

Lipid-Based Nanocarrier Systems for Drug Delivery: Advances and Applications

Yan-Qi Zhao^{1,2} Li-Jun Li^{1,2} Er-Fen Zhou^{1,3} Jiang-Yue Wang^{1,4} Ying Wang^{1,2} Lin-Miao Guo^{1,2}
Xin-Xin Zhang^{1,2*}

¹ State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, People's Republic of China

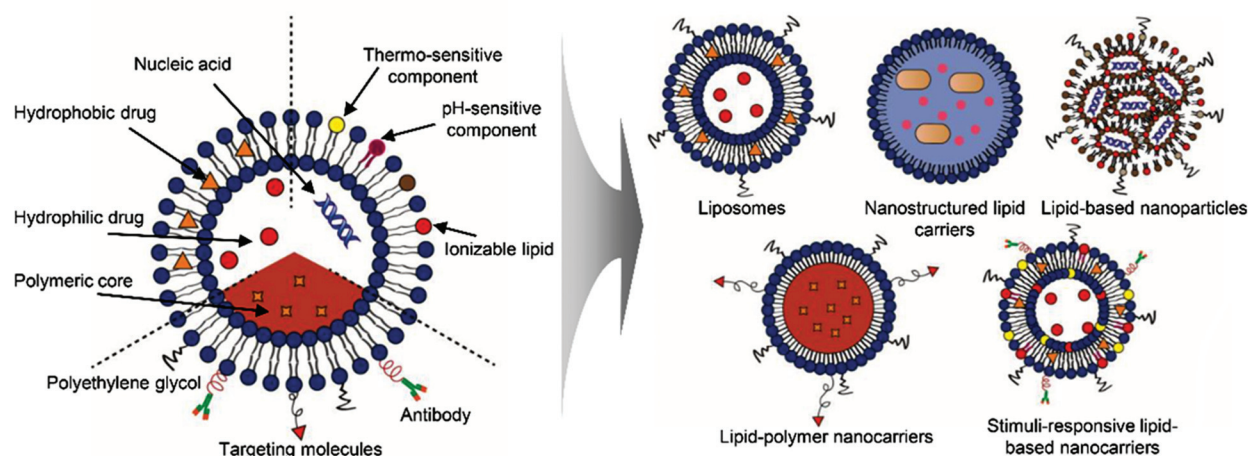
² University of Chinese Academy of Sciences, Beijing, People's Republic of China

³ School of Chinese Materia Medica, Nanjing University of Chinese Medicine, Nanjing, People's Republic of China

⁴ School of Pharmacy, East China University of Science and Technology, Shanghai, People's Republic of China

Address for correspondence Prof. Xin-Xin Zhang, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 501 Haik Road, Pudong Zhangjiang Hi Tech Park, Shanghai 201203, People's Republic of China (e-mail: xinxinzhang@simm.ac.cn).

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Abstract

Lipid-based nanocarriers have been extensively investigated for drug delivery due to their advantages including biodegradability, biocompatibility, nontoxicity, and non-immunogenicity. However, the shortcomings of traditional lipid-based nanocarriers such as insufficient targeting, capture by the reticuloendothelial system, and fast elimination limit the efficiency of drug delivery and therapeutic efficacy. Therefore, a series of multifunctional lipid-based nanocarriers have been developed to enhance the accumulation of drugs in the lesion site, aiming for improved diagnosis and treatment of various diseases. In this review, we summarized the advances and applications of lipid-based nanocarriers from traditional to novel functional lipid preparations, including liposomes, stimuli-responsive lipid-based nanocarriers, ionizable lipid nanoparticles, lipid hybrid nanocarriers, as well as biomembrane-camouflaged nanoparticles,

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and further discussed the challenges and prospects of this system. This exploration may give a complete idea viewing the lipid-based nanocarriers as a promising choice for drug delivery system, and fuel the advancement of pharmaceutical products by materials innovation and nanotechnology.

Introduction

The conventional “free” drugs in the clinical application always exhibit some common problems, such as poor solubility, unfavorable pharmacokinetics, suboptimal biodistribution, and lack of selectivity for target tissues.¹ A drug delivery system (DDS) possesses many advantages over free drug molecules, showing enhanced solubility and improved pharmacokinetics and therapeutic efficacy.¹ Due to the nano size and shape, a nanodrug delivery system could achieve theoretically superior drug delivery efficiency through specific tissue targeting and enhanced cell internalization and transportation to specific organelles.^{2–4} However, the toxicology of nanocarriers always reminds an important issue, especially for medical use.^{5,6} It has been reported that polymeric and metallic nanocarriers may be toxic to the lung, kidney, or central nervous system.⁷ Therefore, scientists have shown great interest in lipid-based nanocarriers with the advantages of being biodegradable, biocompatible, nontoxic, and nonimmunogenic. Lipid-based nanocarriers show great potential in augmenting bioavailability, improving pharmacokinetic profile, reducing toxicity, and achieving the desired concentration of the drug at otherwise inaccessible sites through various mechanisms.⁸

As the first liposome preparation, Doxil approved by Food and Drug Administration (FDA) in 1995 opened a new era of drug delivery using lipid-based nanocarriers. With in-depth research, lipid-based nanocarriers have achieved good results in drug delivery. The initial liposomes were only composed of phospholipids and some pharmaceutical excipients, which led to poor stability and accumulation both *in vivo* and *in vitro*. Researchers later found that some modifications on the surface of liposomes could provide steric hindrance and improve the stability of liposomes, and the most classic modification is PEGylation.⁹ Moreover, other shortcomings of liposomes have been found, including insufficient targeting, rapid elimination from the blood, and capture by the reticuloendothelial system.¹⁰ In recent years, a series of multifunctional lipid-based nanocarriers have been developed to improve the accumulation of drugs in the lesion site for the diagnosis and treatment of various diseases. The rational design of the modification on lipid-based nanocarriers was explored, including proteins, small molecular compounds, and even some synthetic polymer materials, to prolong the half-life of the nanocarriers *in vivo* and cross various pathological barriers for lesion-site targeting. With more in-depth understanding of diseases, drugs delivered by lipid-based nanocarriers are not only small molecular drugs, but also biomacromolecules such as antibodies, messenger RNA (mRNA), and small-interfering RNA

(siRNA). At the same time, a large number of experiments are performed to verify and optimize the lipid-based nanocarriers to meet various requirements of drug delivery.^{11–14}

Lipid-based nanocarriers demonstrate advantages including improved bioavailability, enhanced tumor targeting, and reduced toxicity, showing great potential in clinical translation. In this review, we briefly summarized the characteristics and applications of some traditional lipid preparations, and emphatically introduced the advanced lipid-based nanocarriers. In addition, we further discuss prospects and challenges of the lipid-based nanocarriers.

Traditional Lipid-Based Nanocarriers

Liposomes

Since liposomes were first discovered by Bangham in the early 1960s,¹⁵ and they have been widely studied and applied in drug delivery due to their unique lipid bilayer structure and characteristics (►Fig. 1). Up to now, many liposome preparations have been approved for treatment of bacterial and fungal infections, cancer, and other diseases (►Table 1).

Doxil was the first liposome preparation approved for drug delivery in 1995. The formulation of Doxil contains hydrogenated soybean phospholipids (HSPC), cholesterol (Chol), and distearoyl phosphatidylethanolamine-*N*-[amino (polyethylene glycol)-2000] (DSPE-mPEG2000). Doxorubicin is one of the main “first-line” anticancer drugs and is effective against most types of cancers (including leukemias, lymphomas, and breast, uterine, ovarian, and lung cancers).¹⁶ It is well known that conventional doxorubicin injection has serious cardiotoxicity, which is the main problem limiting its clinical application. Since Doxil adopts PEGylated lipids, it has high stability, prolongs the *in vivo* circulation time, and reduces the toxic and side effects of doxorubicin.¹⁷ In an early study, patients with refractory AIDS-KS administered with Doxil showed partial response rates between 27 and 48% and stable response rates between 26 and 29% as indicated by investigator assessment and indicator lesion assessment.¹⁷ DepoCyt, approved in 1999, is a sterile antimetabolite cytarabine liposome for the treatment of fatal lymphomatous meningitis. Compared with cytarabine, DepoCyt can gradually release the drug into cerebrospinal fluid with a longer half-life and more uniform drug distribution.¹⁸ Another liposome preparation approved by FDA in 2015 was Onivyde, which is an irinotecan liposome injection composed of irinotecan, distearoyl phosphatidylcholine, Chol, DSPE-mPEG2000, and other accessories.¹⁹ Compared with traditional irinotecan, Onivyde has significant advantages, including high drug loading efficacy and extended circulation time. In combination with 5-fluorouracil and

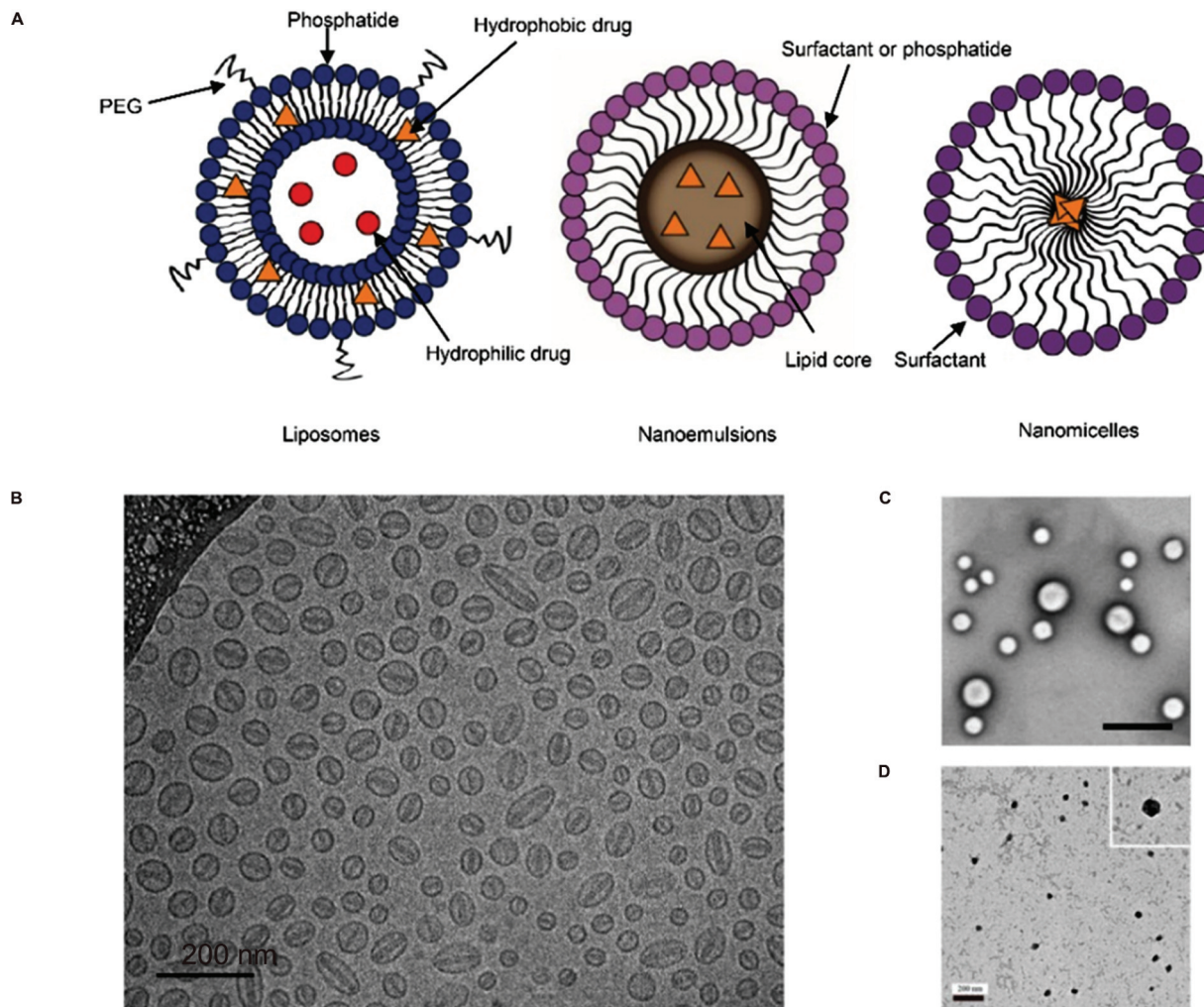


Fig. 1 (A) Structures of liposomes, nanoemulsion, and nanomicelles. (B) Transmission electron microscopy (TEM) images of Doxil. (C) TEM images of nanoemulsions. (D) TEM images of nanomicelles. (Adapted with permission from Zhang et al 2020¹⁷⁹ and Zhu et al 2019¹⁸⁰.)

leucovorin (5-FU/LV), Onivyde is the first agent to be specifically approved for use in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who have progressed following gemcitabine-based therapy.²⁰ In the pivotal phase III NAPOLI-1 trial, intravenous administration of Onivyde + 5-FU/LV to patients with mPDAC was associated with a signifi-

cant approximate to 2-month median overall survival advantage compared with 5-FU/LV alone.^{20,21} It is also worth mentioning that Exparel, bupivacaine hydrochloride multivesicular liposomes, was approved by FDA in 2011 with multivesicular liposome (DepoFoam) technology.²² The amide local anesthetic bupivacaine hydrochloride is often used

Table 1 Partially approved liposome products on the market and indication

Year approved	Active pharmaceutical ingredient	Trade name	Indication
1995	Doxorubicin	Doxil	Kaposi's sarcoma, ovarian and breast cancers ¹⁵¹
1996	Daunorubicin	DaunoXome	Cancers and Kaposi's sarcoma ¹⁵²
1997	Amphotericin B	AmBisome	Aspergillosis ¹⁵³
1999	Cytarabine	DepoCyt	Lymphomatous meningitis ¹⁵⁴
2001	BPD-MA	Visudyne	Choroidal neovascularization ¹⁵⁵
2012	Vincristine	Marqibo	Acute lymphoblastic leukemia ¹⁵⁶
2015	Irinotecan	Onivyde	Metastatic pancreatic cancer ¹⁵⁷
2017	Daunorubicin and cytarabine	Vyxeos	Acute myeloid leukemia ¹⁵⁸

Abbreviation: BPD-MA, benzoporphyrin derivative mono-acid ring A.

for postoperative analgesia in clinical practice, and the action time of ordinary injection is only 5 to 7 hours, but postoperative pain usually lasts 48 to 72 hours, which is often difficult to meet the clinical needs.²³ Exparel used diethylpyrocabonate (DEPC), dipalmitoyl phosphatidylglycerol (DPPG), Chol, and trioctyl glyceride to wrap the drug in a honeycomb shape. Bupivacaine is gradually released as each vesicle bursts, wherein the low phase transition temperature of DEPC (~13°C) can make the drug release easier and take effect more rapidly.²⁴ Exparel can achieve sustained analgesic effect up to 72 hours and effectively control the use of opioids, which has significant clinical advantages.²⁵

Although traditional liposomes have made some achievements as drug delivery carriers, some new issues have emerged as the focus of research. Since the body is a complex physiological environment, liposomes will be absorbed by a large number of proteins or other substances in a short time to form a protein corona. Protein corona can change the physicochemical properties of liposomes, thereby affecting the fate of liposomes *in vivo*.²⁶ More in-depth experimental and clinical data showed that patients will produce PEG-directed immunoglobulin after the first treatment with PEGylated liposomes. After repeated administration, PEGylated liposomes will show accelerated clearance from systemic circulation, the so-called accelerated blood clearance (ABC) effect.²⁷ The ABC effect will greatly reduce the repeated treatment effect of liposomes, thus avoiding the ABC effect as an urgent problem to be solved for PEGylated liposomes.

In general, the current clinical application of several typical marketed liposome formulations has shown certain efficacy, and the mechanism of liposome action *in vivo* has also been studied widely. At present, the main deficiencies of traditional liposomes have been overcome with a variety of means, which is illustrated in detail below.

Lipid-Based Nanoemulsions

Nanoemulsions are emulsions with size ranging from 50 to 500 nm. In general, there are three kinds of nanoemulsion structures: oil-in-water nanoemulsion (O/W), water-in-oil nanoemulsion (W/O), and double continuous nanoemulsion, wherein the O/W type is the majority of them (–Fig. 1).^{28,29} The addition of lipid emulsifiers such as soybean phospholipids, egg yolk lecithin, DPPG, or 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) is critical for the formation of small-sized droplets as it decreases the interfacial tension between the oil and water phases of the emulsion. At the same time, they also play significant roles in stabilizing emulsions through repulsive electrostatic interactions and steric hindrance.³⁰

Lipid-based nanoemulsions have aroused great interest for drug delivery due to their nanometric size, thermodynamic stability, high drug loading capacity, biocompatibility, and their effect for greatly increasing the solubility of insoluble drugs.^{31,32} For example, Diprivan, a propofol nanoemulsion, using soybean oil for injection as an oil phase

and egg phospholipids as emulsifiers, was developed to improve the water solubility of propofol. Compared with ordinary injection, Diprivan can significantly increase the bioavailability of propofol, and has become a commonly used intravenous anesthetic since it came on the market in 1986.^{33–35} CINVANTI (HTX-019) is a novel injectable nanoemulsion formulation of the NK-1RA aprepitant approved by FDA in 2017.³⁶ The compendial excipients used in the CINVANTI intravenous formulation (egg lecithin, ethanol, sodium oleate, soybean oil, and sucrose) allow insoluble aprepitant to be incorporated into an emulsion without synthetic surfactants, and thus avoid associated toxicities.³⁷ CINVANTI is approved for administration as a 30-minute intravenous infusion and 2-minute intravenous push in combination with other agents to prevent chemotherapy-induced nausea and vomiting.^{37,38}

Lipid-Based Nanomicelles

Lipid-based nanomicelles are colloidal dispersions that self-assemble from amphiphilic phospholipid molecules, generally less than 100 nm in diameter, with numerous advantages including improved solubility for insoluble drugs and increased targeting to tumor areas.³⁹ As shown in –Fig. 1, nanomicelles can carry lipophilic drugs in the internal hydrophobic core, and when they are in nonpolar solvents, micelles are oriented in opposite ways to form hydrophilic cores, which can be used to encapsulate macromolecules such as hydrophilic drugs and proteins. This lipid nanocarrier system has not been explored to date, but it could serve as a potential therapeutic diagnostic nanomedicine for cancer treatment.

In recent research studies, a docetaxel-loaded nanomicelle was designed and characterized by Ma and coworkers to treat xenograft breast cancer.⁴⁰ Solutol HS 15 (polyglycol mono- and di-esters of 12-hydroxystearic acid and ~30% free polyethylene glycol) and soybean phospholipid S100 were the main components of the nanomicelles.⁴¹ *In vivo* results suggested that this lipid-based nanomicelle system was effective in inhibiting tumor growth, with little toxicity. In addition, Bahadori et al described a new lipid-based formulation of vinorelbine (VLB) using PEGylated phospholipid micelles, which can overcome the loading and stability problems of stealth liposomal formulation of VLB.⁴² Their results indicated that the VLB nanomicelles showed ~6.7-fold higher antitumor activity against MCF-7 breast cancer cells, compared with free drugs.⁴³ Furthermore, they reported enhanced aqueous solubility and therapeutic efficacy of several anticancer drugs when incorporated in phospholipid micelles.^{43–45} Collectively, lipid-based nanomicelles show great potential in drug delivery and are worth exploring in the near future.

Stimuli-Responsive Lipid-Based Nanocarriers

Although traditional liposomes have been widely used in DDSs due to their advantages of low toxicity and good

biocompatibility, there are still some problems such as unexpected drug release and low targeting. To optimize the traditional liposomes, scientists have developed stimuli-responsive liposomes which can maintain structural stability in the circulation system and normal tissues, but change under the stimulation of specific environmental conditions (pH changes, enzyme transformations, redox reactions, and temperature responsiveness, etc.) to release the encapsulated drugs or genes and target the specific site (►Fig. 2).

As we know, some pathological sites have different pH profiles from that of normal tissues (e.g., tumors are often more acidic than healthy tissue, with extracellular pH values averaging 6.8–7.0, but some as low as 5.7⁴⁶). Therefore, scientists introduced pH-sensitive peptides or pH-sensitive polymers into the traditional liposomes; these modifications lead to conformation change in an acidic environment to release therapeutic agents, so as to improve the therapeutic effect.^{47,48} The pH-responsive lipid-based nanocarrier DDS falls into two categories based on the changes in the pH gradient outside and within the cells: one is the polymer's variations in conformation or dissolution behavior under the extracellular pH microenvironment,^{47–50} and the other possibility is that the delivery system will dissolve under the intracellular endosomal pH environment due to the breakage of groups that are acid stimuli in the nanocarriers.^{51–54} A classic example is the combination of phosphatidylethanolamine (PE) or its derivatives with compounds containing an acidic group (e.g., carboxylic group) that acts as a stabilizer at neutral pH. Soares et al utilized the polymorphic phase behavior of the natural phospholipid 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) that adopts a bilayer

structure (L α phase) at neutral pH and an inverted hexagonal phase II at low pH, inducing membrane destabilization and the release of contents.⁵⁵

Furthermore, there are many esterases or proteases such as matrix metalloproteinases (MMPs) and phospholipase A2 (PLA2) in a tumor microenvironment, which play important roles in tumor growth, invasion and metastasis, and their concentration and activity are much higher than those in a normal tissue.⁵⁶ Thus, enzyme-responsive carrier systems most often rely on the cleavage of esters or amides in short peptide sequences of liposomes by these enzymes to release the therapeutic agent selectively.^{57,58} Chen et al proposed a MMP2-responsive integrated immunochemotherapeutic strategy to deliver paclitaxel (PTX) and anti-CD47 (aCD47) by detachable immune liposomes (ILips).⁵⁹ This enzyme-responsive carrier system represented a promising approach to synchronously enhance immune response and tumor-killing effects, improving the therapeutic efficacy against triple-negative breast cancer. Lee et al synthesized PEG-Gly-Leu-Phe-Gly (GLFG) using DSPE-PEG (5000) amine, DPPC, and (2,3-dioleoyloxy-propyl)-trimethylammonium-chloride (DOTAP) as lipid materials after PEG modification.⁶⁰ Adriamycin-loaded GLFG liposomes were further prepared. These liposomes are degraded by cathepsin B enzyme, which is overexpressed in several cancer cell types and exhibits an effective anticancer effect on HepG2 cells *in vitro* and inhibits cancer cell proliferation in a zebrafish model. Ji et al developed a β -cyclodextrin (β -CD)-modified MMP-2-responsive liposome, which can be cleaved in MMP-2-overexpressed tumor cells.⁶¹ The liposomes based on the lipid materials DSPE-PEG (3400)-RGD and DSPE-PEG (3400)-pep-CD are combined with chemotherapy drugs to regulate pancreatic

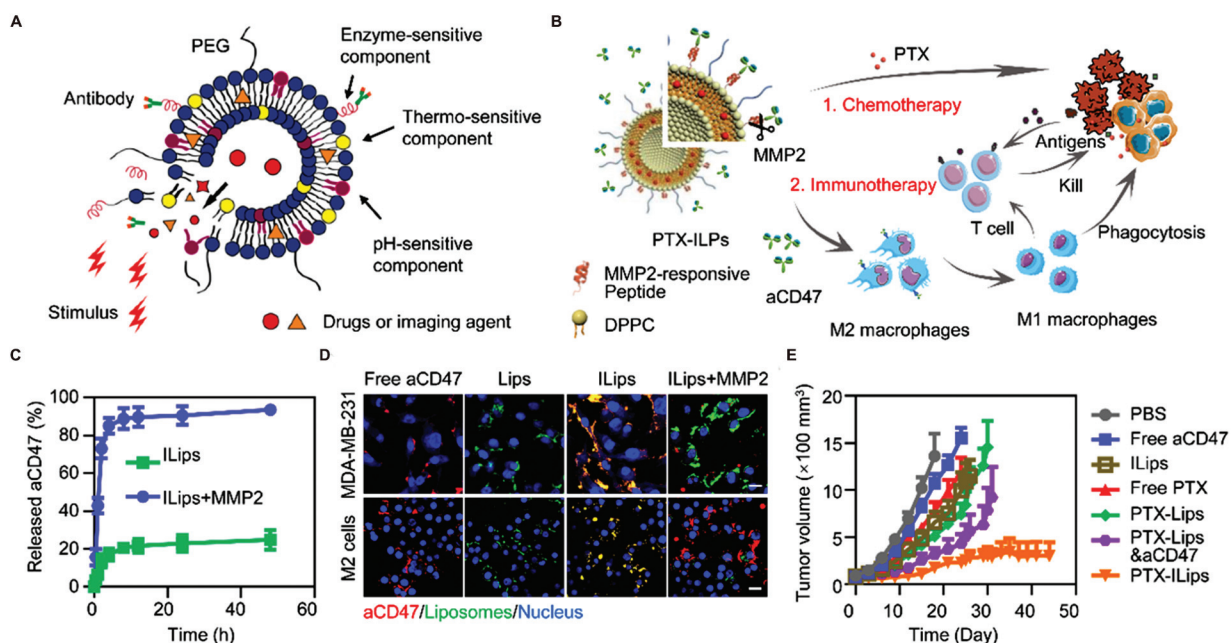


Fig. 2 Potential of stimuli-responsive smart nanocarriers. (A) Structure diagram of stimuli-responsive lipid-based nanocarriers. (B) MMP2-responsive liposomes designed for the enhanced therapeutic efficacy against triple-negative breast cancer. (C) Release of anti-CD47 (aCD47) from ILips with or without MMP2 incubation. (D) Cellular uptake of free aCD47, Lips, and ILips in MDA-MB-231 cells and M2 macrophages. (E) Tumor growth profiles in mice treated with MMP2-responsive liposomes. (Adapted with permission from Chen et al 2021⁵⁹.)

stellate cells, and achieve targeted delivery of antitumor drugs for pancreatic cancer therapy.

In addition, redox-sensitive smart nanocarriers were designed based on the high expression of oxidoreductase (such as glutathione-peroxidase) in cancer cells. The level of glutathione (GSH) in tumor sites is 100 to 1,000 times higher than that in normal tissue interstitium.^{62,63} Redox-sensitive chemical bonds are broken in response to the stimulation of high GSH concentration, resulting in carrier degradation and drug release. At present, disulfide bond as the most widely used chemical bond among redox sensitive carriers⁶⁴ is often used to connect polymer materials to lipids, which can be broken in the tumor site. Fu et al developed PTX-loaded liposomes functionalized with TAT (the most frequently used cell-penetrating peptides) and PEG based on the soybean phosphatidylcholine (SPC) and DSPE-PEG.⁶⁵ Under physiological conditions, TAT was shielded by the PEG layer and liposomes exhibited a long blood circulation.⁶⁵ At tumor sites, PEG could be detached in the presence of the exogenous reducing agent (GSH) and TAT was exposed to facilitate cell internalization.⁶⁵ PTX-C-TAT-LP with GSH strongly inhibited the proliferation of murine melanoma B16F1 tumor cells and showed a high tumor inhibition rate (69.4%) in B16F1 tumor-bearing mice.⁶⁵

Ionizable Lipid Nanoparticles

In recent years, nucleic acid-based gene therapy has been widely concerned and applied in the treatment of cancer, genetic diseases, and other diseases.⁶⁶ Ionizable lipid nano-

particles (LNPs) are the most clinically advanced nano-delivery system to maintain the stability of therapeutic nucleic acids,⁶⁷ and achieve effective delivery into cells for gene regulation.⁶⁸ LNPs, in the modern definition, are nano-sized lipid systems made of two or more (generally four) lipids at varying ratios.⁶⁹ Common lipid types are ionizable lipids, phospholipids, cholesterol, and PEGylated lipids.⁷⁰ LNP is positively charged at acidic pH, where it binds well with negatively charged nucleic acids. It is neutral in blood (physiological pH environment) and can reduce the toxic effects of cationic lipids. LNP can be internalized by cells through endocytosis, and then release the drugs into the cytoplasm through endosomal escape, which plays an important role in the intracellular function of mRNA, not only protecting mRNA from degradation, but also allowing nucleic acid to enter cells (► Fig. 3).^{67,70,71}

Onpattro is the first approved siRNA drug in the world and the first gene therapy drug based on the LNP administration system for the treatment of peripheral multiple nerve diseases.⁷² It is worth mentioning that Onpattro is prepared by a new ionizable cationic lipid material (6Z,9Z,28Z,31Z)-heptatriacont-6,9,28,31-tetraene-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA), referred to as MC3. MC3 has a unique pH-dependent charge variability, which is positively charged under acidic conditions, while neutral under physiological pH conditions. LNP containing considerable siRNA can be prepared because positively charged MC3 and negatively charged nucleic acid are attracted under acidic conditions. Under physiological conditions, neutral LNP can avoid the toxicity and side effects caused by cationic

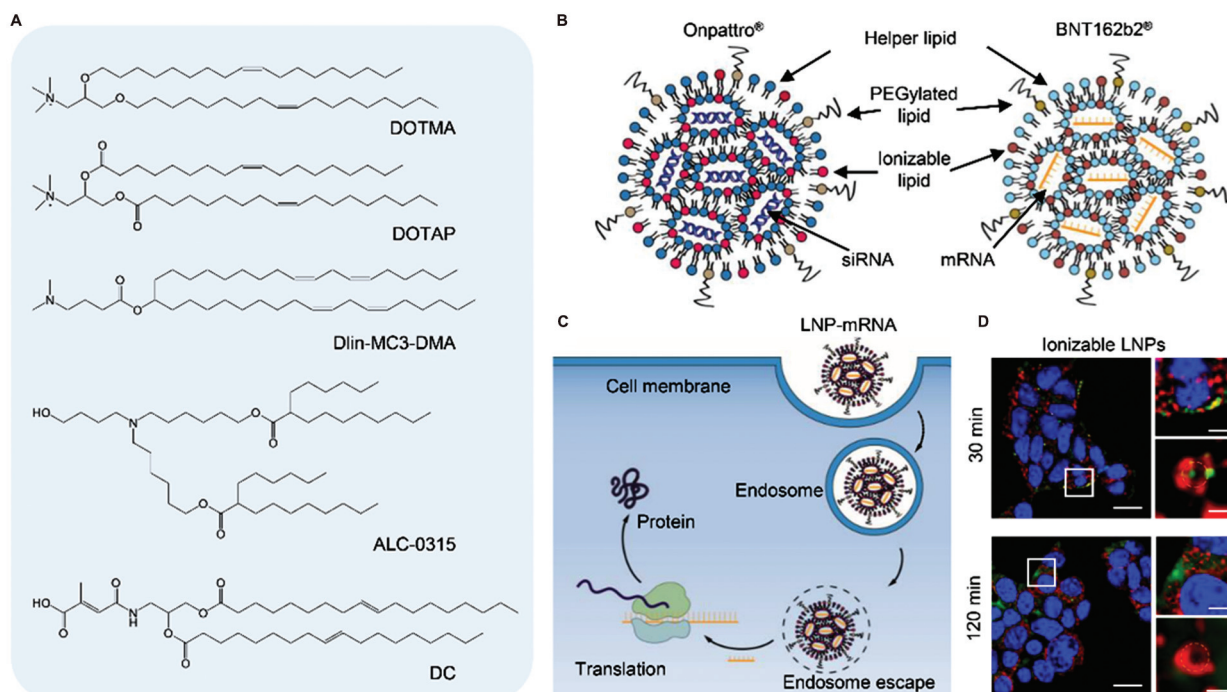


Fig. 3 (A) Chemical structure of ionizable lipid materials for nucleic acid delivery. (B) Structure diagram of Onpattro and BNT162b2 LNP, two approved nucleic acid drugs. (C) Intracellular mechanism of LNP loaded with mRNA. (D) Confocal images of HepG2 cells transfected with siRNA-loaded DC-based LNPs, showing the endosome (red) escape of siRNA (green). (Adapted with permission from He et al 2018⁸⁰.) LNP, lipid-based nanoparticle; siRNA, small-interfering RNA.

lipids.⁷³ Delivery of RNAs to target cells by clinically translational LNPs provides vast opportunities to tackle a series of life-threatening diseases including the novel coronavirus disease 2019 (COVID-19).⁷⁴ In 2020, two mRNA vaccines, BNT162b2 and mRNA-1273, received emergency authorization for use from the FDA and European Medicines Agency as the vaccines for the prevention of COVID-19. BNT162b2 is a LNP-formulated nucleoside-modified mRNA vaccine.⁷⁵ ((4-Hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyl-decanoate) (ALC-0315), an ionizable lipid, is the key component of BNT162b2 and shows better delivery efficacy and pharmacokinetics than MC3.¹²

The global mRNA research and development is gradually rising, and various biological drug companies have invested a lot of research and development efforts in LNP technology. A large number of LNP-based mRNA vaccines are currently under development for influenza, human immunodeficiency virus, Zika, variants of COVID-19, and other infectious diseases. LUNAR-COV19 (ARCT-021), a novel coronavirus vaccine, is in clinical trials. Based on their experience in fighting bone fever and yellow fever, the research team used an mRNA vaccine that mimics the coronavirus and can reproduce itself.⁷⁶ Moderna Inc.'s mRNA-1345 Respiratory Syncytial Virus (RSV) vaccine is another vaccine in the clinical trial stage. This mRNA vaccine uses the same LNP as the Moderna COVID-19 mRNA vaccine and contains optimized protein and codon sequences.⁷⁷

At present, research studies are focusing on designing LNP with both the ability of targeting and endosomal escape.⁷⁸ For example, Dhaliwal et al constructed mRNA-loaded cationic LNP using DPPC, DOTAP, and Chol, with an mRNA encapsulation efficiency of 80%. The mRNA was enriched in the brain by nasal administration.⁷⁹ He et al synthesized an ionizable lipid named DC and developed DC-based LNPs, termed DCLC nano-transformers. DC-based LNPs were negatively charged in physiological pH (pH = 7.4) and nearly neutral in endosome. Upon protonation at acidic pH, the positive surface charge of DC LNPs induces endosomal membrane fusion, thus facilitating the release of siRNA into the cytoplasm. DC LNPs delivered cyclin-dependent kinase 1 (CDK1)-siRNA efficiently, leading to up to 95% reduction of CDK1 mRNA in HepG2 cells *in vitro*, and significantly suppressed the HepG2 tumor growth in nude mice.⁸⁰ In addition, Rosenblum et al developed a safe and efficient LNP for the delivery of Cas9 mRNA and single-guide RNA, using an ionizable lipid from a novel ionizable amino lipid library which is based on hydrazine, hydroxyl-amine, and ethanolamine linkers with a linoleic fatty acid chain and amine head groups. The prepared LNP can specifically deliver CRISPR components to bone marrow, thereby enhancing gene editing of hematopoietic stem cells and bone marrow cells. This is important for the development of therapies for inherited blood disorders such as sickle cell anemia.⁸¹

RNA therapy has made remarkable progress in recent years, thanks to the development of LNPs, especially their key component, ionizable lipids. At present, many studies have used ionizable lipids with different structures to improve the physicochemical properties or nucleic acid delivery efficien-

cy of LNP, such as ionized polymer lipids and ionized biodegradable lipids.⁷⁴ For example, Dahlman et al found that C15 epoxy-modified low-molecular-weight polyethylene imine (7C1) could achieve the most efficient nonliver siRNA delivery.⁸² Similarly, Lin et al found that G0-C14 confers high accumulation of ionizable polymer lipids effective for transfection of various RNA therapeutics in tumors.⁸³ The biodegradable MC3 replacement (L319) is produced by replacing a double bond at each tail with a primary ester because of the slower degradation rate of the dioleoyl tail in MC3. L319 not only maintained its efficacy *in vivo*, but also showed rapid elimination and improved tolerability.⁸⁴

Although LNPs for nucleic acid vaccines and therapies have shown great prospects in the prevention and treatment of diseases, several challenges need to be addressed to reach the full potential of RNA therapeutics. A key challenge is that current intravenous administration of LNP may cause reactions associated with infusion.⁸⁵ In this regard, the optimization of linker chemistry and inclusion of anti-inflammatory properties deserve further study. On the other hand, the large-scale production of LNPs cannot be ignored that the number of companies producing functional lipids and LNP remains limited. Simplified synthesis and accelerated ionized lipid screening using combinatorial chemistry may alleviate this problem.⁸⁶ The future direction of LNP research and development is to expand the application range of drug and gene delivery, optimize the effective delivery of vectors to target cells, and reduce ineffective delivery to nontarget cells. It is believed that continuous structural modification and screening will enable LNPs to have greater development prospects.

Lipid-Polymer Nanocarriers

Liposomes have been widely used in DDSs due to the low toxicity and good biocompatibility; however, their application is restricted by susceptibility to uncontrollable drug release, instability, insufficient drug loading, and so on.⁸⁷⁻⁸⁹ Polymer-based nanosystems are stable inside the cells, and show controlled drug release behavior.⁹⁰⁻⁹³ Therefore, to overcome the limitations of liposomes, researchers designed lipid-polymer hybrid nanocarriers, which consist of a hydrophobic polymeric core, a lipid shell surrounding the polymeric core, and a hydrophilic polymer layer outside the lipid shell (► Fig. 4). In general, the most commonly used lipids are zwitterionic, cationic, anionic, and neutral phospholipids such as lecithin, DPPC, 1,2-dipalmitoyl-3-trimethylammonium-propane (DPTAP), DOTAP, or DOPE. The interaction between the static electricity carried by the lipid and the polymer with opposite charge was utilized to promote cellular uptake and improve the stability of nanocarriers.⁹⁴ This core-shell structure combines the advantages of both liposomes and polymer nanoparticles, including high biocompatibility and stability, improved drug payload, controlled drug release, longer circulation time, and superior *in vivo* efficacy.

In a recent study, Yang et al prepared a novel folic acid receptor-targeted lipid-polymer hybrid nanoparticle,⁹⁵ in

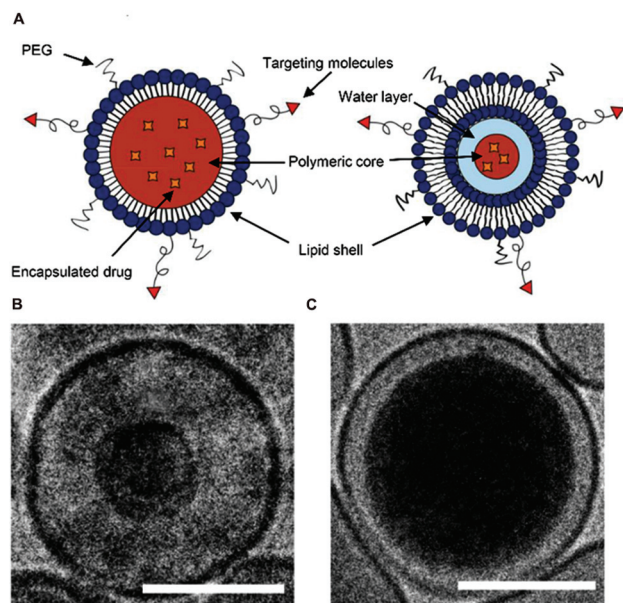


Fig. 4 (A) Lipid-polymer nanocarrier composition. It is formed from a polymer core shelled with lipids and covered with an outer layer of PEG with or without targeting molecules. (B) Cryo-TEM images of PLGA₁₆₀-Lip-F127_{5%}NP. (C) Cryo-TEM images of PLGA₁₆₀-Lip-F127_{5%}NP. (Adapted with permission from Yu et al 2018¹⁸¹.)

which two drugs (doxorubicin and edelfosine) were stably loaded into the hydrophobic poly (lactic-co-glycolic acid) cores and the lipid shell was made of lecithin and DSPE-PEG as lipid materials. The protective lipid layer can effectively reduce the release of the encapsulated drugs in the body circulation, thus reducing the side effects to normal cells. PEG on the lipid shell can improve the stability of particles and prolong their systemic circulation. The lipid-polymer hybrid nanocarriers with multiple properties of high drug loading, sequential drug release, improved physiological stability, prolonged blood circulation, and tumor-specific targeting are promising for the delivery of multiple drugs in the treatment of osteosarcoma. In another research, Li and associates developed a phospholipid polymer hybrid anti-HER2 nanoparticle (SALI-NP-HER2) loaded with salinomycin to target HER2-positive breast cancer cells.⁹⁶ SALI-NP-HER2 inhibited the breast tumor growth more effectively than nontargeted nanoparticles or salinomycin alone. These research studies encourage further exploration of lipidic nanocarriers to be envisaged for beneficial prospects in the field of cancer treatment.

Biomembrane-Camouflaged Nanocarriers

A novel biomimetic platform of nanocarriers fabricated by various membranes derived from innate cells (such as tumor cells, erythrocytes, immunocytes) has drawn enormous attention. Cell-membrane-camouflaged nanocarriers formed by fusion of biological membrane and nanomaterials retain both intricate biological functions of cell membranes and favorable physicochemical characteristics of nanoparticles.⁹⁷ These innate cell membranes composed of phospho-

lipid, protein, and cholesterol endow nanocarriers with delivery capability to specific lesions, escaping from protein adsorption and phagocytosis of a reticuloendothelial system to realize prolonged circulation *in vivo* (►Fig. 5).^{97,98}

In recent years, Zhang et al successfully prepared neutrophil membrane-coated nanoparticles that inherit the antigenic exterior and associated membrane functions of the source cells and they show significant therapeutic efficacy by ameliorating joint damage and suppressing overall arthritis severity.⁹⁹ Pitchaimani et al fabricated liposomes infused with natural killer (NK) cell membranes for targeted tumor therapy.¹⁰⁰ The results suggested that the biomimetic liposomes that kept NK cell membrane-associated targeting protein on their surface exhibited a higher affinity toward cancer than normal cells and enhanced tumor homing efficiency *in vivo* with an extended plasma residence time of 18 hours. Zhou and associates¹⁰¹ fused tumor-derived extracellular vesicle (TDEV) membranes and phospholipids to fabricate TDEV hybrid lipid nanovesicles (LEVs). The TDEV membrane endows LEVs with “homing” targeting ability and facilitates specific internalization into parent hepatocellular carcinoma (HCC) cells primarily through a heparan sulfate proteoglycan-mediated pathway. LEVs can escape from endosomal degradation and promote the delivery of siRNA through the Golgi and endoplasmic reticulum to achieve highly efficient transfection of siRNA. The reported LEVs enhanced the antitumor efficacy in HCC-bearing mice through effective gene silencing of CDK1. In addition, Miao et al constructed elastic poly-(ethylene glycol)-diacrylate hydrogel nanoparticles coated with red blood cells membrane (RBC-ENPs) which retain the special physiological properties of RBCs. RBC-ENPs not only exhibit reduced opsonization in macrophages and ultralong circulation, but also deform like RBC and achieve excellent diffusion in tumor extracellular matrix, leading to improved multicellular spheroid penetration and tumor tissue accumulation. *In vivo* results showed that doxorubicin-loaded RBC-ENPs exhibited superior antitumor efficacy to the first-line chemotherapeutic drug PEGylated doxorubicin liposomes.¹⁰² These biomembrane-camouflaged nanocarriers exhibit superior efficacy and high safety for disease treatment, which stands for a promising direction of nanocarriers.

Solid Lipid Nanoparticle and Nanostructured Lipid Carriers

As an alternative carrier system to traditional colloidal carriers, solid lipid nanoparticle (SLN) whose particle matrix consisted of a solid lipid was first introduced by Müller et al in 1991.^{103,104} However, due to the use of solid lipids, such as stearic acid and other long-chain saturated fatty acids, SLN drug loading is unsatisfactory. The second generation of LNPs, nanostructured lipid carriers (NLCs), was soon developed to overcome some potential limitations or disadvantages of SLN while maintaining the numerous advantages of the system (►Fig. 6).^{103,105} In this kind of nanoparticles, the matrix is composed of a blend of a solid and a liquid lipid instead of only one solid lipid.^{103,106} The lipid materials used

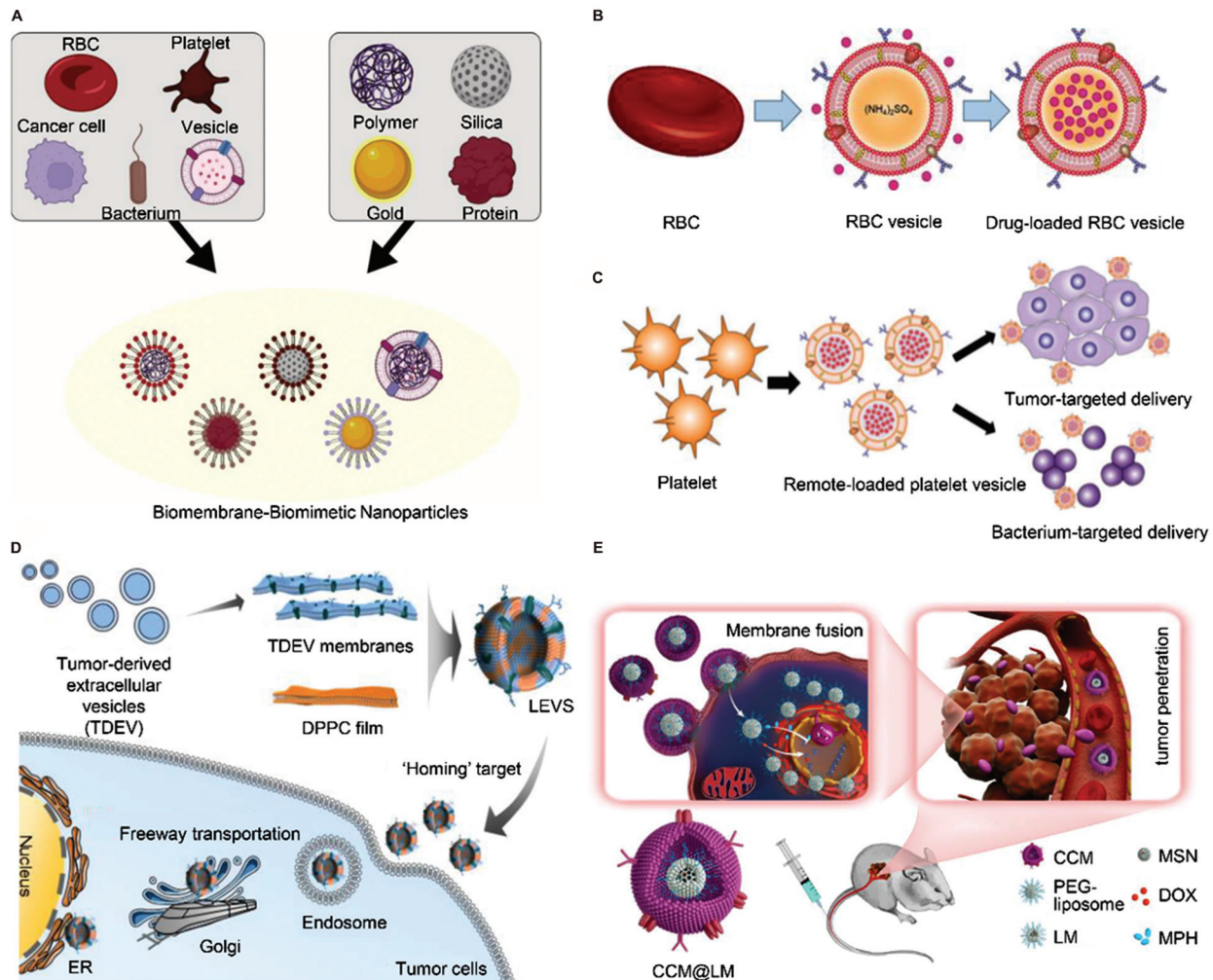


Fig. 5 (A) Composition of biomembrane-camouflaged nanoparticles. (B) Schematic diagram of red blood cell (RBC) membrane-derived nanovesicles. (C) Remote-loaded platelet vesicles for targeted drug delivery. (D) Tumor-derived extracellular vesicles with advantage of "homing" target for tumor delivery. (E) CCM@LM with cancer cell membrane coating showed efficient drug delivery by membrane fusion. (Adapted with permission from Zhang et al 2017,¹⁸² Ying et al 2018,¹⁸³ Zhou et al 2022,¹⁰¹ and Nie et al 2019¹⁸⁴.)

for SLN and NLC production usually resemble the physiologic lipids.¹⁰⁷ Examples include natural and synthetic triglycerides, monoglycerides, diglycerides, natural and synthetic waxes, and fatty alcohols including their esters and lipid peptides. In particular, synthetic mono-, di-, and triglycerides are suitable to be used as both individual substances and mixtures.¹⁰⁸ The characterization of the degree of lipid crystallinity and the modification of the lipid are strongly correlated with drug incorporation and release rates.¹⁰⁵ Different lipid compositions also have an influence on the size of SLN and NLC particles, which may further affect drug release rate, biodistribution, and cellular uptake of the nanoparticles.¹⁰⁹ The lipid matrix endows NLC a particular nature which can vary from an imperfect crystallization to an amorphous structure.¹¹⁰ Therefore, NLC has higher drug incorporation capacity and stability during storage because of the special nanostructure compared with SLN.^{103,104,110}

In recent years, due to the biodegradable and biocompatible characteristics,¹¹¹ SLN and NLC have shown potential success for several administration routes in medicine, such as for oral,^{112–115} dermal,^{116–118} parenteral,¹¹⁹ ocular,^{120,121}

pulmonary,¹²² and brain targeting.^{7,123–126} SLN and NLC applied to the skin can improve stability, drug targeting and penetration, and increase skin hydration compared with other drug nanocarriers. Therefore, they are considered as promising DDSs in treating skin disorders.¹²⁷ Mahmoud et al developed a promising DDS of oxiconazole nitrate-loaded SLN topical gel to enhance the drug effectiveness for the treatment of tinea infection.¹²⁸ They used stearic acid to construct oxiconazole nitrate-loaded SLN. The results revealed that the prepared oxiconazole nitrate SLN had drug entrapment efficiency ranging from 41.34 to 75.07% and revealed a decrease of the drug crystallinity in the prepared SLNs. Clinical study for the prepared oxiconazole nitrate SLN gel showed better patient satisfaction and clinical improvement compared with the corresponding approved product.¹²⁸ For the advantages of compatibility with ocular tissues and adhesive properties related to nanometric size, SLN and NLC have shown potential as innovative carriers for lipophilic drug substances to overcome hurdles in treating the eye posterior segment.¹²⁰ Balguri and his group used Compritol 888 ATO to fabricate indomethacin (IN)-loaded

SLN and NLC to investigate their potential use in topical ocular delivery.¹²⁹ The NLC maintained significantly higher IN concentrations in all ocular tissues tested compared with the other formulations evaluated *in vivo*. The results suggest that the modified SLN and NLC can serve as viable vehicles for ocular delivery.¹²⁹

However, it is important to note that the approved formulations are mainly cosmetic, not pharmaceutical products.¹³⁰ Even though the number of research groups working with SLN and NLC and the number of publications in the drug delivery field have distinctly increased, few SLNs and NLCs have reached clinical trials. Some challenges such as large-scale manufacturing processes, sterilization, tailoring strategies, stability, and regulatory issues need to be overcome before SLN or NLC may become commercially available products with approved therapeutic indications.^{131,132}

Lipid-Inorganic Nanocarriers

Inorganic nanocarriers have been developed rapidly in the field of biomedicine including cancer imaging and therapy,¹³³ biomolecular sensing,¹³⁴ and gene delivery.¹³⁵ The structure of inorganic nanocarriers is always composed of two regions: a core containing the inorganic component and a shell region that provides a suitable substrate for the conjugation of biomacromolecules or protects the core region from unwanted physicochemical interactions in the biological microenvironment (→ Fig. 7).¹³⁶

As we all know, the lipid structure can be used as delivery vehicles for a wide range of drugs and genetic materials because of their biocompatibility, safety, high drug loading, and capability to simultaneously carry imaging agents and ligands as well.^{137,138} To combine the advantages of both classes of nanocarriers, a paramount focus has been shifted

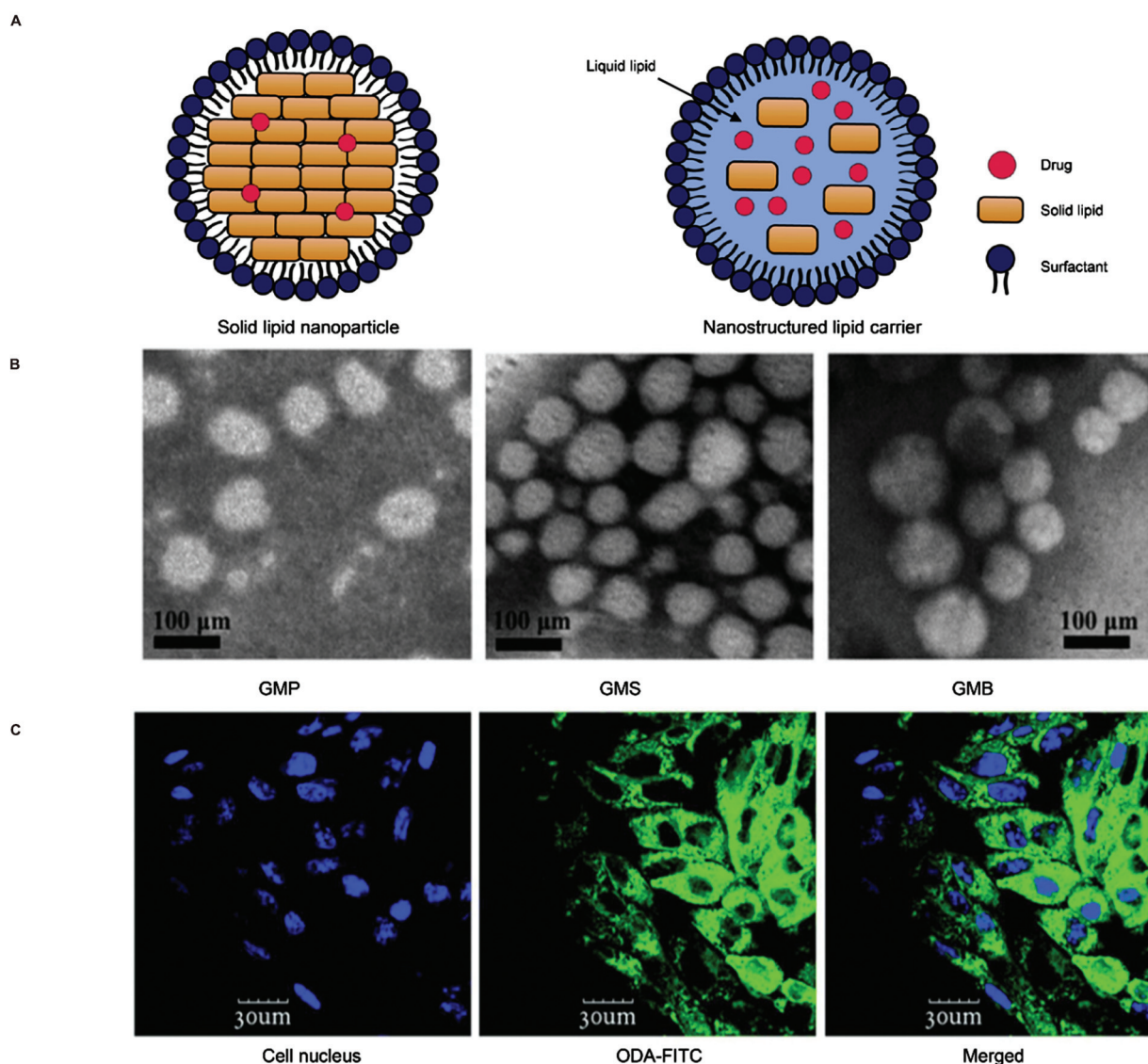


Fig. 6 (A) Structures of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). (B) Morphology of various SLNs observed by TEM. GMP, GMS, and GMB are the SLNs prepared with glycerol monopalmitate (GMP), glycerol monostearate (GMS), and glycerin monobehenate (GMB), respectively. (C) Endocytosis of SLNs. (Adapted with permission from Guihong et al 2016¹⁸⁵.)

toward an exploration of hybrid lipid–inorganic nanomaterials.¹³⁸ These core–shell type lipid-coated nanoparticle systems, which provide the most prominent advantages of both liposomes such as biocompatibility and polymeric/inorganic nanoparticles such as mechanical properties, offer a new approach to cancer treatment.¹³⁹ It was reported by a plethora of investigational studies that gold (Au) was used as an inorganic nanomaterial for preparing hybrid lipid–inorganic nanoparticles.¹³⁸ In a study, Kong and his team developed cationic lipid-coated gold nanoparticles (L-AuNPs) for efficient intracellular delivery of therapeutic siRNA, in which 3β-[N-(N',N'-dimethylaminoethane)-carbamoyl]-cholesterol (DC-Chol), DOPE, and Chol were used to construct cationic liposome-encapsulated gold nanoparticles.¹⁴⁰ The results showed that the cationic lipid coating significantly enhanced the cellular uptake and gene silencing effect of L-AuNPs, and considerably reduced the cytotoxicity of inorganic materials. In addition, the potential of semiconducting nanoparticles (quantum dots [QDs]) in biological imaging applications is better improved by combining with the lipid-based nanoparticles. Liu et al synthesized highly luminescent lipophilic CdSe/ZnS core–shell QDs with an emission maximum at 556 nm which were successfully encapsulated into SLN using the thin-layer ultrasonication technique.¹⁴¹ SLN in the nanocomposite particles improves some problems associated with QDs such as biocompatibility and stability.¹⁴¹ Notably, the composition of the outer leaflet lipids should be carefully chosen as they can greatly affect the pharmacokinetics and tissue distribution of the final nanoparticles.¹⁴² Despite significant advances in the area of laboratory-based applications of core/shell nanopar-

ticles in the biomedical field for diagnosis of diseases and drug delivery, clinical trial or applications are in the infancy stage.¹⁴³

Current Status and Future Perspectives

As one of the most promising drug carriers, lipid-based nanocarriers have attracted more and more attention in the pharmaceutical field due to their good biocompatibility, low immunogenicity, and specific targeting. As far, lipid-based nanocarriers have been developed rapidly in the fields of anticancer drugs, gene therapy, vaccine development, and so on, and the indications of listed products are mostly concentrated in the fields of tumor, infection, and analgesia. In addition to lipid-based nanocarriers, other nanocarriers have also been widely used in the field of drug delivery due to their superior delivery ability, for example, mesoporous silica and self-assembled nanoparticles of organic polymer materials. However, they also have similar problems to lipid-based nanocarriers in clinical transformation and industrial production.

Clinical Translation

Although a large number of basic studies have focused on optimizing the structure of lipid-based nanocarriers to enhance targeted delivery, there seems to be difficulties from basic research to clinical translation. Although lipid-based nanocarriers have shown superior therapeutic effects at the cellular level and in animal models, lipid-based

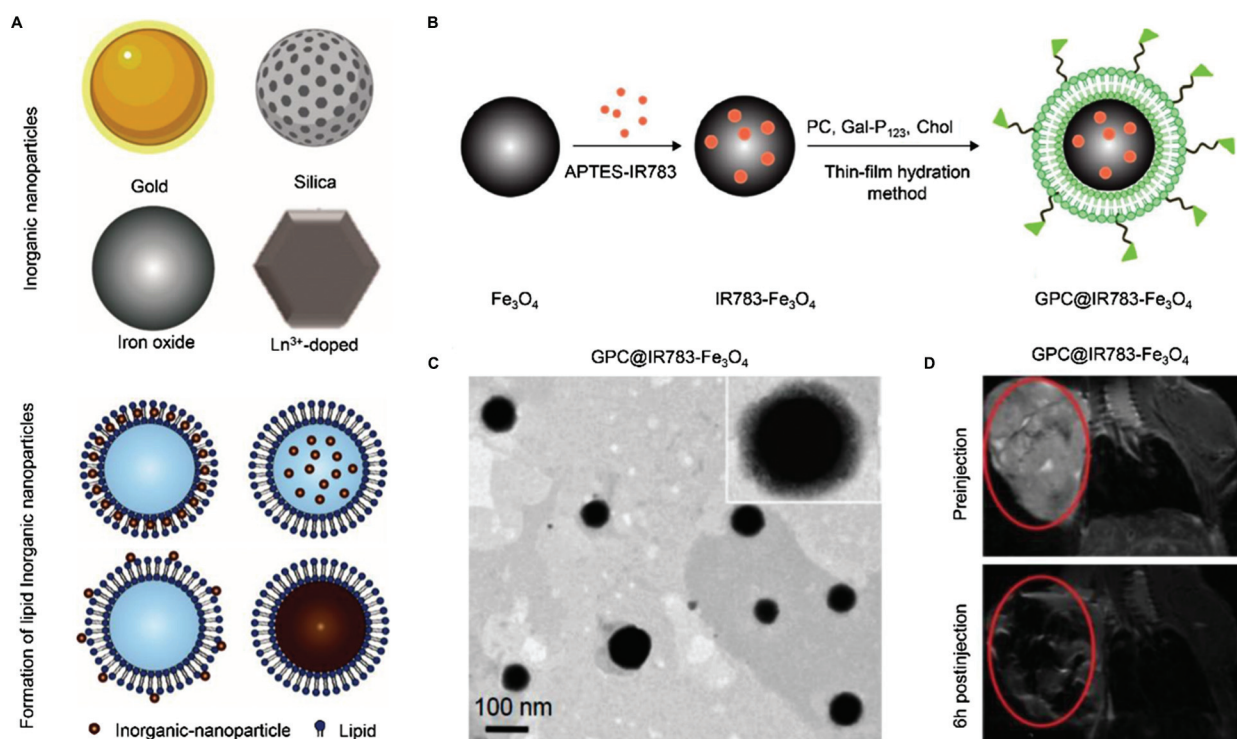


Fig. 7 (A) Structure of lipid-inorganic nanocarriers for drug delivery. (B) Schematic illustration of the construction of GPC@IR783-Fe₃O₄ nanoparticles. (C) TEM images of GPC@IR783-Fe₃O₄. (D) *In vivo* coronal MRI images of BALB/c mice at 0 and 6 hours after intravenous injection of GPC@IR783-Fe₃O₄. The region in the red circle was xenograft tumor. (Adapted with permission from Liang et al 2017¹⁸⁶.)

Table 2 Common methods of fabricating lipid-based nanocarriers

Type of methods	Method	Advantage	Disadvantage	Application	Ref.
Top-down	High-pressure homogenization	<ul style="list-style-type: none"> Narrow particle size distribution Low cost Scalable 	<ul style="list-style-type: none"> High energy or pressure requirement 	<ul style="list-style-type: none"> SLN NLC LDC 	112,119,159,160
	Media milling	<ul style="list-style-type: none"> Wider commercial and industrial application 	<ul style="list-style-type: none"> Risks of contamination Abrasion Long milling times 	<ul style="list-style-type: none"> Lipid-nanoparticle suspension 	144,161–164
	Thin film hydration	<ul style="list-style-type: none"> No special equipment Simple setup 	<ul style="list-style-type: none"> Low encapsulation efficiency Poor stability Difficult to scale up 	<ul style="list-style-type: none"> Liposomes 	137,165
Bottom-up	Self-assembly	<ul style="list-style-type: none"> Precise Low energy requirements The resultant nanostructures often show more comprehensive and superior properties 	<ul style="list-style-type: none"> High defects Low uniformity Low reproducibility 	<ul style="list-style-type: none"> Lipid-polymer nanoparticles Lipid-inorganic nanoparticles 	164,166–169
	Precipitation	<ul style="list-style-type: none"> Simple setup Quick No special equipment 	<ul style="list-style-type: none"> Nanoparticles produced are mostly amorphous Mixing conditions cannot be precisely controlled 	<ul style="list-style-type: none"> SLN 	144,170–172
	Evaporation	<ul style="list-style-type: none"> Simple setup Reproducible Economical 	<ul style="list-style-type: none"> Nanoparticles produced are mostly amorphous Limited to compounds which are soluble in a volatile organic solvent 	<ul style="list-style-type: none"> SLN Lipid-polymer nanoparticles Liquid-crystalline lipid nanoparticles 	144,173–176
	Microfluidics	<ul style="list-style-type: none"> Continuous flow Precise control of reaction time High temperature controllability Shorter diffusion distance in a micro channel 	<ul style="list-style-type: none"> Nanoparticles stacked in the grooved structures Low size controllability 	<ul style="list-style-type: none"> Liposomes LNP 	137,177,178

Abbreviation: LDC, lipid–drug conjugate; NLC, nanostructured lipid carrier; SLN, solid lipid nanoparticle.

nanocarriers often show side effects in clinical application, which may be due to the differences between species and the complex physiological environment in human body. Lipid-based nanocarriers adsorb additional particles in the body, such as proteins, thereby changing their properties. How to simulate human environment *in vitro* and effectively characterize the interaction between lipid-based nanocarriers and the body is particularly important.

Industrial Production

Different methods are investigated to produce various nanocarriers. The current approaches of fabricating lipid-based nanocarriers can be categorized into top-down and bottom-

up methods (–Table 2).^{137,144} Top-down techniques make large particles smaller via grinding, spraying, or pyrolysis to produce nanoparticles, while bottom-up techniques start with precursors and use deposition techniques or self-assembly of molecules to fabricate nanoparticles.¹⁴⁵ At present, the preparation of lipid-based nanocarriers mostly remains at the stage in laboratory. Large-scale production of lipid-based nanocarriers is a big challenge, with many problems to be solved, such as particle size distribution, drug loading rate, encapsulation efficiency, sterility, and stability. The sterility level is very important for pharmaceutical preparations, especially for injection. Due to the unique composition and properties of lipid-based nanocarriers, the sterilization is still an urgent problem to be solved; it

may damage the lipid-based nanocarriers under certain sterilization conditions.¹⁴⁶ Another problem limiting production of lipid-based nanocarriers is stability. Lipid-based nanocarriers may experience fusion, embedding material escape, lipid oxidation, and many other problems during storage, resulting in a decline in the therapeutic effect and even toxic side effects. It is necessary to maintain good stability of lipid-based nanocarriers throughout the period from production to application. The application of drying technology to the prepared lipid-based nanocarriers may be an effective means to improve the stability of lipid-based nanocarriers.¹⁴⁷ In addition, the lack of adjuvant research and the special industrial equipment are the factors limiting the clinical transformation of lipid-based nanocarriers. Furthermore, we also need to establish new regulations to regulate the development of this industry. Therefore, industrial production of lipid-based nanocarriers is a big challenge because it involves multistep, multitesting processes and requires innovation in this field.

Future Perspectives

Studies have shown that reasonable lipid selection can improve the biological distribution of lipid-based nanocarriers and achieve more effective treatment.¹⁴⁸ As discussed above, the development of ionizable lipids has made remarkable progress in RNA therapy. Therefore, searching for novel lipid materials with biodegradability and multifunctionality is necessary for the design of lipid-based nanocarriers. In addition, combining various cell-derived biofilms with nanomaterials is a promising strategy, because it not only retains the complex biological functions of biofilms, but also inherits the physical and chemical properties of nanoparticles. The improvement of preparation process also promotes the development of lipid-based nanocarriers, for example, microfluidics has demonstrated superior advances for the synthesis of lipid-based structure. The *in vivo* fate of lipid-based nanocarriers affects the final therapeutic efficacy. Developing real-time observation technology to evaluate the *in vivo* fate of lipid-based nanocarriers would provide more effective guidance for the reasonable design of these delivery systems.

Conclusion

This review was intended to provide an overview of the progress in the application of lipid-based nanocarriers from traditional lipid preparations to novel functional lipid preparations. As the most common class of FDA-approved nanomedicines,² lipid-based nanocarriers offer many advantages including biocompatibility, high bioavailability, low toxicity, targeting, and controlled release ability. Through structural optimization, surface modification, and material combination, the safety, encapsulating capacity, stability, pharmacokinetics, bio-distribution, and therapeutic benefit of lipid-based nanocarriers can be controlled as a result. The clinical development of lipid-based nanocarriers has

demonstrated their potential in the treatment of a range of diseases.

Although there are many approved lipid-based nanocarrier therapies in the market and some are in clinical trials, the clinical translation of lipid-based nanocarriers still has a long way to go, including the unsolved problems of lipid-based nanocarriers themselves, such as seeking more targeted and the biological characteristics given by lipid carriers in the body circulation, although these characteristics are not desired. Furthermore, there are still production obstacles for clinical translation, including repeatability between batches, encapsulation efficiency of some candidate drugs, effective sterilization methods, and storage stability.¹⁴⁹ However, it is worth mentioning that translational nanomedicines have been streamlined for years, perhaps even decades, due to the tremendous scientific achievements that have occurred in response to the COVID-19 pandemic.¹⁵⁰ Lipid-based nanoparticles have played a pivotal role in the success of COVID-19 vaccines, which has exciting implications for the future of nanotechnology-enabled drug and gene delivery. Therefore, we believe that through the collaborative efforts of scientists in different fields, lipid-based nanocarriers will bring more achievements in the future.

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Conflict of Interest

The authors declare no conflict of interest.

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