	Unknown.	No.	[41,42,71]
ASP	Passive targeting and liver targeting.	ASGPR-mediated endocytosis.	Endosome pathway.	Unknown.	Unknown.	Kidney.	Biodegradable.	[43,136]
Chitosan	Suitable for developing targeted carriers.	Adsorptive endocytosis.	Endosome pathway.	Endosomal escape.	Unknown.	Liver and kidney (Urine and feces).	Biodegradable.	[45,149,175–177]

(Continued)

Table 5 (Continued).

Types of Targeted Drug Delivery Carriers	Targeting	Interaction with Cells	Intracellular Transport Pathway	Endosome/ Lysosomal Escape	Drug Release	Excretion	Degradability	References
Biomimetic nanoparticles	Active targeting.	Endocytosis or membrane fusion.	Endosome / Lysosome pathway (entering cells by endocytosis).	Endosomal/ lysosomal escape can be achieved by design.	Unknown.	Unknown.	Biodegradable.	[44,62,112]
EVs	Passive targeting.	Endocytosis.	Endosome-lysosome pathway.	Endosomal/ lysosomal escape.	Unknown.	Unknown.	No.	[72,81,112,178]
Yeast	Passive targeting and phagocytic cell targeting.	Endocytosis.	Endosome-lysosome pathway.	No.	Unknown.	Liver and kidney.	Degradable.	[9,17,55]
AAV vectors	Passive targeting. (AAV8: liver targeting; AAV1, AAV5: central nervous system targeting.)	Clathrin-mediated endocytosis	The late endosome and lysosome compartments pathway.	Endosome/ lysosomal escape.	Unknown.	AAV2 and AAV9: kidney.	Degradable.	[56,73,179–181]
Ad vectors	Suitable for developing targeted carriers.	Endocytosis.	Endosome pathway.	Endosome escape.	The viral shell is decomposed in the endosome, and V and VI proteins help the viral genetic material escape from the endosome to the cell nucleus.	Unknown.	Unknown.	[56,73]
Lentiviral vectors	Suitable for developing targeted carriers.	Membrane fusion.	Cytoplasm pathway.	N/A ^a	Fuse with the cell membrane and directly release the drug into the cytoplasm.	Unknown.	Unknown.	[56,97,162]

Notes: ^a“N/A” means “not applicable”.

Abbreviations

LNPs, Lipid-based nanoparticles; FDC, Ferritin drug carrier; TfR, Transferrin receptor; PMs, Polymeric micelles; AuNPs, Au nanoparticles; SeNPs, Selenium nanoparticles; Se, Selenium; LDHs, Layered double hydroxides; QDs, Quantum dots; ASP, Angelica sinensis polysaccharide; EVs, Extracellular vesicles; AAV, Adeno-associated viral; AD, Adenoviral; EPR, Enhanced permeability and retention; ApoE, Apolipoprotein E; PEG, Polyethylene glycol; HA, Hyaluronic acid; FR, Folate receptor; Tf, Transferrin; MZ@PNM, Penetrating macrophage-based nanoformulation; MZ@PNM-GCP, Penetrating macrophage-based nanoformulation encapsulating hydrogel; RES, Reticuloendothelial system; GQDs, Graphene quantum dots; CNC, Core-shell nanocarrier coated by cationic albumin; RTC, Reverse transcription complex; ROS, Reactive oxygen species; CARPA, Complement activation-related pseudoallergy.

Declaration on the Use of AI

We did not use AI tools to help us draft this manuscript.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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