frontiers | Frontiers in Nanotechnology

REVIEW
published: 15 July 2022
doi: 10.3389/fnano.2022.948705

Application of Nanoparticles in Tumour Targeted Drug Delivery and Vaccine

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Cancer is a major cause of death worldwide, and nearly 1 in 6 deaths each year is caused by cancer. Traditional cancer treatment strategies cannot completely solve cancer recurrence and metastasis. With the development of nanotechnology, the study of nanoparticles (NPs) has gradually become a hotspot of medical research. NPs have various advantages. NPs exploit the enhanced permeability and retention (EPR) of tumour cells to achieve targeted drug delivery and can be retained in tumours long-term. NPs can be used as a powerful design platform for vaccines as well as immunization enhancers. Liposomes, as organic nanomaterials, are widely used in the preparation of nanodrugs and vaccines. Currently, most of the anticancer drugs that have been approved and entered clinical practice are prepared from lipid materials. However, the current clinical conversion rate of NPs is still extremely low, and the transition of NPs from the laboratory to clinical practice is still a substantial challenge. In this paper, we review the *in vivo* targeted delivery methods, material characteristics of NPs and the application of NPs in vaccine preparation. The application of nanoliposomes is also emphasized. Furthermore, the challenges and limitations of NPs are briefly discussed.

Keywords: cancer, nanoparticles, liposomes, targeting mechanism, tumour therapy

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Specialty section:
This article was submitted to Biomedical Nanotechnology, a section of the journal Frontiers in Nanotechnology

Received: *29 May 2022*
Accepted: *24 June 2022*
Published: *15 July 2022*

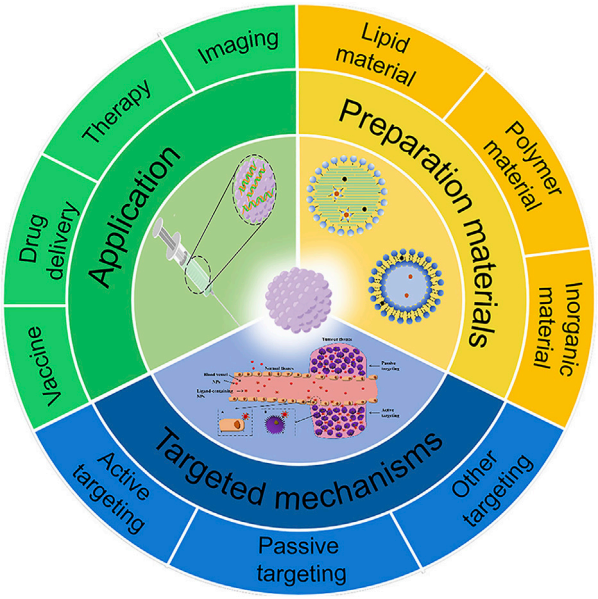
Citation:
Tu Y, Yao Z, Yang W, Tao S, Li B, Wang Y, Su Z and Li S (2022) Application of Nanoparticles in Tumour Targeted Drug Delivery and Vaccine. Front. Nanotechnol. 4:948705. doi: 10.3389/fnano.2022.948705

1 INTRODUCTION

1.1 Health Challenges of Tumour Therapy

Cancer is a disease caused by the uncontrolled growth of malignant cells, also known as malignant tumours. Cancer cells are characterized by strong invasiveness. Currently, cancer is a major cause of death worldwide, and nearly 1 in 6 deaths is caused by cancer each year. According to *the World Cancer Report 2020*, there are approximately 9.96 million cancer deaths worldwide; the common types of cancer associated with death are lung cancer (1.8 million deaths, approximately 18%), colorectal cancer (935,000 deaths, approximately 9.4%), and liver cancer (830,000 deaths, approximately 8.3%) (Liu et al., 2021) (**Figure 1**).

Cancer has become a common public health problem worldwide. Traditional cancer treatment strategies include surgery, radiotherapy, chemotherapy, and immunotherapy. However, these methods still cannot completely prevent cancer metastasis and postoperative recurrence, which are substantial challenges in clinical practice. Additionally, common chemotherapy also has its own limitations, such as multidrug resistance (Barker et al., 2015), cardiotoxicity (Chang and Wang, 2018), and infertility (Brigden and McKenzie, 2000), among other complications, as well as poor drug selectivity against cancer. These severe side effects greatly limit the clinical treatment of cancer.



GRAPHICAL ABSTRACT |

Therefore, to overcome these shortcomings, it is urgent to introduce a new drug delivery platform to enhance the ability to target tumours and reduce side effects.

1.2 Application of Nanoparticles in Cancer and Vaccine

In recent years, NP drugs have gradually become a hotspot in medical research. The size of NPs is in the nanometre range (approximately less than 1 μm), and NPs generally have physical interfaces (Sheena et al., 2020). NPs are mainly divided into polymers (Rapoport, 2007), inorganic NPs (Arami et al., 2015; Wang et al., 2016) and liposomes (Tan et al., 2021). Liposomes are composed of phospholipid molecules and are less toxic than are inorganic NPs. In addition, their phospholipid bilayer structure can not only encapsulate hydrophobic drugs and hydrophilic drugs but can also simultaneously deliver 2 drugs, enabling more types of drugs to be encapsulated and greatly improving drug delivery efficiency (Xiang et al., 2012). In addition, liposomes have good biocompatibility and biodegradability.

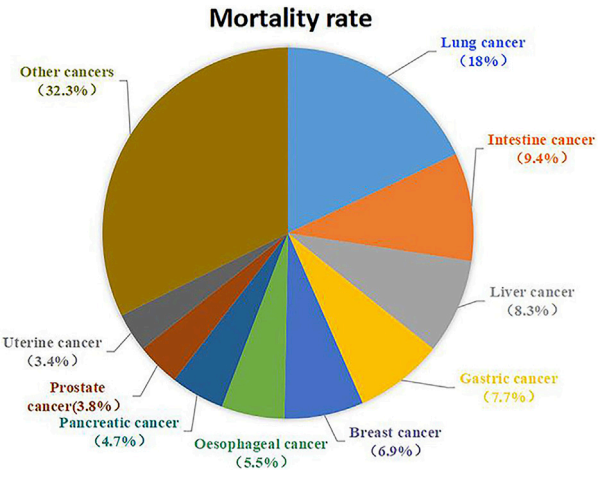


FIGURE 1 | 2020 Mortality rates for different tumours (Liu et al., 2021).

The emergence of NPs and their development in cancer treatment have had an important impact on clinical chemotherapy. NP drug delivery platforms can address various shortcomings of traditional treatment strategies. First, NPs can improve targeted drug delivery; the structural design of NPs can be modified so that they can more effectively deliver therapeutic drugs to the tumour site, thus minimizing the toxic side effects of the drugs and adverse reactions at sites external to the target. Second, NPs can deliver higher local drug concentrations to tumour site *via* enhanced permeability and retention (EPR), thereby improving drug availability and drug sensitivity and overcoming the multidrug resistance of tumour cells (Maeda et al., 2000). Third, NP drug delivery platforms can be used in combination with a variety of drugs to reduce the toxic side effects of chemotherapy drugs and improve the tumour microenvironment (TME) (Zhang et al., 2020a). However, due to the heterogeneity of the EPR effect, drug delivery remains very poor (Leroux, 2017). Therefore, in-depth explorations of how NPs enter tumour tissues is the first step to better target nanodrugs to tumours and improve the clinical conversion rate.

Because of the coronavirus disease 2019 (COVID-19) pandemic, the global emphasis on vaccines has increased, and vaccine research and development technologies have rapidly improved. As a powerful development platform for vaccines,

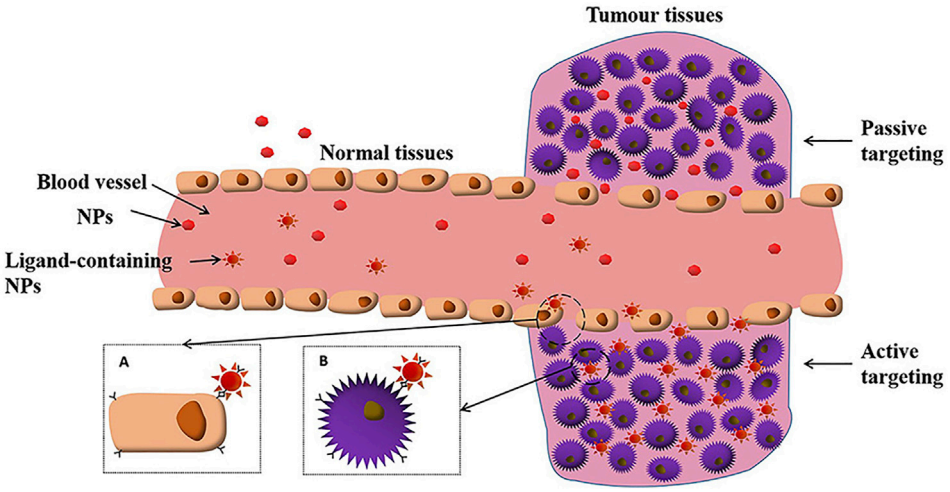


FIGURE 2 | Schematic illustration of the EPR effect, Active and Passive targeting. In tumour tissues, endothelial cells are irregular and have large gaps. Therefore, NPs tend to accumulate in tumor tissues much more than in normal tissues. In active targeting, targeting ligand-modified NPs can bind to specific receptors on tumor cells or tumor endothelial cells.

nanotechnology can be used in both therapeutic and preventive vaccines. They can be used as transport systems to enhance the function of antigen-presenting cells or as an immune enhancer to activate immune responses. In addition, NPs can play roles in drug targeting, sustained and controlled drug release.

In summary, NPs provide an important strategy and new direction for tumour treatment and vaccination. In this paper, the targeted delivery mechanisms of NPs in cells and *in vivo* are briefly described, and the material characteristics of NPs and the application of NPs in tumour-targeted therapy and vaccine preparation are reviewed.

2 *IN VIVO* TUMOUR-TARGETED DELIVERY MECHANISMS OF NPS

The efficacy of antitumour drugs largely depends on whether the drugs are delivered to the correct location (Bae and Park, 2011). To achieve drug-targeted therapy, it is necessary to find effective drugs, appropriate targets, and the right mode of delivery (Danhier et al., 2010). The distribution of traditional chemotherapeutic drugs in the body is nonspecific, and the high toxicity of those drugs can cause excessive damage to normal tissues and cells. Therefore, the long-term goal of cancer treatment is to increase the healthy lifespan and mobility of patients by reducing the systemic toxicity of drugs (Byrne et al., 2008). While the characteristics of NPs meet the needs for antitumour drug delivery, the specific tumour targeting of NPs allows drugs to exhibit better pharmacokinetic characteristics and reduce systemic toxicity while improving drug specificity and increasing intracellular drug delivery (Bae, 2009). Therefore, NP drug delivery platforms have become strategies to overcome the nonspecificity of chemotherapeutic drugs (Jain and Stylianopoulos, 2010). We firstly talk about two common modes of tumour-targeted delivery as shown in **Figure 2**.

2.1 Passive Targeting

Passive targeting is based on enhanced permeability and retention effect (EPR) (Matsumura and Maeda, 1986; Torchilin, 2011) The rapid growth of tumours results in large gaps in vascular endothelial cells, leading to more drugs entering tumour tissue. The imperfect lymphatic reflux function of tumour tissue results in the long-term retention of drugs at the tumour site. The EPR effect is known as the "royal gate" (Danhier et al., 2010) and is the gold standard for the design of antitumour drugs and the physiological basis for the entry and accumulation of macromolecules and small particles in tumours. The presence of NPs can not only reduce the toxic side effects of chemotherapy drugs but also enhance the EPR effect and improve the targeting ability and efficacy of drugs (Torchilin, 2007a). For example, Doxil (pegylated liposomal doxorubicin) has a drug concentration that is 10 times higher than that of free doxorubicin at the tumour site (Torchilin, 2007b).

Except for tumours with blood vessels, such as prostate cancer or pancreatic cancer, almost all fast-growing tumours exhibit the EPR effect (Maeda et al., 2001; Din et al., 2017; Fang et al., 2020a). NPs must be of a certain size to exploit the EPR effect. The size of the drug in blood circulation must be larger than the renal clearance threshold to ensure long-term circulation. Therefore, the size of the NPs must be greater than 10 nm (Maeda et al., 2009; Maeda et al., 2013). Second, the size of NPs should be smaller than the lumen size of the vasculature at the tumour site; therefore, they need to be smaller than 100 nm (Noguchi et al., 1998; Liu et al., 2018a). In-depth studies have found that NPs that are approximately 50 nm have the highest efficacy on primary and metastatic tumours (Tang et al., 2014a). In addition to size, other NP properties, such as biocompatibility and surface charge, impact the EPR effect (Kobayashi et al., 2014; Ulbrich et al., 2016).

Currently, there are many anticancer drug preparations based on the EPR effect. Among them, the earliest passive targeting drug is a polymer-conjugated drug prepared by Maeda et al.,

TABLE 1 | Targets and targeting agents in tumour cells, tumour microenvironment, and vasculature.

Target location	Target	Targeting ligands	Indications	Ref.
Tumour cells	TfR	Tf	Colon cancer, ovarian cancer	Nogueira-Librelotto et al. (2017)
	FR	Folate	Ovarian cancer, kidney cancer	Kumar et al. (2019)
	LHRHR	LHRH	Breast, ovarian, endometrial	Deng et al. (2008)
	VIPR	VIP	VIPoma	Tang et al. (2014b)
	ASGP-R	Galactosamine	Liver cancer	Li et al. (2018)
	Protein kinase CK2	4,5,6,7-tetrabromobenzotriazole	Breast, prostate cancer	(Trembley et al., 2010; Zaman et al., 2019a)
	HER2/neu	Anti- HER-2 (Trastuaumab)	Glioma、breast cancer	Lopez et al. (2018)
	Trop-2	Antl-Trop-2 (Pr1E11)	Urothelial carcinoma, breast cancer	Ikeda et al. (2015)
	ENPP3	Antl-ENPP3 (AGS16F)	Clear cell renal cell carcinoma、astrocytomas	Doñate et al. (2016)
	GD2	Anti-GD2 (Dinutuximab)	Neuroblastoma、Small Cell Lung Cancer	Nazha et al. (2020)
	GPNMB	GPNMB-specific monoclonal antibody (CR011)	Melanoma、glioma	Taya and Hammes, (2018)
	SLAMF7	Anti-SLAMF7	Multiple myeloma、lymphoma	Kikuchi et al. (2020)
	EGFR/EGF	Anti-EGFR (Erbitnx)	Colorectal cancer, non-small cell lung cancer	Kaufman et al. (2021)
	CD56	Anti-CD56 (lorvotuzumab)	Merkel cell carcinoma、multiple myeloma	(Huang et al., 2020; Esnault et al., 2022)
	CD38	Anti-CD38 (Daratumumab)	prostate cancer、multiple myeloma	Bonello et al. (2018)
	CD70/CD27	Anti-CD70, Anti-CD27	Liver cancer、lymphoma	Wajant, (2016)
	CD44	Hyaluronic acid (HA)	Bladder cancer, melanoma prostate cancer	Cai et al. (2019)
	CD38	Anti-CD38	Prostate cancer、multiple myeloma	van de Donkvan de Donk, (2018)
	CD19	Anti-CD19 (ADCT-402)	Leukemia	Zammarchi et al. (2018)
	MEK	MEK Inhibitors (Trametinib)	Melanoma	Cheng and Tian, (2017)
	ROS1	NTRK/ROS1 inhibitor (SIM 1803-1A)	Ovarian cancer, non-small cell lung cancer	Wang et al. (2020)
	RET	selective RET inhibitors (pralsetinib、selpercatinib)	Thyroid cancer, kidney cancer, gastrointestinal stromal tumor	Subbiah and Cote, (2020)
	CD20	Anti-CD20 (Rituximab)	Lymphoma, leukemia	Yao et al. (2017)
	CD30	Anti-CD30 (Brentuximab)	Lymphoma	Merli et al. (2016)
	CD52	Anti-CD52 (Alemtuzumab)	Leukemia	Jiang et al. (2009)
	BTK	Anti- BTK (LOXO-305)	Leukemia, Lymphoma	Radionuclide, (2021)
	HDAC	HDAC inhibitor (ST7612AA1)	Lymphoma, multiple myeloma	Cini et al. (2018)
	ALK	ALK/ROS1 inhibitor (ZX-29)	Non-small cell lung cancer	Gou et al. (2020)
Tumour microenvironment	MMPs	MMP2 sensitive penetrating peptide (ACPP)	Human fibrosarcoma、gliomatosis cerebri	Li et al. (2015)
	HIF	HIF-2α inhibitor (Belzutifan)	Lymphoma, multiple myeloma	CowmanCowman and Koh, (2022)
	PARP	PARP inhibitor (Olaparib)	Ovarian cancer	Zhou et al. (2021)
	PI-3K	PI3K inhibitor (Cal-101)	Leukemia, lymphoma	Macias-Perez and Flinn, (2013)
	mTOR	mTOR protein specific inhibitor (rapamycin)	Breast, Pancreatic, Kidney Cancer	Gopalakrishnan et al. (2018)
	CDK4/6	CDK4/6 inhibitor (Ribociclib)	Breast cancer	O'Leary et al. (2016)
	CXCR4	CXCR4 inhibitor (LFC131)	Melanoma	Wang et al. (2015a)
	EpCAM	Apt	Kidney cancer, Lung cancer	Zhao et al. (2019)
	BRAF	RAF inhibitors (Vemurafenib)	Melanoma	Zaman et al. (2019b)
	BCMA	anti-BCMA (Belantamab mafodotin)	Multiple myeloma	Sanchez et al. (2021)
	CD79b	anti-CD79b (10D10)	Melanoma, non–small cell lung cancer, mesothelioma, prostate	Williams et al. (2008)
	PD-1	PD-L1, PD-L2	Breast cancer、stomach cancer, non-small cell lung cancer	Huang et al. (2021a)
	CTLA-4	Anti- CTLA-4 (Lpilimumab)	melanoma, non–small cell lung cancer, mesothelioma, prostate	Rowshanravan et al. (2018)
Tumour vasculature	VEGFR/VEGF	Small molecule TKI	Liver cancer, stomach cancer, colorectal cancer	Kaufman et al. (2021)
	ROBO4	MIR-204	Bladder cancer, breast cancer	Li et al. (2019)
	Integrin ($\alpha v\beta 3$, $\alpha v\beta 5$)	Arg-Glycine-Asp (RGD) Asn-Gly-Arg (NGR)	Stomach, breast, esophagus, lymphoma, etc.	Wu et al. (2019)
	VCAM-1	Anti-VCAM-1 (212Pb-αVCAM-1)	Lung, breast, stomach, and melanoma cells	Corroyer-Dulmont et al. (2020)
	Aminopeptidase N/CD13	cCNGRC peptides	Liver cancer	Graziadio et al. (2016)
	PDGFR		Glioblastoma	Yousso ufian et al. (2008)

(Continued on following page)

TABLE 1 | (*Continued*) Targets and targeting agents in tumour cells, tumour microenvironment, and vasculature.

Target location	Target	Targeting ligands	Indications	Ref.
		recombinant human IgG Mab (IMC-3G3)		
	FGF/FGFR	Pan-FGFR Inhibitors (JNJ-42756493)	Bladder cancer, breast cancer, endometrial cancer	Wang et al. (2021a)

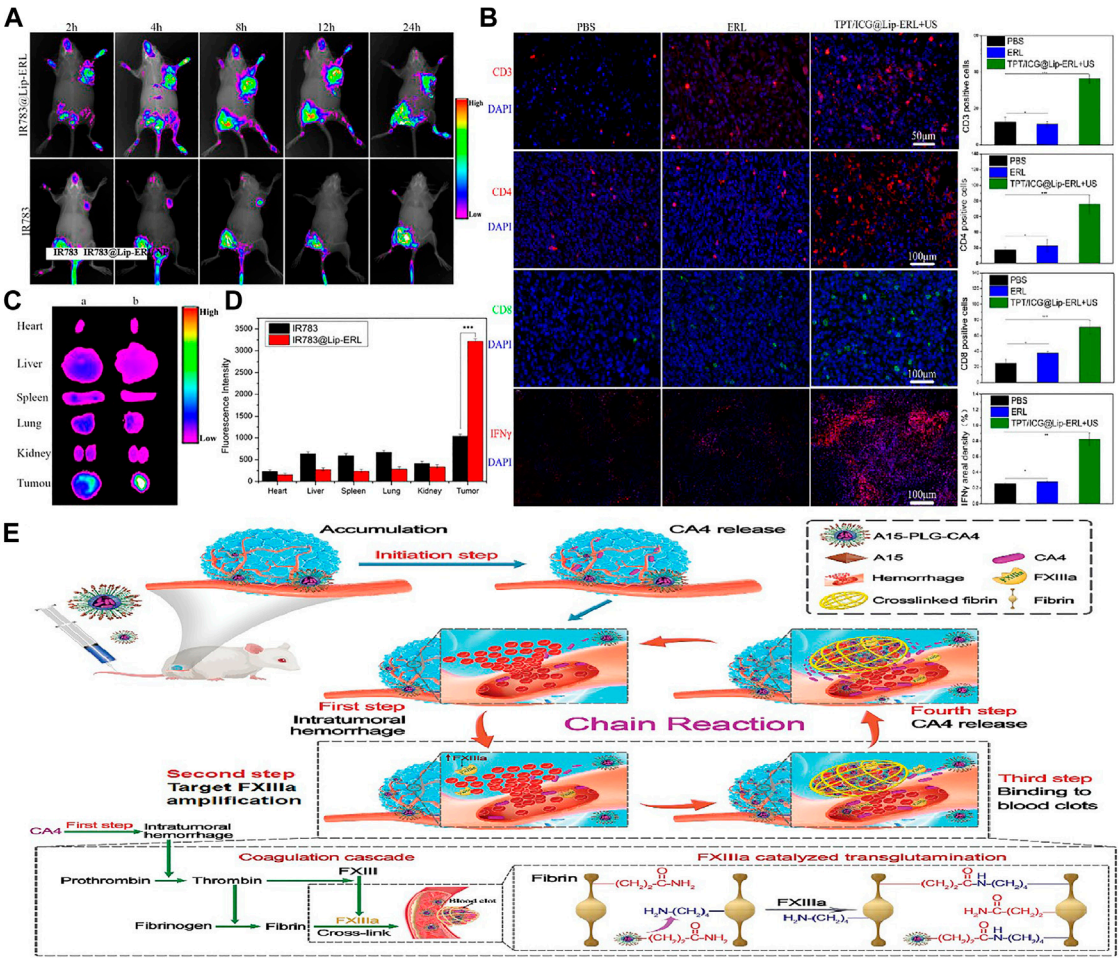


FIGURE 3 | (A) Semiquantitative mean fluorescence intensity results of organs and tumours. Data are expressed as mean ± SD (n = 3). **(B)** *In vivo* images of 4T1 tumour-bearing mice administrated with free DiR or CTP/CDDP/DiR at different times. **(C)** *Ex vivo* images of organs and tumours excised from tumour-bearing nude mice at 12 h after intravenous injection of different drugs. **(D)** Semiquantitative mean fluorescence intensity results of organs and tumours. Data are expressed as mean ± SD (n = 3). **(E)** Schematic illustration of the self-amplifying tumour-homing nanotherapeutic platform, A15-PLG-CA4, characterized by chain reactions. **(A,B,C,D)** is reprinted with permission from reference (Chen et al., 2021). **(E)** is reprinted with permission from reference (Wang et al., 2021b).

i.e., SMANCS (Maeda, 2001). This anticancer polymer was approved in 1993 by the Japanese government for the treatment of liver cancer (Maeda et al., 1985; Maeda, 1994). Despite continuous in-depth research on the EPR effect, there is still great controversy regarding the EPR effect and clinical treatment. First, Shrey et al. used mathematical models and animal models to study murine and human tumours and showed that endothelial gaps were not the reason for the entry of NPs into solid tumours. There were only 26 intercellular spaces in 313 blood vessels. The overall coverage rate was only 0.048%, and only 7 of these 26 intercellular spaces were interendothelial channels; the remaining 19 were intercellular channels. The gaps on the tumour were 60 times smaller than that required for the observed accumulation of NPs (Sindhwani et al., 2020). Second, based on a literature survey of NP delivery from 2006 to 2016, it was found that only 0.7% (median) of drug-containing NPs

entered solid tumours. In addition, more than 95% of targeted NPs cannot reach tumours during intravenous administration; therefore, the current clinical efficacy cannot significantly improve (Wilhelm et al., 2016). Because the EPR effect is a dynamic phenomenon, one possible cause of this situation is the heterogeneity of the EPR effect, that is, tumour vascular occlusion or embolism, which has become one of the main obstacles to the targeting of drug-containing NPs (Gerlinger et al., 2012; Fisher et al., 2013).

2.2 Active Targeting

Active targeting refers to the binding of NPs modified with targeting ligands to specific receptors on tumour cells or the tumour endothelium on the basis of passive targeting, thereby allowing tumour-specific targeting. In the selection of targeting ligands, receptors that are expressed on all types of tumour cells should be selected, and the selected targeting receptors should only be overexpressed on tumour cells (Adams et al., 2001). Commonly used tumour cell receptors include transferrin receptor (TfR), folate receptor (FR), glycoproteins, and epidermal growth factor receptor (EGFR) (**Table 1**).

Active targeting plays a dominant role in the targeted delivery of NPs. Schleich et al. (Schleich et al., 2014)compared nontargeted and single-targeted NPs and found that the accumulation of NPs in the single-targeted group was more than 2.5 times higher than that in the passively targeted group. In the process of active targeting, two decisive factors can be adjusted. The first factor is the abundance of tumour surface receptors. The long-term targeted delivery of nanodrugs can lead to a reduction in gene expression or to gene mutations, which will lead to a reduction in the efficacy of targeted nanodrugs and the development of multidrug resistance (Li et al., 2017; Hayashi and Konishi, 2021). Chen et al. (Chen et al., 2021) prepared chitosan oligosaccharide (COS)-coated and sialic acid (SA) receptor-targeted nano-micelles and found that these nano-micelles inhibited tumour epithelial mesenchymal metastasis by downregulating the expression of Hypoxia Inducible Factor-1α (HIF-1α), Glutathione (GSH), Multidrug Resistance-associated Protein 2 (MRP2) and Matrix Metalloproteinase 9 (MMP9). The results showed that these nano-micelles significantly enhanced the antitumour effect *in vivo* and *in vitro*, providing an effective strategy for the treatment of drug-resistant metastatic tumours (**Figures 3A–D**). The second factor is the selection of targeting agents for receptors (Zhukov and Tjulandin, 2008; Ma yer, 2009). Wang et al. (Wang et al., 2021b) selected coagulation peptide (A15) as a targeting agent to generate a self-amplified tumour nanotherapy platform with a chain reaction mechanism (**Figure 3E**). After the administration of drugs to mice, the total CA4 concentration in A15-PLG-CA4-treated C26 tumours was 2.9 times that in the control group at 24 h, the total BLZ945 concentration (24 h) in the C26 tumours treated with A15-PLG-CA4/BLZ945 was 3.8-fold more than that in the tumours treated with A15′-PLG-CA4/BLZ945, with a significant antitumour effect.

2.3 Other Modes

Besides the above two common modes of tumour-targeted delivery, there are also a variety of transport modes. Transcytosis is an active vesicle-mediated delivery pathway that is often used by macromolecules to cross biological barriers. The EPR effect has long been recognized as the main factor for the entry of NPs into tumour cells (Gerlowski and Jain, 1986). However, the EPR effect has always been controversial with regard to clinical application (Danhier, 2016; Nel et al., 2017). In 2015, Anders proposed that the EPR effect is not a common feature of all solid tumours (Hansen et al., 2015). Recently, Chan et al. found that transcytosis may be the main mode of entry of NPs into tumours. The effect of transcytosis on the enrichment of NPs at tumour sites was investigated. The observation of 3 sizes of gold NPs (AuNPs) *via* transmission electron microscopy (TEM) provided direct evidence of transcytosis; moreover, after blocking the transcytosis pathway, only 3–25% of the total AuNPs entered tumours *via* the EPR effect, indicating that transcytosis may play a dominant role. However, the mechanism of transcytosis and the triggering factors remain unclear. Studies have shown that receptor-glycoprotein binding (Nel et al., 2017) and charge inversion (Schulz et al., 2019; Fang et al., 2020b) may trigger transcytosis. Therefore, it is possible that transcytosis can be used to improve the efficiency of targeted drug delivery by NPs.

Targeted drug delivery mechanisms mediated by the TME are also feasible methods. The TME is hypoxic, has a low pH, and generates an inflammatory response and immunosuppression. It contains a large number of interstitial cells and immune cells and is an environment in which tumour cells depend on for survival (Schulz et al., 2019). Smart nanodrug delivery platforms utilize the internal phenomena of the TEM [e.g., low pH (Bener et al., 2020), overexpressed enzymes (Liu et al., 2017), and hyperthermia] or external stimuli (e.g., light, heat, and magnetic fields) to control the release of drugs (Shrestha et al., 2021). pH-responsive nano-formulations use pH changes to cause conformational or solubility changes, charge reversal, and chemical bond cleavage. The control and release of drugs from the tumour environment are achieved through the acidic environment of the tumour mesenchyme combined with acid-sensitive chemical bonding, thereby facilitating the endocytosis and targeting of nano-agents (Bener et al., 2020; Lin et al., 2020). By comparing poly(ethylene glycol)-poly(benzyl-l-aspartate) (PPA) and poly-imino-poly(benzyl-l-aspartate) (PIPA) block copolymers, Pu et al. (Pu et al., 2019) found that PIPAH had a better drug release rate and antitumour effect than that of pH-insensitive PPAH because the imine bond of PIPAH utilizes the acidic condition of the TME to more effectively release the active drug.

3 BIOMATERIALS OF NPS

Nanoparticles have unique properties that can improve drug biocompatibility, reduce drug toxicity, and enter tumour sites in a specific manner. These properties are closely related to the prepared materials. The preparation materials of nanoparticles mainly include lipid materials, polymer materials and inorganic materials as show in **Table 2**. Next, we discuss the lipid and polymer materials.

TABLE 2 | Nanoparticle preparation materials, methods and characteristics.

	Material	Preparation methods	Different characteristics	Common characteristics
Lipids (Cheng and Tian, 2017)	(2,3-Dioleyl-propyl)-trimethylamine (DOTAP) 1,2-Dioleoyl-sn-glycero-3-phospho-choline (DOPC) 1,2-Dipalmitoyl-sn-glycero-3-phos-phocholine (DPPC)	Microfluidic technologies Detergent dialysis Supercritical fluid method Thin film hydra-tion method Reverse phase evaporation method	Affordable scale-up manufacture, high drug loading efficiency, well-tolerated, high bioavailability	Excellent biocompatibility, Low toxicity Biodegradability Low immunogenicity
Nanopoly-mer (Chen et al., 2020)	Poly-(lactic-co-glycolic acid) (PLGA) Polyhydroxyalkanoates (PHAs) Cyclodextrins (CDs) Polylactic acid (PLA)	Emulsification/solvent Evaporation Nanoprecipitation Salting-out methods Supercritical technology Electrospraying Methods	Availability of various polymers, higher dynamic stability and thermodynamic stability	
Inorganic (Wang et al., 2016)	Gold Silica Carbon Calcium phosphate	Lithography Liquid-phase method Chemical Reduction Methods Thermal decomposition	Unique physical/chemical properties, versatile synthetic strategies, easy surface functionalization	

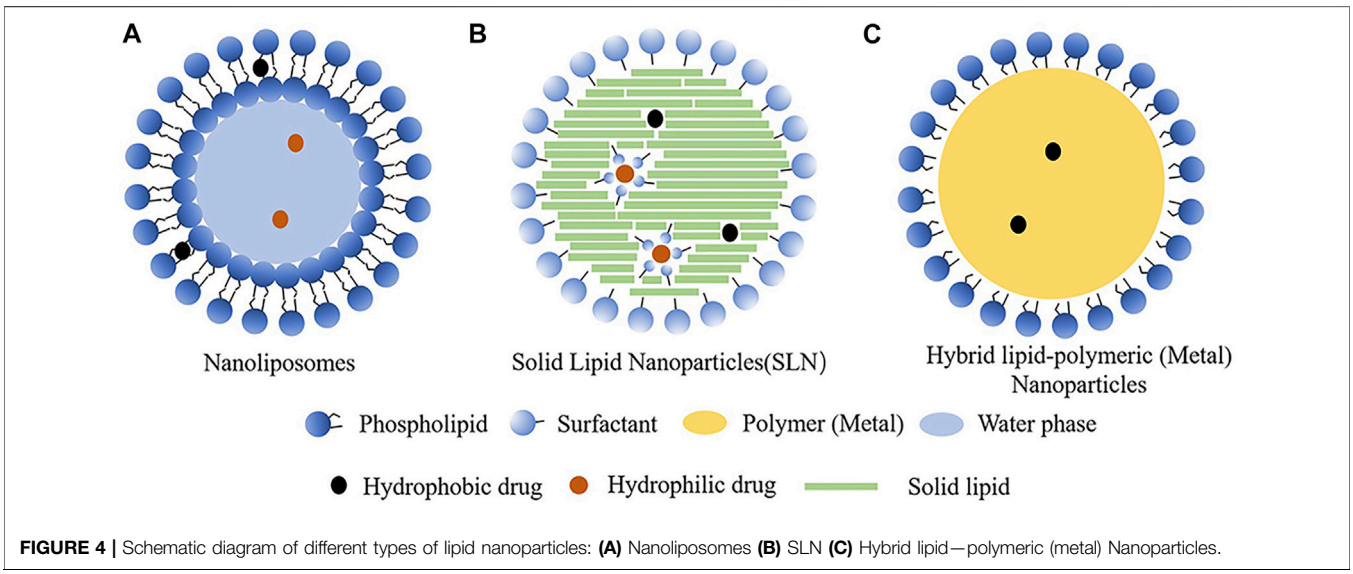


FIGURE 4 | Schematic diagram of different types of lipid nanoparticles: **(A)** Nanoliposomes **(B)** SLN **(C)** Hybrid lipid—polymeric (metal) Nanoparticles.

3.1 Lipid Materials

Lipid materials are biofriendly, highly versatile, biocompatible and have low toxicity. In addition, lipid materials can reduce the adverse reactions of the body to other exogenous biological carriers. Therefore, lipid materials have always been excellent carrier materials for the preparation of drugs. Different types of lipid nanoparticles can be prepared using lipid materials as show in **Figure 4** (Feeney et al., 2016).

Liposomes are the most common lipid-based carriers prepared from lipid materials (Plaza-Oliver et al., 2021). Currently, a variety of liposome preparations have been approved by the FDA for clinical use (Nguyen et al., 2016). Liposomes have good encapsulation capacity for water-soluble and fat-soluble drugs, crystalline drugs, biological macromolecules and are excellent drug carriers (Bangham et al., 1965). The superior properties of liposomes have led to their extensive application in anticancer treatments. First, liposomes can improve the delivery of chemotherapeutic drugs and improve the therapeutic effect of drugs. Li et al. (Li et al., 2021) prepared curcumin-loaded liposomes (Cur + Lip) that were sequentially coated with chitooligosaccharides (Cur + Lip-Cos) and negative phospholipids (Cur + Lip-Cos-PC) to improve the water solubility and encapsulation rate and thus delay the release of Cur. Second, The Lips were then fixed in an injectable thiolated chitosan hydrogel which enhanced the antitumour effect. Xu et al. (Xu et al., 2019) constructed bifunctional liposomes (DOX-ACF + Lip) that overcome chemotherapy resistance caused by hypoxia. In addition, liposomes can be modified with other ligands and functional components. The range of drug delivery of conventional liposomes has been extended by modifying them to increase their cycle time (e.g., long-cycle liposomes) (Zylberberg and Matosevic, 2016), to increase their local drug delivery concentration (e.g., liposome gel systems) (Zeng et al., 2020) or for gene delivery (e.g., cationic liposomes) (Ahmad et al., 2021; Zhao et al., 2021a). Solid lipid nanoparticles (SLNs) are solid micelle drug delivery systems made of natural or synthetic solid lipid materials as carriers and encapsulated drugs in lipid cores (Araujo et al., 2021). Compared with liposomes, SLNs exhibit better physical stability and higher drug loading capacity and bioavailability. Due to their low molecular mobility, SLNs can more accurately control the release of the drug payload in the cancer microenvironment (Tenchov et al., 2021). Kumar

et al. (Pandian et al., 2021) developed and evaluated rutin-loaded SLNs for the treatment of brain tumours. The study found rutin-loaded SLNs have superior characterization for their physicochemical properties. Its biocompatibility and stability have been confirmed *in vitro*. At 54 h after injection, the distribution of rutin in the brain was 15.23 ± 0.32%, and prepared rutin- loaded SLNs were stable in circulation for up to 5 days. Therefore, rutin-loaded SLNs can be used as carriers for the targeting of tumours across the blood–brain barrier (BBB).

3.2 Polymer Materials

Nanopolymer materials have a wide range of applications in biomedicine. They have adjustable molecular designs, are highly stable, and have structural diversity (Zhang et al., 2019a). Nanopolymer materials are currently the mainstream nanodrug carrier. For example, the nanopolymer micellar paclitaxel (pm-Pac) provides a new option for advanced lung cancer chemotherapy. The objective remission rates (ORRs) for pm-Pac and paclitaxel treatment were shown to be 50 and 26%, respectively, and the safety analysis indicated that the incidence of serious adverse events in the pm-Pac group was lower, only half of that in the paclitaxel group (Shi et al., 2021).

Biodegradable biopolymers are one of the most important biomaterials. In recent years, the development of degradable biopolymers to replace nondegradable polymers has been a trend (Kirillova et al., 2021). NPs composed of early polymer materials exhibited rapid and effective clearance. However, due to their non-degradability, these NPs accumulated in the body, resulting in chronic toxicity and inflammatory responses. Therefore, the development of biodegradable polymer materials has received extensive recognition and attention (Anju et al., 2020). After degradable biopolymers carry drugs to specific target sites, they begin to slowly degrade into smaller nontoxic substances, ultimately being metabolized by the body. Biopolymers can be classified based on the source, i.e., natural (such as polysaccharides and chitosan) and synthetic (such as polyesters and their copolymers). Because these biodegradable biomedical polymer materials have good biosafety, they are often used in biological tissue engineering and 3D scaffolds (Maity and Cha kraborti, 2020). In addition, some biodegradable biopolymers, such as polyglycolic acid (PGA) and poly(lactic-co-glycolic acid) (PLGA), have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as materials for drug preparation (Palma et al., 2018). For specific applications in the medical field, the functionalization of biodegradable biopolymer materials is one of the development trends in the future (Masood, 2016; Gagliardi et al., 2021).

3.3 Inorganic Materials

Inorganic nanomaterials can be easily prepared into different shapes and sizes in different tumour environments, which are good carriers for preparing tumour vaccines. Therefore, they are widely used in the biomedical field (Liu et al., 2020). However, most inorganic nanomaterials are non-biodegradable, causing direct cytotoxicity, and the aggregation of some potential inorganic nanoparticles can easily lead to vascular occlusion (Fadeel and Garcia-Bennett, 2010; Mukherjee and Patra, 2016). At the same time, inorganic nanomaterials tend to cause non-specific drug leakage, which limits the development of inorganic nanomaterials (Gorbet and Ranjan, 2020). Common inorganic nanomaterials can be mainly divided into two categories: non-metallic and metallic.

There are many kinds of metal nanomaterials. The currently developed nano-metal materials include gold, titanium, thallium, zinc, etc. (Gussone et al., 2014). Photothermal therapy (PTT) is a kind of cancer treatment with high specificity and low toxicity. Qiuhong Zhang (Zhang et al., 2020b) developed a highly efficient near-infrared photothermal agent (NIR-II PTA) based on liquid exfoliated $FePS_3$ nanosheets. Using the properties of iron, the prepared nanosheets showed an ultra-high specific surface area, improved the catalytic activity of Fenton, and achieved a photothermal conversion efficiency of 43.3%, while realizing cancer chemodynamic therapy (CDT). Iron-based metal nanomaterials have the potential to be a new nanotherapeutic platform.

The biosafety of non-metallic nanomaterials is better than that of metal nanomaterials. Silicon-based nanomaterials are one of the most widely used non-metallic nanomaterials. They are easy to synthesize and manipulate. They also have many unique advantages in *in vivo* applications, such as excellent biocompatibility, versatile surface chemistry, etc (Wang et al., 2021c). Chen Qi et al. (Chen et al., 2020) developed organic-inorganic hybrid hollow mesoporous silica nanoparticles (HMONs) as vaccine carriers, and used dopamine to modify the surface to improve the controllability of biodegradation and drug release. Molecular disulfide-bonded hybrid backbones enable stepwise degradation in a reducing tumour microenvironment. The results showed that HMONs had an effective slow-release effect, significantly inhibited the proliferation of tumour cells, and achieved anti-tumour effects *in vivo* through the dual-reaction release of the tumour microenvironment. In general, the nanoparticles have good application prospects in tumour vaccines.

4 CLINICAL APPLICATION OF NPS IN TUMOUR THERAPY AND VACCINES

4.1 Application of NPs in Tumour Therapy

As mentioned above, the emergence of NPs can greatly improve current cancer treatment as show in **Figure 5**. NPs can be used as carriers to deliver cargo to cancer cells. NPs can improve the efficacy of drugs by improving their safety, tolerability and their targeting (Almanghadim et al., 2021). In photothermal therapy, NPs can be used as carriers of photothermal agents for tumour elimination. Cheng et al. (Cheng et al., 2021) used self-designed hybrid therapeutic NPs loaded with photothermal agents; after the intravenous injection of NPs, laser irradiation was used to achieve excellent photothermal therapeutic outcomes; the results showed that the tumour was completely eliminated, immunogenic cells died, and a large number of tumour-related antigens were generated. Moreover, NPs can also be directly used as photothermal agents for tumour therapy (An et al., 2021).

In addition, NPs also play a substantial role in the early diagnosis and treatment of tumours. Currently, for tumour

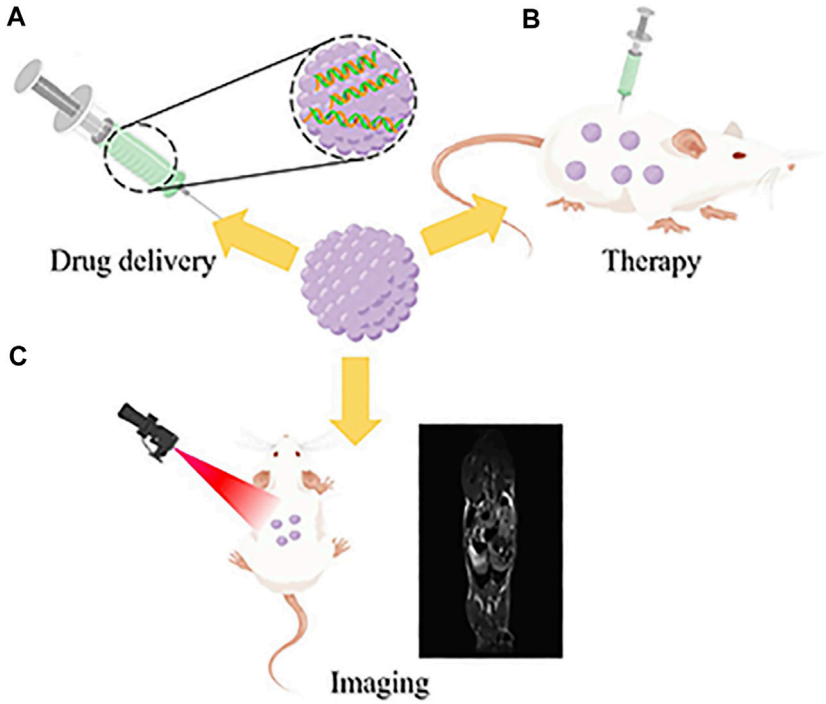


FIGURE 5 | Clinical application of NPs.

TABLE 3 | Antitumour nanodrugs currently approved for marketing (Danhier, 2016; Liu et al., 2018b).

Drugs	Company	Application	Time to market
SMANCS	Astellas Pharma Inc	Liver cancer and kidney cancer	1993
Oncaspar	SIGMA TAU	Acute lymphocytic leukaemia	1994
Doxil	Janssen	Breast cancer, uterine cancer, ovarian cancer	1995
DaunoXome	Galen	Kaposi's sarcoma	1996
Ontak	Eisai	Skin T-cell lymphoma	1999
DepoCyt	PACIRA PHARMS	Lymphoma meningitis	1999
Myocet	Elan	Breast cancer	2000
Eligard	TOLMAR THERAP	Prostate cancer	2002
Lipusu	Luye Pharma Group	Breast cancer, lung cancer, ovarian cancer	2003
Abraxane	ABRAXIS Bioscience	A variety of cancers, metastatic pancreatic cancer	2005
Genexol-PM	Samyang	Breast cancer, small cell lung cancer	2007
MEPACT	IDM Pharma SA	Osteosarcoma	2009
Nanotherm	MacForce	Glioblastoma	2010

imaging, the distribution of imaging contrast agents and tracers in the body is not well understood, the clearance rate is fast, the pharmacokinetics are poor, and there are certain adverse reactions. NPs open a new path for cancer imaging (Xu et al., 2018). Sun et al. (Sun et al., 2014) used nanorods as substrates, and the surfaces were modified with PEG and ^{64}Cu to successfully apply them in PET. Wang et al. (Wang et al., 2015b) generated superparamagnetic iron oxide nanoparticles (SPIONs) coated with dSiO2 as core–shell NPs and labelled them with near infrared fluorescence material and an anti-CD146 monoclonal antibody for magnetic resonance imaging. The MKN 45 xenograft tumour model can be clearly identified as early as 30 min after injection.

Paclitaxel (PTX) is currently one of the most effective drugs for the treatment of cancer. However, its availability is limited due to its low solubility and various side effects. In clinical practice the use of PTX as an NP carrier can effectively reduce the toxic effect of PTX on noncancerous cells and significantly reduce the survival rate of all cancer cells (Danışman-Kalındemirtaş et al., 2021). Currently, a variety of NP drugs have been approved for the treatment of tumours (**Table 3**).

4.2 Application of NPs in Vaccines

NPs are good candidates for the preparation of vaccines. Nanovaccines are safer and more stable and have better versatility (Mamo and Poland, 2012; Yadav et al., 2018). In the application

TABLE 4 | Cancer vaccines that are in the clinical trial stage.

Drug name	Indications	Clinical trial stage	R&D company	Ref.
Non- nanovaccines				
Tedopi	Lung cancer	Stage III	OSE Immunotherapeutics	Cappuzzo et al. (2022)
PolyPEPI1018	Colorectal cancer	Stage I/II	MAYO CLINIC	Hubbard et al. (2019)
AV-GBM-1	Brain tumours	Stage II	Aivita Biomedical	Bota et al. (2021)
Ilixadencel	Kidney cancer	Stage II	Immunicum AB	Lindskog et al. (2022)
VRP-HER2	Breast cancer	Stage I/II	Duke University	Ragelle et al. (2017)
NeuVax	Breast cancer	Stage III	America (unknown)	(Berry et al., 2013; Jain et al., 2015)
Alpha-lactalbumin vaccine	Breast cancer	Stage I	Cleveland Clinic	Budd et al. (2022)
ABI-009	Non-muscle invasive bladder cancer	Stage I/II	AADi	Cappuzzo et al. (2022)
Nanovaccines				
mRNA-4157	Bain cancer	Stage I/II	Moderna	Bauman et al. (2020)
BNT111	Melanoma tumor	Stage I/II	PFIZER/BioNTech	Loquai et al. (2021)
mRNA-2416	Lymphoma and metastatic ovarian cancer	Stage I	Modern	Porciuncula et al. (2021)
mRNA-2752	Lymphoma	Stage I	Modern	Patel et al. (2020)
Lipo-MERIT	Melanoma	Stage I/II	BioNTech	Loquai et al. (2020)
mRNA-5671	Pancreatic cancer	Stage I	Moderna/Merck Sharp & Dohme	Wei and Hui, (2022)
Gardasil, Gardasil-9	HPV type 6,11,16,18, 31,33,45,52,58 and genital warts	Listed	GlaxoSmithKline/Merck Sharp & Dohme	Das and Ali, (2021)
Her-2/neu peptide-based vaccine	Metastatic breast cancer	Stage I	unknown	Wiedermann et al. (2010)
L-BLP25	Non-small cell lung cancer (NSCLC)	Termination	Merck Sharp & Dohme	Butts et al. (2011)

of tumour vaccines, NPs have greatly improved the efficacy of vaccines and reduced the number of drug administrations (Sulczewski et al., 2018; Wadhwa et al., 2020). Many studies have reported the preparation of synthetic vaccines based on NPs; such vaccines have the potential to enhance the corresponding immune response (lymph node transport efficiency) and improve vaccine delivery (Fu et al., 2018; Kheirollahpour et al., 2020). Zhuang et al. (Zhuang et al., 2016) used lipid-enveloped zinc phosphate hybrid (LZnP) NPs to deliver polypeptides (TRP2180-188 and HGP10025-33) and Toll-like receptor 4 agonists. The results indicated that LZnP NPs increased the secretion of cytokines and the number of $CD8^+$ T cells. Compared with free antigens and single peptide-loaded nano-vaccines, nano-vaccines had significant antitumour effects in the treatment and prevention of melanoma in a mouse model.

The emergence of nanomedicine has accelerated the development of vaccines. As one of the nine adjuvants approved by regulatory authorities, liposomes play an indispensable role in the preparation of vaccines (Delany et al., 2014; Dowling and Levy, 2015). Currently, there are only a few cancer vaccines on the market worldwide (such as HPV vaccines), but many cancer vaccines are already in the clinical stage (**Table 4**). It is believed that with the development of liposomes, liposomes will be widely used as high-quality materials in vaccine preparation.

4.2.1 Application in Traditional Vaccines

In vaccine applications, nanoliposomes can be used as carriers of immunostimulants to improve the capacity of immunostimulants (Zamani et al., 2018; Huang et al., 2021b). Zhang et al. (Zhang et al., 2019b) synthesized lipid NPs to carry imiquimod (IMQ), a toll-like receptor 7/8 (TLR 7/8) agonist, and monophosphoryl lipid A (MPLA), a TLR4 agonist. The results from the tumour treatment experiments indicated that the lipid NPs were more effective than other preparations at inhibiting tumour growth and that the loading of immune checkpoint blockade agents further enhanced the antitumour effect. In addition, lipid nanoparticles (LNPs) can also be used as carriers for drug delivery. Noh et al. (Kim et al., 2012; Noh et al., 2017) designed and synthesized immunomodulatory liposomes (denoted as "tumosomes") that can simultaneously deliver cancer antigens and adjuvants. These "tumosomes" have 2 lipid adjuvants, namely, MPLA and DDA, which have risk signals that can be used as pathogen characteristics. Experiments have shown that "tumosomes" effectively improve antitumour immune function, antigenicity and antigen uptake efficiency. This method induces and enhances the antitumour immune response and transforms the tumour into a vaccine. In addition, the vaccine can also be used in combination with other cancer treatment methods to improve the efficacy of cancer treatment.

In addition to acting as carriers, LNPs can also be used as adjuvants to prolong the biological half-life of vaccines and the ability of antigen-presenting cells to take up antigens (Kno tigová et al., 2015). They induce the production of immune regulatory cytokines, activate inflammation, local inflammation and cell recruitment, and induce faster, more extensive and stronger immune response (Park et al., 2018). Kocabas et al. (Kocabas et al., 2020) prepared dual- adjuvant liposomes by co-encapsulating cGAMP and oligodeoxynucleotides (ODN) containing unmethylated CpG motifs (CpGODN) into sterically stabilized cationic liposomes (SSCLs). The SSCLs promoted the formation of type I and type II interferons, the dual-adjuvant liposomes enhanced the immunostimulatory properties of cGAMP and CpGODN, promoted

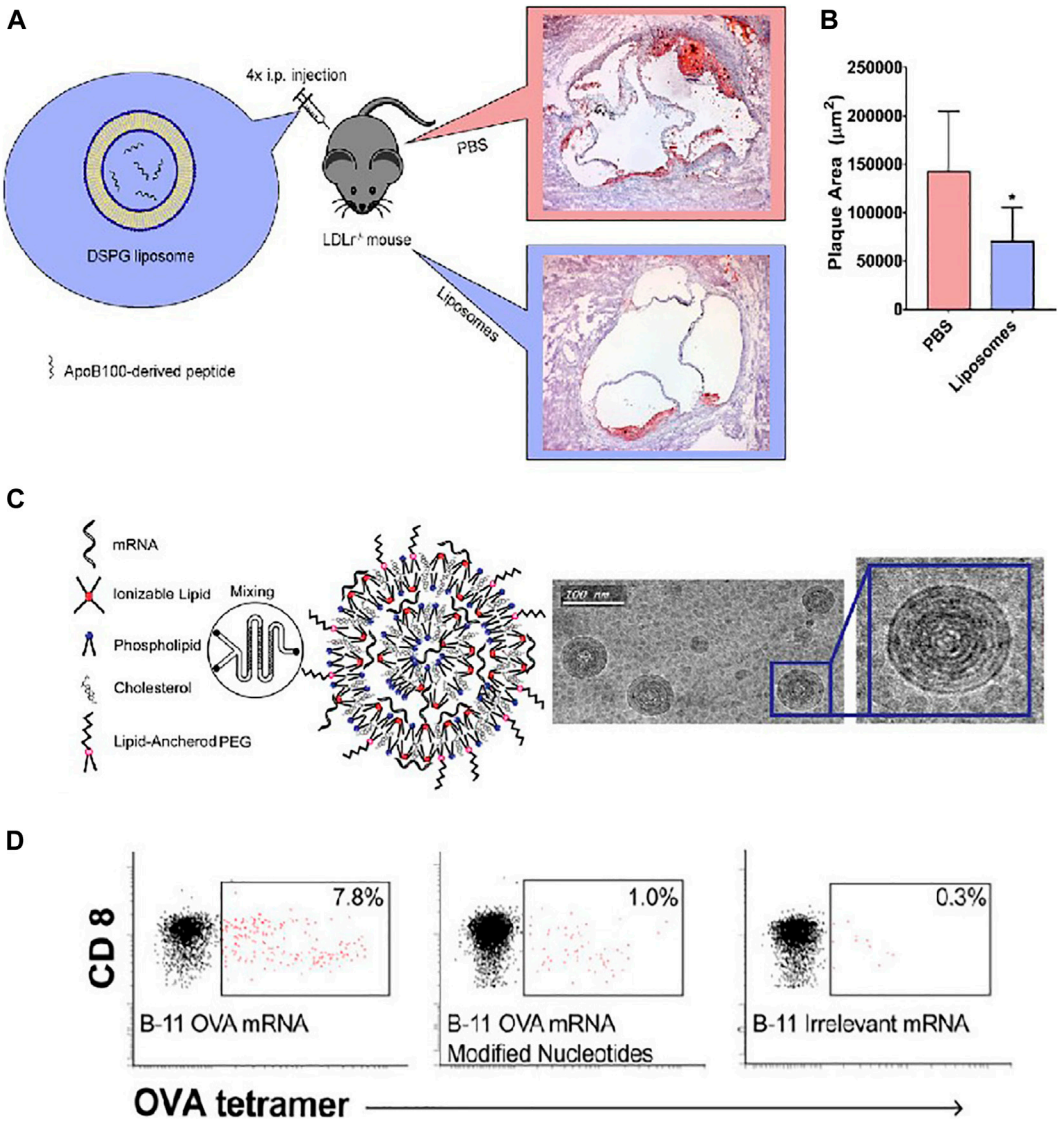


FIGURE 6 | (A) Representative images of sections of the aortic valve area in a mouse receiving PBS or DSPG/p3500-liposomes. **(B)** Lesion area as determined by Oil-Red-O staining in a mouse receiving PBS or DSPG/p3500-liposomes. **(C)** "Sandwich" structure and Cryogenic transmission electron microscopy image of the LNP solution. **(D)** Representative FACS profiles of mice treated with the indicated conditions. **(A,B)** is reprinted with permission from reference. (Benne et al., 2018). **(C,D)** is reprinted with permission from reference (Oberli et al., 2017).

Th1 immunity, and caused melanoma remission by approximately 70%, and the lipid preparations reversed macrophage polarization to an M1 inflammatory phenotype. Farzad et al. (Farzad et al., 2019) coupled the P435 HER2/neu-derived peptide with drugs to establish an effective nanoliposome vaccine, which can be used as an adjuvant. The liposomal P435 preparation induced IL-4 in mice, and the Lip + DOPE + P435 preparation stimulated IFN-c. The authors concluded that Lip + DOPE + P435 is a promising candidate for the development of an effective vaccine for HER2-positive breast cancer.

Cationic liposomes are often used in the development of vaccines because cationic liposomes can better interact with negatively charged ions in the cell membrane than can other types of liposomes (Thi et al., 2021). This storage effect leads to a prolonged antigen release time at the injection site, and the effective transfection of macromolecules (such as pDNA and mRNA) also requires the presence of positively charged cationic lipids (Habrant et al., 2016). Additionally, studies have found that compared with negatively charged NPs, positively charged NPs can be rapidly taken up by cells (Zaki et al., 2011). However, these cationic lipids show higher cytotoxicity than do neutral or anionic lipids; therefore, their application has certain limitations (Wei et al., 2015). To allow more drugs to be prepared into NPs and used in the preparation of vaccines, negatively charged or neutral nanoliposomes must be developed. Naomi Benne et al. (Benne

et al., 2018) inoculated atherosclerotic mice with anionic DSPG-Nanoliposomes and found that anionic DSPG-liposomes can serve as a useful delivery vector to induce antigen-specific Tregs, and that empty anionic liposomes reduce plaque size and cellular content to a similar extent as injection of apoptotic cells. The ApoB100-derived peptides were then encapsulated in anionic liposomes for administration. Anionic liposomes were found to significantly reduce plaque formation by about 50% and increase plaque stability. These results indicate that anionic DSPG-Nanoliposomes have potential as a delivery system in vaccination against atherosclerosis (**Figures 6A,B6**).

4.2.2 Application in DNA Vaccines

Currently, liposome-based nanodrug delivery systems are mainly used in the development and application of modern vaccines, of which nucleic acid vaccines are the mainstay (D'Amico et al., 2021; Alfagih et al., 2021). Nucleic acid vaccines have good stability and can be produced rapidly (Iavarone et al., 2017; Rockman et al., 2020). There are currently 2 types: DNA vaccines and RNA vaccines. DNA vaccines prevent diseases by injecting plasmids used for encoding. After the injection of plasmids, cells directly produce antigens, thereby causing a protective immune response (Gary and Weiner, 2020). Won (Youn et al., 2020) designed a DNA vaccine against HPV virus-specific antigens and found that the GX-188E vaccine induced HPV-16 E6- and E7-specific T-cell responses in patients with precancerous lesions, thereby alleviating cervical lesions. A small-scale clinical trial showed that PD-L1 antibody can treat patients with advanced refractory cervical cancer. However, due to the weak immunogenicity and short half-life of DNA vaccines, only a number of DNA vaccines are used in veterinary medicine (e.g., melanoma vaccines for dogs (Gummow et al., 2020)); no DNA vaccines are currently used in humans (Liu, 2019). As an excellent delivery system, LNPs can enhance the humoral and cellular immune responses of DNA vaccines, thereby compensating for the shortcomings of DNA vaccines and enabling their further development (Gary and Weiner, 2020). Zhao et al. (Zhao et al., 2021b) developed a novel liposome-polymer hybrid NP (pSFV-MEG/LNPs) for the delivery of multi-epitope self-replication DNA vaccines. These LNPs induced a strong humoral and cellular immune response compared with that generated with common preparations, with approximately 3.22-fold and 1.6-fold increases, respectively. The research and development (R&D) of DNA vaccines against COVID-19 has received close attention, and more than ten COVID-19 DNA vaccines are used in clinical practice worldwide. Among them, the COVID-19 DNA vaccine ZyCoV-D developed by Zydus Cadila has received emergency use authorization by the Indian drug regulatory agency, becoming the world's first COVID-19 DNA vaccine (Abdulla et al., 2021).

4.2.3 Application in mRNA Vaccines

mRNA vaccines are based on the mRNA sequences of pathogen antigen proteins. After delivery into the body, antigen proteins are produced through translation to induce specific immune responses in the body and ultimately eliminate cancer cells (Pardi et al., 2018). mRNA vaccines have multiple advantages. First, they reduce the risk of T-cell function failure caused by persistent antigen exposure. Second, as the smallest genetic carrier, mRNA is non-infectious and does not integrate in the genome, playing its role exclusively in the cytoplasm, thereby avoiding genetic risks and increasing safety. In addition, the *in vivo* delivery of mRNA is fast and effective (Maruggi et al., 2019). Compared with traditional vaccines, mRNA vaccines can simultaneously deliver multiple antigens and immunomodulators, and the manufacturing process is simple, fast and inexpensive (Sahin et al., 2014); Compared with DNA vaccines, mRNA vaccines have faster action and good efficacy (Maruggi et al., 2019; Teo, 2021). However, mRNA vaccines are unstable in the body and have strict transport conditions, which limits their use (Guevara et al., 2019). The encapsulation of mRNA vaccines in LNPs greatly improves their stability and plays a key role in the transport of mRNAs to cells (Guan and Rosenecker, 2017; Hajj and Whitehead, 2017). Oberli et al. (Oberli et al., 2017) reported an LNP for the delivery of mRNA vaccines. They treated B16F10 melanoma with LNPs containing mRNA coding for the tumour-associated antigens gp100 and TRP2, resulting in tumour shrinkage and in an extension of overall survival in treated mice. They concluded that LNPs are a promising mRNA vaccine vector capable of inducing a strong cytotoxic T-cell response (**Figure 6C,D**).

Due to the COVID-19 pandemic, mRNA vaccines have attracted the attention of many pharmaceutical companies, such as Pfizer and Moderna. The FDA has issued emergency use authorizations for 2 mRNA vaccines. The efficacies of Pfizer/BioNTech's BNT12b2 and Modern's mRNA-1273 were 95 and 94.1%, respectively (Teo, 2021). However, the original intention of mRNA vaccine innovation was to develop anticancer vaccines. Moderna has released its new cancer vaccine mRNA-4157, which is a personalized cancer vaccine based on lipid encapsulation. A clinical trial found that in 10 patients with advanced brain cancer, the total remission rate was 50% and the disease control rate (DCR) was up to 90% (Bauman et al., 2020). In addition, the injectable liposome formulated mRNA vaccine BNT111 developed by Pfizer/BioNTech for melanoma tumours has achieved good efficacy and good safety. This vaccine can control cancer by enhancing the immune system and improving immune targeting. This is an effective immunotherapy for patients with melanoma. It is also the world's first mRNA vaccine for tumours (Sahin et al., 2020).

5 CONCLUSION AND DISCUSSION

In this paper, we reviewed the *in vivo* targeted delivery mechanisms, application evolution of NPs. NPs provide a novel drug delivery platform for tumour drugs and can improve the efficiency of tumour treatment and reduce the side effects of tumour treatment. However, the mechanisms by which NPs enter tumours are still unclear, and further studies are needed. In the future, the focus of research on NPs should shift from the design of their structures to targeting, so that more NP drugs can be applied in clinical practice.

In recent years, the rapid development of nanotechnology has made NPs not only a hotspot for tumour treatment but also a hotspot for vaccine preparation. The focus of future research on tumour vaccines should be on safety and efficacy in tumour treatment and prevention. In the preparation of tumour vaccines, common preparation issues include the insufficient delivery of antigens and the insufficient release of drugs, limiting the development of vaccines. NPs are safe, can be modified for the controlled release of cargo and for targeting, and have a high antigen uptake rate and strong immunogenicity. Therefore, they are ideal carriers for the preparation of tumour vaccines. Currently, the nanodrugs available on the market are mainly liposomes and polymer micelle preparations. Compared with other NPs, nanoliposomes have better biocompatibility and biodegradability. However, the application of nanoliposomes in vaccines is still at an early stage of development and has certain limitations. The development of noncationic nanoliposomes, the mechanism of nanoliposome delivery systems, and the safety of vaccines all require further in-depth studies. We believe that when these remaining problems are properly addressed, NPs will transition from the laboratory to clinical application, launching a new era in cancer treatment.

AUTHOR CONTRIBUTIONS

SL and ZS contributed to the conception of this review. YT, ZS, and SL analyzed literatures and wrote the manuscript. YT, ZY, and ST completed figures drawing. YT, WY, YW, SL, and ZS revised the manuscript. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work was financially supported by Zhejiang Provincial Natural Science Foundation of China under Grant No. LGF21H040001, Wenzhou City Public Welfare Science and Technology Project (ZY2019005), The Graduate Scientific Research Foundation of Wenzhou University.

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GLOSSARY

ALK anaplastic lymphoma kinase
ASGP-R Asi-aloglycoprotein receptor
BTK Bruton's tyrosine kinase
CA4 combretastatin A4
cGAMP Cyclic GMP-AMP
CTLA-4 cytotoxic T lymphocyte-associated antigen-4
DDA Dimethyldioctadecylammonium bromide
EGF Epidermal Growth Factor
EGFR growth factor receptor
EPR enhanced permeability and retention
EpCAM Epithelial cell adhesion molecule
FGF Fibroblast growth factors
FR folate receptor
GD2 Disialoganglioside
GPNMB glycoprotein non-metastatic melanoma protein B
HDAC histonedeacetylases
HIF hypoxia inducible factor
ICAM-1 intercellular cell adhesion molecule-1
LHRHR Luteinizing hormone releasing hormone receptor
LNPs lipid nanoparticles
MPLA 3-O-desacyl-4′-monophosphoryl lipid A
MEK Mitogen-activated extracellular signal-regulated kinase
MMPs matrix metalloproteinases
mTOR mammalian target of rapamycin
NPs nanoparticles
PARP poly ADP-ribose polymerase
PD-1 Programmed cell death protein 1
PDGFR platelet-derived growth factor receptor
PI-3K phosphatidylinositol 3-kinase
ROBO4 Roundabout homolog 4
ROS1 Reaciveoxygenspecies
SA sialic acid
SLN Solid Lipid Nanoparticle
TEM transmission electron microscopy
TME tumour microenvironment
TfR transferrin receptor
VIPR Vasoacitve intestinal peptide receptor
VEGF vascular endothelial growth factor