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Review Article

From mechanisms to applications: Research advances and translational prospects of endogenous targeting LNPs

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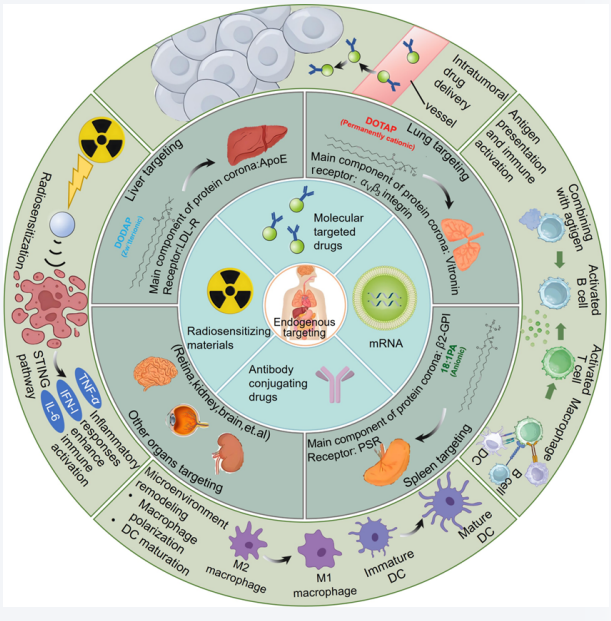
ABSTRACT: Selective organ-targeting (SORT) lipid nanoparticles (LNPs) have emerged as a transformative platform in precision medicine, enabling efficient and safe delivery of therapeutic agents to specific organs. This review explores the mechanistic foundations, design strategies, and biomedical applications of SORT LNPs. Key targeting mechanisms include dynamic protein corona formation, which mediates tissue-specific uptake through endogenous interactions, and the rational modulation of nanoparticle size, surface chemistry, and material composition to manipulate *in vivo* biodistribution. Recent advancements highlight targeted delivery systems for the liver, lungs, and spleen, leveraging both passive and active targeting as well as endogenous cues. Despite the clinical success of mRNA and siRNA therapies, challenges such as immunogenicity, biodistribution complexity, and interspecies translation remain. This review provides a comprehensive overview of SORT development, offering insights into the next generation of intelligent, biocompatible, and organ-specific nanomedicines for cancer and immune-related diseases.



KEYWORDS: nanoparticles, lipid nanoparticles, lipid nanoparticles (LNPs), organ-selective targeting, endogenous targeting, protein corona, clinical translation

1 Introduction

Over the past few decades, nanocarrier-based drug delivery systems have experienced rapid development in the field of disease treatment. Nanoparticles (10–1000 nm) have been demonstrated as highly efficient platforms for the loading and targeted delivery of specifically engineered cargos. The unique characteristics of nanotechnology have significantly improved drug delivery by enhancing drug solubility and stability, enabling controlled drug release, prolonging systemic circulation, overcoming tissue barriers, increasing accumulation in target tissues, and promoting cellular uptake and intracellular transport [1, 2]. Driven by the limitations of conventional treatment approaches, nanotechnology has been increasingly adopted to develop safer and more effective therapeutic strategies. Nanoparticle-based delivery systems have consequently evolved rapidly, now encompassing a wide range of treatment modalities including molecularly targeted agents [3, 4], antisense

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oligonucleotides [5, 6], small interfering RNA (siRNA) [7–10], mRNA [11], and DNA inhibitory oligonucleotides [12].

The complex pathological mechanisms underlying many diseases pose significant challenges to conventional therapies, prompting the development of immunotherapy strategies that precisely modulate the human immune system to combat diseases, demonstrating broad application prospects. Over the past decade, the field of immunotherapy has achieved major breakthroughs, particularly in the regulation of specific immune responses.

Among various nano-platforms, lipid nanoparticles (LNPs) have emerged as a leading candidate due to their distinctive advantages. Validated in numerous clinical trials, LNPs represent the most advanced and successfully applied nucleic acid delivery platform to date. The core of LNPs lies in their modular four-component structure—comprising ionizable lipids, helper phospholipids, cholesterol, and polyethylene glycol (PEG)-lipids—a sophisticated design that synergistically addresses the aforementioned challenges [13]. This system enables efficient nucleic acid encapsulation through self-assembly into protective structures, maintains a "stealth" profile in the bloodstream to extend half-life, and, most importantly, utilizes ionizable lipids that protonate in the acidic endosomal environment. This protonation induces a structural phase transition, disrupts the endosomal membrane, and facilitates efficient endosomal escape, thereby releasing functional nucleic acids into the cytoplasm [14].

However, this sophisticated design still faces fundamental challenges in achieving extrahepatic tissue targeting. Conventional strategies rely on the active conjugation of "targeting ligands" such as antibodies, peptides, or small molecules onto the LNP surface to precisely recognize specific cell surface receptors. In practice, however, the efficacy of this approach is often compromised by the complex biological environment *in vivo*: upon entering the systemic circulation, LNPs are rapidly enveloped by plasma proteins and other biomolecules, forming a "protein corona". This corona not only obscures the meticulously designed targeting ligands, preventing their binding to the intended receptors, but more fundamentally, it "redefines" the biological identity of the LNPs [15]. Consequently, the ultimate *in vivo* fate of LNPs is often dictated by the composition of the protein corona rather than the initial ligands.

It is precisely this challenge that has spurred the development of a novel strategy that shifts from a passive to an active approach—endogenous targeting utilizing the protein corona for organ-specific delivery. Researchers have realized that instead of attempting to completely suppress or combat corona formation, it is more advantageous to actively guide and exploit it. By precisely tuning the lipid composition, surface charge, and physicochemical properties of LNPs, specific endogenous proteins (e.g., apolipoprotein E, ApoE) can be purposefully "recruited" to form a functional, guiding protein corona on the LNP surface. For instance, incorporating permanently cationic lipids into the formulation can significantly alter the corona composition, thereby reprogramming the natural liver accumulation tendency of LNPs towards specific organs such as the lungs [16] or spleen [17]. This "selective organ targeting (SORT)" strategy eliminates the need for complex ligand modifications [18]. Instead, it cleverly leverages the body's natural protein transport systems, opening a promising new avenue for achieving precise nucleic acid delivery beyond the liver.

Beyond targeted delivery, SORT platforms possess the unique ability to modulate biological responses through precise delivery of therapeutic molecules, regulation of local microenvironments, or interaction with specific cells. By rationally designing the composition and surface properties of nanoparticles, it is possible to achieve precise targeting of specific tissues while simultaneously regulating local biological responses [19–21]. This synergistic effect provides new strategies for developing more effective treatments for various diseases (Fig. 1).

This review aims to systematically summarize recent advances in SORT LNPs design strategies, explore how they utilize endogenous mechanisms to achieve efficient organ tropism, combine its applications in immunotherapy, and provide in-depth discussion on designing LNPs that can simultaneously optimize delivery precision and therapeutic outcomes.

2 Endogenous targeting: A paradigm shift in nanoparticle delivery

Traditional targeting strategies, primarily encompassing passive and active targeting, have demonstrated considerable promise in early-stage research. However, their limitations become increasingly apparent with more in-depth investigations. Passive targeting relies mainly on the enhanced permeability and retention (EPR) effect—which leverages the aberrant vascular architecture (hyperpermeability) and impaired lymphatic drainage of tumor tissues to facilitate a certain degree of nanomedicine accumulation at the tumor site [22–24]. However, this effect exhibits significant interindividual heterogeneity and tissue variability, resulting in relatively limited targeting specificity. Its adaptability and controllability within complex pathological contexts remain insufficient, thereby hindering precise lesion localization.

Active targeting improves targeting efficiency by functionalizing nanoparticles with specific ligands (e.g., antibodies, peptides, or small molecules) that bind to receptors or antigens. However, this approach faces several issues, such as targeting efficiency being limited by ligand-receptor binding, receptor saturation, or reduced targeting efficiency over time [4, 25, 26]. Furthermore, synthetic ligands may trigger immune responses or be rapidly cleared, compromising the stability of nanoparticles *in vivo* [27]. The circulation time of active targeting nanoparticles is also dependent on carrier modifications and surface characteristics, making them susceptible to clearance by the reticuloendothelial system (RES). Additionally, the static nature of ligands lacks dynamic regulatory capacity, limiting their ability to navigate complex biological barriers and reducing their immunomodulatory potential, as their function is primarily restricted to direct action on target cells.

With the advancing understanding of human physiological characteristics, endogenous targeting mechanism in nanomedicine. Endogenous targeting represents a specialized form of passive targeting, which harnesses intracellular natural mechanisms or signaling pathways to achieve the targeted delivery of therapeutic agents or genes. This approach typically relies on pre-existing molecular tools within the body (e.g., small molecules, nucleic acids, or proteins) to directly intervene in or modulate intracellular signaling pathways. This strategy leverages the body's physiological and pathological features, such as blood flow dynamics, microenvironmental differences (e.g., acidity, hypoxia, enzyme activity), and immune cell functions to achieve efficient organ- or tissue-specific targeting [28]. Compared to traditional passive and active targeting, endogenous targeting offers multiple advantages. Its recognition mechanism combines passive targeting with

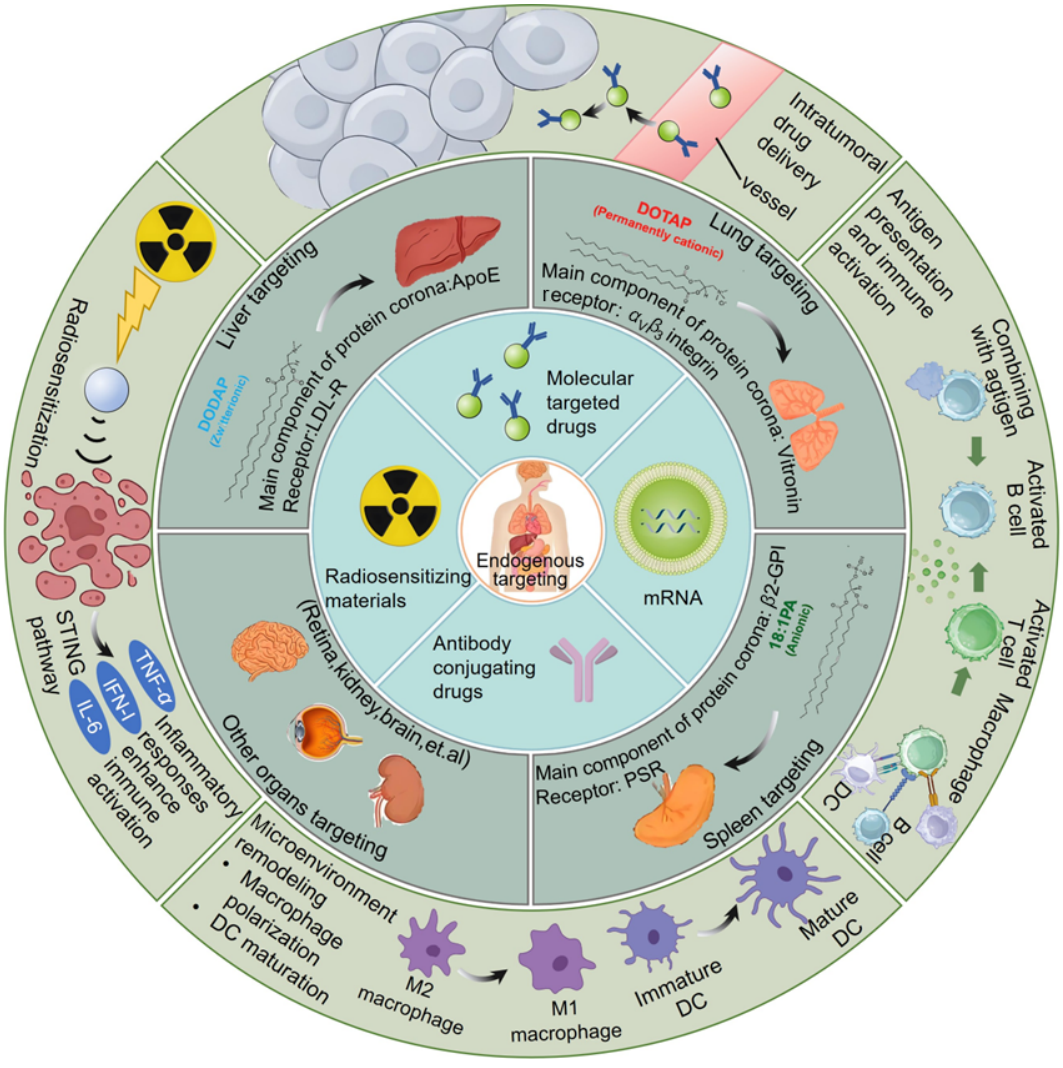

Figure 1 Endogenous targeting-guided nanoparticle delivery: Design strategies and applications.

physiological selectivity, allowing for precise delivery based on natural physiological and pathological characteristics. The carrier design often uses natural cell membranes or biocompatible materials, effectively reducing immunogenicity and extending circulation time, thereby minimizing non-specific clearance and enhancing penetration of tissue barriers, such as the blood-brain barrier or tumor tissues. Its core lies in skillfully leveraging the inherent recognition and transport mechanisms of biological systems, rather than relying on exogenous targeting ligands. Within this paradigm, the formation and regulation of the protein corona become a critical link in achieving precise organ targeting. Therefore, a deep understanding of the composition, dynamic evolution, and interaction mechanisms of the protein corona with target organs can provide concrete implementation pathways and design principles for endogenous targeting strategies.

3 Organ-selective targeting mechanisms

3.1 Protein corona formation

3.1.1 Adsorption and desorption of protein crona

The selective organ targeting mechanism is potentially influenced by the composition and conformation of biological proteins that adsorb onto the surface of materials following systemic administration. Research on the interaction between proteins and surfaces, including colloids, has been reported for over a century [29]. Although nanoparticles have been extensively studied for biomedical applications, it was not until 2007 that the concept of a biomolecular corona forming on their surfaces was formally introduced. Initially referred to as the "protein corona" due to its origins in studying the association or dissociation kinetics of proteins on nanoparticles, this concept has evolved alongside expanding research revealing that numerous non-protein biomolecules—such as lipids, nucleic acids, and carbohydrates—also adsorb onto nanoparticle surfaces to form a coating. Consequently, the terminology transitioned to "biomolecular corona" or "biocorona" to inclusively describe these spontaneously formed biomolecular layers. Presently, the protein corona, as a core component of the biomolecular corona, continues to serve as a pivotal nexus for investigating the interactions between nanomaterials and biological systems, bridging foundational protein-centric studies with the broader landscape of biomolecular interactions at the nano-bio interface [30]. Subsequently, in 2021, Dilliard et al. proposed a three-step endogenous targeting mechanism for tissue-specific mRNA delivery via SORT LNPs.

First, the dissociation of PEGylated lipids from the LNP surface exposes embedded SORT molecules. Second, a range of serum proteins selectively adsorb onto these exposed SORT moieties. Third, the adsorbed proteins engage with cognate receptors on target cells, thereby facilitating the preferential cellular uptake of LNPs in specific tissues [30]. This process suggests that the protein corona may play a critical role in nanoparticle targeting, with its dynamic composition potentially influencing tissue-specific recognition.

While the formation of a protein corona in the systemic circulation has been shown to guide initial tissue targeting, recent evidence suggests that its post-internalization dynamics may further modulate nanoparticle fate and targeting efficiency. Building upon this concept, Han et al. [31] further demonstrated that the selective dissociation of the protein corona following cellular internalization may also regulate nanoparticle targeting efficiency. Specifically, following endocytosis, the protein corona gradually dissociates from nanoparticles in acidic intracellular compartments (e.g., early endosomes at pH 6.5–5.5), with the corona being sorted into multivesicular bodies (MVBs) for eventual lysosomal degradation or partial excretion via exosomes. Meanwhile, nanoparticles enter recycling endosomes (REs) and are either extruded back into circulation via exocytic pathways or cleared by the reticuloendothelial system. This dynamic dissociation process may be mechanistically linked to endosomal pH gradients (from early to late endosomes) and conformational changes in corona proteins. For instance, acidic environments likely induce corona desorption or remodeling, re-exposing targeting ligands on nanoparticle surfaces to enhance their binding affinity for tissue-specific cell surface receptors. Notably, under simulated endosomal pH 4.5 conditions, the stability of the protein corona was markedly reduced, further supporting the hypothesis that acidic microenvironments trigger corona shedding [31].

These mechanistic insights align with Dilliard's three-stage model, providing a systematic framework to elucidate the complete lifecycle of protein coronae in nanoparticle systemic circulation. Specifically: (1) Upon entering the bloodstream, nanoparticles undergo PEG shedding and rapidly adsorb serum proteins to form a dynamic corona, enabling tissue targeting via corona-associated proteins; (2) post-internalization, acidic intracellular environments trigger corona dissociation from nanoparticles, with the corona degraded via lysosomal pathways while nanoparticles are either recycled into circulation via exocytosis or cleared by the reticuloendothelial system (RES) (Fig. 2). This paradigm integrates extracellular corona-mediated targeting with intracellular corona-nanoparticle decoupling, resolving the spatiotemporal duality of corona functionality *in vivo*.

3.1.2 *Factors affecting protein corona formation*

Typically, the protein concentration in plasma ranges from 60 to 80 g/L [32]. Nanoparticles injected into the bloodstream are rapidly (< 30 s) coated by proteins, forming a protein corona [33]. Notably, upon entering the bloodstream, nanoparticles tend to first bind to high-abundance, low-affinity proteins, which are then dynamically replaced by low-abundance, high-affinity proteins—a phenomenon first observed by Vroman et al. in 1980, known as the Vroman effect [34]. The protein layer formed by the initial binding is commonly referred to as the "soft corona", characterized by loose binding and a high tendency for replacement. In contrast, the later-formed protein layer, known as the "hard corona", binds more tightly and is typically irreversible [35]. The various forces facilitating nanoparticle-protein interactions include hydrogen bonds, van der Waals interactions, electrostatic interactions, hydrophobic interactions, and π-π stacking interactions [36]. The factors influencing protein corona formation can be broadly classified into two categories: the intrinsic properties of the nanoparticles and environmental factors. The former includes the size, shape, and surface modifications of the nanoparticles, while the latter mainly encompasses factors such as temperature and the types of proteins present in the surrounding medium (Fig. 3). These factors will be discussed in detail below.

The size of nanoparticles plays a crucial role in the formation of the protein corona. For instance, Piella et al. [37], in their study on the *in vitro* formation of protein coronas on highly monodisperse

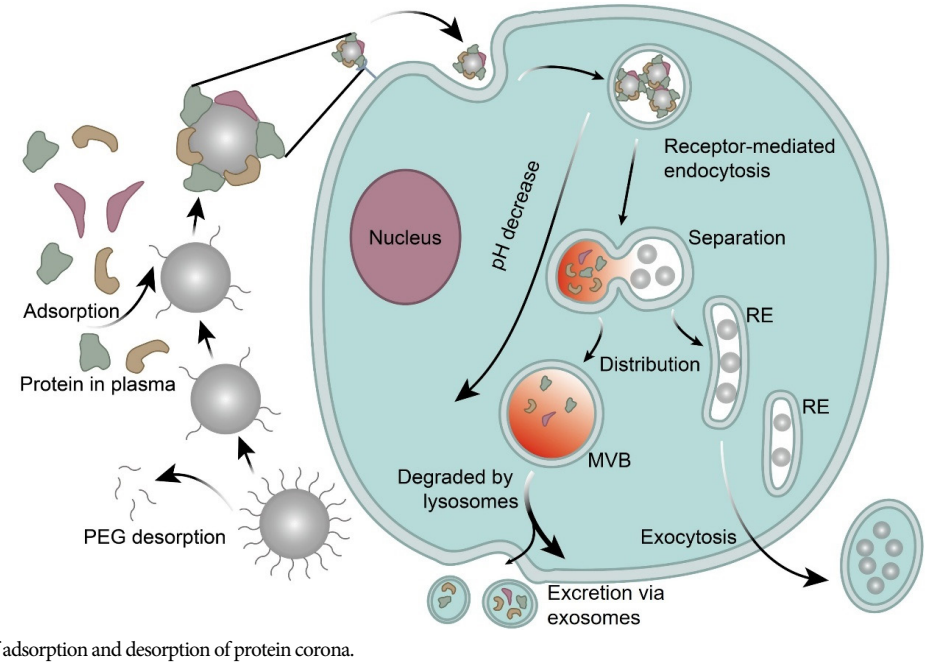

Figure 2 Mechanism of adsorption and desorption of protein corona.

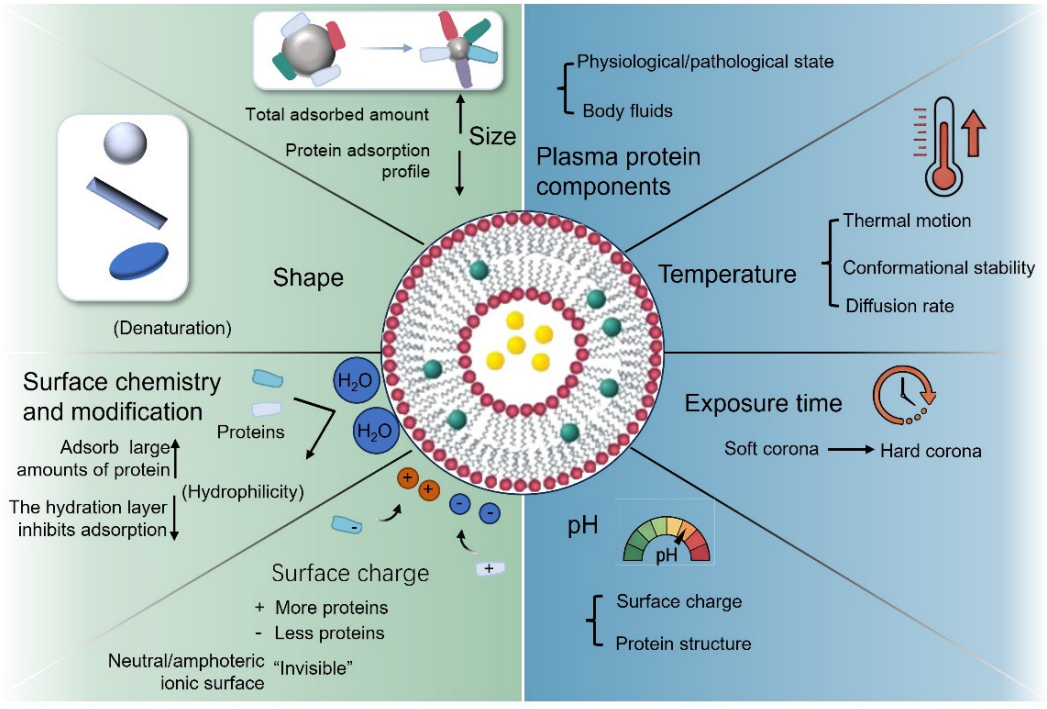

Figure 3 Factors affecting protein corona formation.

citrate-stabilized gold nanoparticles ranging from 3.5 to 150 nm, revealed the critical role of nanoparticle size in protein adsorption dynamics. They found that particle size significantly influenced the characteristics of the protein corona formed on the outer layer: smaller nanoparticles formed thinner protein coronas and facilitated faster corona formation. Notably, earlier work by Perevedentseva et al. [38] demonstrated that lysozyme adsorption on 100 nm nanodiamonds (ND) reached saturation within 10–15 min, while 5 nm NDs required 30–40 min for saturation. This suggests that nanoparticle size is indeed a key factor controlling adsorption kinetics. Furthermore, smaller nanoparticles may lead to more complex protein corona compositions. Garcia-Alvarez et al. [39] found that compared to 70 nm gold nanostars (AuNSs), 40 nm AuNS exhibited fewer proteins, yet the protein types were more diverse.

The shape of nanoparticles significantly influences the formation of the protein corona. Chithrani et al., through their study on the uptake of gold nanoparticles by mammalian cells, demonstrated that shape can affect the surface curvature and contact area of the nanoparticles, leading to differences in protein adsorption sites, thereby influencing protein binding [40]. Similarly, Chaudhary and colleagues observed that the helical content of hemoglobin and human serum albumin (HSA) decreased when bound to nanoparticles, with the shape transition from spherical to triangular nanoparticles. This suggests that the shape of nanoparticles plays a critical role in altering protein conformation upon binding [41].

Common surface modification techniques, such as covalently attaching, adsorbing, or encapsulating PEG onto nanoparticle surfaces, can reduce protein adsorption. A study by Benetti et al. demonstrated that PEG-modified 60 nm gold nanoparticles exhibited significantly lower protein adsorption compared to citrate-stabilized gold nanoparticles of the same size. However, this difference was not as pronounced for 10 and 200 nm nanoparticles, indicating that both surface modification and nanoparticle size are crucial factors influencing protein adsorption [42]. Furthermore, the density of surface ligands on nanoparticles also affects the adsorption affinity and variety of proteins [43].

Other external environmental factors also significantly influence protein corona formation which should not be overlooked. Temperature, in particular, has a notable impact on the protein corona composition of nanoparticles. A study by Mahmoudi et al. reported the effect of exposure temperature on the protein corona composition of magnetic nanoparticles. Using fluorescence correlation spectroscopy (FCS), they found that the formation of monolayers of HSA and apotransferrin (apo-Tf) was strongly temperature-dependent [44]. Similarly, Wang et al. utilized FCS to study the binding of bovine serum albumin (BSA) to carboxylated CdSe quantum dots (QDs-COOH) at different temperatures (25 and 37 °C), and observed that increasing temperature led to a reduction in protein corona thickness [45].

The physiological state of an individual can alter the composition of the protein corona, thereby exerting differential effects on the biodistribution of nanoparticles. In murine models of hypercholesterolemia, the distribution of nanoparticles within the organism exhibits significant disparities compared to that in normocholesterolemic controls. Research has elucidated that in the plasma of hypercholesterolemic mice, nanoparticles demonstrate a propensity for accumulation in organs such as the liver, spleen, and brain, while their distribution in the lungs is markedly reduced. This phenomenon underscores that alterations in the protein corona under pathological conditions can modulate the *in vivo* distribution patterns of nanoparticles, suggesting that the design of nanomedicines must meticulously account for the physiological and pathological states of patients.

In addition, factors such as surface charge, plasma gradients, and circulation time also influence the formation of the protein corona [46, 47]. It is important to note that due to the highly complex nature of the *in vivo* environment, the formation of the protein corona under *in vivo* conditions differs from that observed *in vitro* [48]. The proteins adsorbed onto the nanoparticles together form

unique biological characteristics, which interact with specific targets and exhibit distinctive *in vivo* targeting behaviors. Therefore, an in-depth investigation into the factors influencing protein corona formation is essential, as it can guide the precise regulation of nanoparticle targeting behaviors *in vivo*, ultimately leading to the development of clinically effective biomedical nanomaterials.

3.2 Organ-targeted delivery via protein corona on nanoparticles

3.2.1 Challenges posed by the protein corona to nanoparticle delivery efficacy

The composition and stability of proteins adsorbed on nanoparticle surfaces critically influence cellular recognition and intracellular trafficking, thereby affecting systemic circulation, biodistribution, and clearance of nanoparticles *in vivo*. Early studies have demonstrated that plasma protein adsorption-mediated opsonization impacts their circulation and cellular uptake, involving opsonins such as complement proteins, immunoglobulins, albumin, and apolipoproteins. These plasma proteins readily associate with nanoparticle surfaces to form a protein corona, promoting the uptake of liposomes by specific cells through complement activation and specific or non-specific binding pathways, or leading to their sequestration, degradation, and clearance by the mononuclear phagocyte system (MPS) [49]. This poses challenges for drug delivery systems, including liposomes, prompting subsequent research to explore strategies to circumvent serum protein adsorption on nanoparticle surfaces, such as modifications with polymers like PEG and encapsulation with endogenous cell membranes [50]. Conversely, the adsorption of BSA on nanoparticle surfaces can reduce particle adhesion to cell membranes, thereby decreasing their uptake by monocytes and macrophages.

Moreover, protein corona formation may sterically hinder or obscure targeting ligands on nanoparticle surfaces, impairing their ability to engage with target cell receptors and consequently diminishing targeting efficiency. Using fluorescent silica nanoparticles, Mirshafiee et al. [15] observed that the targeting efficiency of nanoparticles significantly decreased after serum incubation and protein corona formation compared to non-incubated nanoparticles. It is worth noting that in some cases, protein corona formation does not significantly affect, or may even enhance, the targeting ability of nanoparticles. Research by Dai and colleagues [51] shows humanized A33 monoclonal antibody-modified multilayer nanoparticles showed no significant change in their binding ability to cell surfaces after protein corona formation. This may be attributed to variations in the binding affinity, size, density, chain length, and conjugation methods of different targeting ligands. Moreover, the protein corona formed *in vivo* differs from that formed *in vitro*, and its dynamic changes may further complicate its impact on nanoparticle targeting efficiency.

3.2.2 Impact of protein corona on the in vivo biodistribution of nanoparticles

The adsorption of blood proteins plays a pivotal role in dictating the biodistribution of nanoparticles across tissues and organs. Studies have shown that gold nanoparticles (GNPs) conjugated with specific plasma proteins, such as albumin and apolipoprotein E (ApoE), exhibit markedly reduced retention in the liver. Specifically, albumin-coated 15 nm GNPs accumulate more in the lungs and brain compared to citrate-modified and ApoE-modified GNPs [52]. Additionally, apolipoprotein A-I (ApoA-I) has been found to influence the targeting potential of nanoparticles in the brain [53]. These findings highlight distinct protein corona components can act as biological "zip codes", directing nanoparticles toward specific organs, thereby impacting both therapeutic efficacy and off-target effects.

In a 2021 study employing proteomic analysis, Dilliard et al. [30] elucidated the distinctive composition and mechanistic roles of protein coronae on SORT nanoparticles. The SORT-LNP system investigated was constructed by incorporating a fifth SORT molecule into traditional four-component LNPs. These conventional LNPs themselves contain a key "ionizable cationic lipid" as the core functional component. For instance, the benchmark mDLNP used in the study utilizes the dendrimer lipid 5A2-SC8, while other ionizable lipids such as DLin-MC3-DMA (used in the approved drug Onpattro) and C12-200, which are also compatible with the SORT strategy, represent this category. These ionizable lipids become protonated and positively charged under acidic pH conditions, which is crucial for mRNA encapsulation and endosomal escape, and their base LNPs inherently exhibit liver-targeting propensity.

Building upon this foundation, the research demonstrated that organ-specific delivery is achieved through the adsorption of unique serum protein ensembles: Liver-targeting SORT nanoparticles rely on the synergistic interaction between apolipoprotein E (constituting 13.3%–13.9% of the corona) and albumin, where ApoE mediates hepatocyte internalization via binding to the low-density lipoprotein receptor; spleen-targeting nanoparticles are characterized by β2-glycoprotein I (constituting 20.1%), which drives splenic macrophage enrichment through phosphatidylserine receptor engagement; lung-targeting nanoparticles depend on vitronectin (constituting 12.2%) binding to $\alpha v\beta 3$ integrins on pulmonary endothelial cells [18]. These disparities stem from the regulatory influence of SORT molecule chemistry—such as the anionic lipid 18PA, the permanently cationic lipid DOTAP, and the ionizable cationic lipid DODAP—on protein adsorption (Fig. 4). It is noteworthy that DODAP itself belongs to the category of ionizable lipids; when added as a SORT molecule to an LNP already containing another ionizable lipid (e.g., 5A2-SC8), it synergistically enhances ApoE adsorption, thereby potentiating liver targeting. SORT molecules with distinct structural and electrostatic properties selectively recruit specific proteins via electrostatic interactions, generating organ-specific protein coronae that enable precision delivery through receptor-mediated endocytosis [30]. This mechanism not only establishes a direct correlation between nanoparticle surface chemistry and *in vivo* fate but also provides a theoretical foundation for overcoming hepatic sequestration and designing next-generation nanocarriers with enhanced tissue selectivity and therapeutic precision.

3.3 Methods for protein corona characterization

The composition, structure, and dynamic evolution of the protein corona are core factors determining the *in vivo* fate of nanoparticles. Its precise characterization is the cornerstone for the development of nanomedicine. However, current protein corona research faces a significant challenge: characterization results are highly dependent on the technological platforms and experimental protocols used, leading to poor comparability of data across

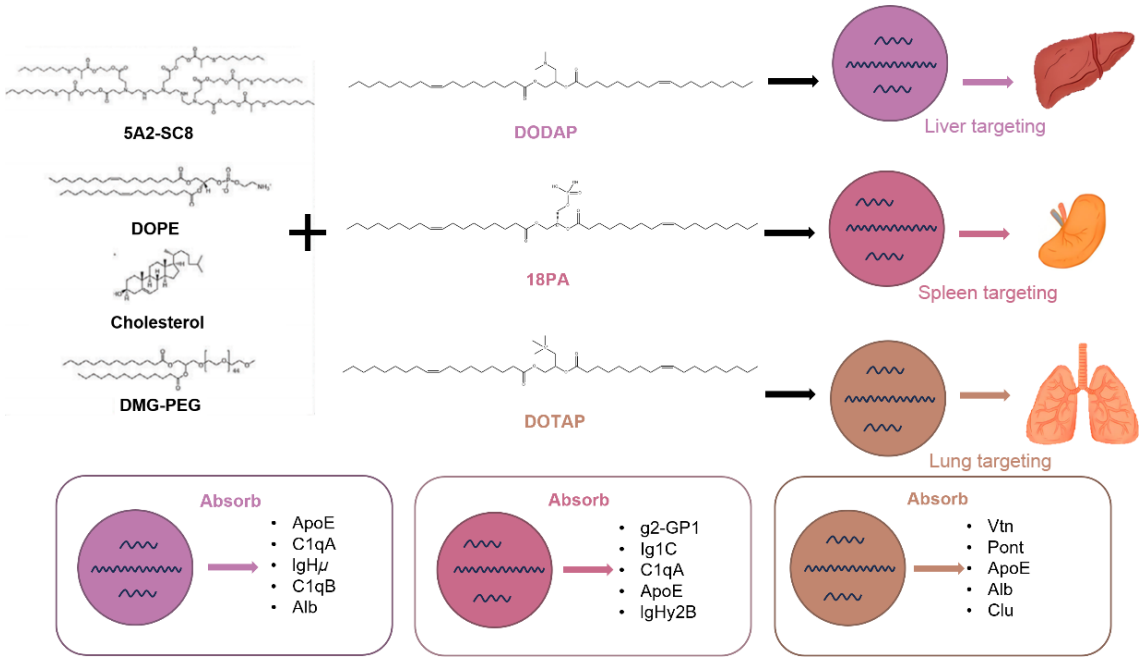

Figure 4 Composition and key protein corona components of organ-targeting LNPs.

different laboratories and even core facilities. For instance, a systematic study sent identical protein corona samples to 17 proteomics core facilities in the United States for liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis. The results revealed that out of a total of 4022 unique proteins identified, only 73 (1.8%) were commonly recognized by all facilities, highlighting the substantial heterogeneity faced by current protein corona data in cross-study comparisons [54].

This finding raises critical questions about the current methodological framework. Although LC-MS/MS serves as the gold standard for qualitative and quantitative analysis, capable of identifying and quantifying hundreds of protein corona components in a single run, its high sensitivity and throughput allow for systematic revelation of the profound influence of nanoparticle physical properties—such as size, surface chemistry, and even chirality—on the corona composition (e.g., studies have shown that even a 10-nanometer difference in size can significantly alter the binding amount of nearly 40% of proteins [55]). However, differences between laboratories in sample preparation, instrument configuration, database search parameters, and data processing workflows significantly affect the final number of protein identifications, quantitative results, and biological interpretation.

Beyond compositional analysis, understanding the kinetics of protein interactions is crucial. Techniques such as surface plasmon resonance (SPR) and bio-layer interferometry (BLI) can monitor protein adsorption and dissociation in real-time under label-free conditions, providing key kinetic parameters for distinguishing between soft and hard protein coronas with different affinities. For example, Baimanov et al. [56], by developing a BLI-based Fishing method—an *in situ* analytical technique that utilizes bio-layer interferometry by immobilizing nanoparticles on sensors to monitor and elute soft and hard corona proteins in layers in real-time—achieved for the first time *in situ*, dynamic, and layered analysis of the soft corona on nanoparticles. This work clarified the important role of the soft corona in regulating the biological effects of nanomaterials and revealed the influence of surface chirality on protein corona composition and biological fate: surface chirality guides the formation of distinct protein corona "fingerprints", thereby significantly altering the *in vivo* behavior of nanoparticles. For instance, D-form nanoparticles are cleared from the blood faster than L-form particles because their soft corona is enriched with more readily recognized proteins. Furthermore, specific recognition-based techniques like the enzyme-linked immunosorbent assay (ELISA) are suitable for the precise quantification of specific functional proteins (e.g., apolipoproteins, immunoglobulins), aiding in the analysis of the protein corona's role in immune recognition and metabolic regulation. More cutting-edge protein corona sensor array technology, by combining the composite protein corona "fingerprints" formed from the interaction of different nanoparticles with biological samples with machine learning, has successfully achieved early diagnosis of various cancers, marking an important transition for protein corona research from fundamental understanding to clinical diagnostic application (Fig. 5) [57].

4 Research progress on selective organ-targeting nanoparticles

Recent advances in protein corona research have laid a robust theoretical foundation for manipulating the adsorption of specific endogenous proteins through the rational design of nanoparticle composition. Detailed investigations have revealed that by modulating the physicochemical properties—particularly the material constituents—of nanoparticles, it is possible to precisely govern the formation and composition of the protein corona. This, in turn, critically influences the nanoparticles' *in vivo* transport dynamics and organotropism. The selective adsorption of distinct plasma proteins onto nanoparticles composed of different materials results in divergent biodistribution profiles and targeting behaviors, thereby presenting a powerful strategy for achieving organ-specific delivery. These findings highlight the potential of composition-driven protein corona engineering as a rational approach for

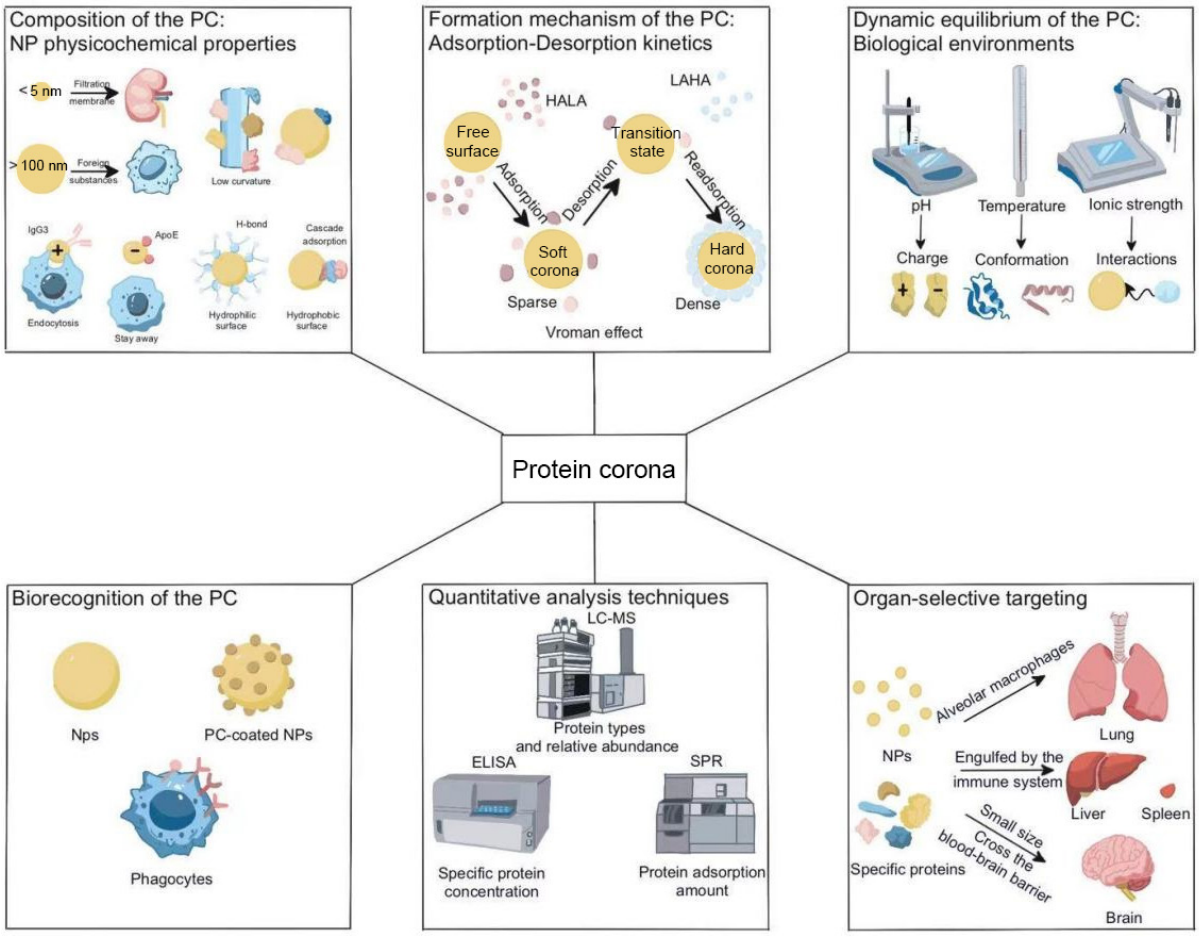

Figure 5 Formation, analysis, and regulatory impact of the protein corona on LNP *in vivo* behavior.

enhancing the precision and efficacy of nanoparticle-based drug delivery systems, representing a significant milestone in the translational application of nanomedicine.

4.1 Liver targeting

4.1.1 Physiological characteristics of the liver

The liver, as a vital organ in the human body, plays a pivotal role in drug metabolism and excretion, with its unique physiological characteristics exerting profound influences on drug delivery. Receiving blood from both the gastrointestinal tract and the heart, the liver is characterized by an extensive network of sinusoids, which are lined with endothelial cells and Kupffer cells. This structural arrangement facilitates efficient blood flow and material exchange within the liver. Hepatocytes, constituting 70%–85% of liver cells, perform critical functions such as metabolism, endocrine regulation, and secretion, implying that drugs entering the liver undergo intricate metabolic processes [58]. Kupffer cells, specialized macrophages, are capable of clearing foreign substances, and during drug delivery, nanoparticles larger than 150 nm are prone to capture by these cells, thereby altering drug distribution [59]. Hepatic stellate cells (HSCs), dispersed in the space of Disse, become activated in response to liver injury, potentially leading to fibrosis or cirrhosis, which can further modify the drug's microenvironment [60]. Additionally, the biliary system within the liver, responsible for bile secretion and excretion, may contribute to the elimination of drugs through bile, ultimately impacting their therapeutic efficacy.

4.1.2 Liver organ-selective targeting strategies

Due to the propensity of nanoparticles to accumulate in the liver, passive targeting through size control can, to some extent, direct nanomaterials to the liver [61, 62]. However, their uncontrolled accumulation in extrahepatic organs limits their broader application. Earlier studies have established relatively mature strategies for liver targeting. For instance, targeting hepatocytes via the glycyrrhizin/glycyrrhetinic acid receptor [63], HSCs through the mannose 6-phosphate/insulin-like growth factor II receptor, retinol-binding protein receptor, and platelet-derived growth factor (PDGF) receptor [64, 65], as well as Kupffer cells and endothelial cells via scavenger receptors [66] and mannose receptors [67], enables active targeting of specific liver cell types. Additionally, combined targeting strategies integrate passive and active targeting approaches. For example, the preparation of lactosyl-norcantharidin *N*-trimethyl chitosan nanoparticles achieves passive tissue targeting through size control, while leveraging asialoglycoprotein receptor recognition for hepatocyte-specific uptake, thereby enhancing targeting efficacy [68].

The rise of endogenous targeting has spurred novel strategies for precision drug delivery. To enhance hepatic targeting specificity, increasing efforts focus on engineering nanoparticle surfaces with ligands that promote selective adsorption of apolipoproteins such as ApoE. For instance, Johnson et al. [69] synthesized two structurally similar lipids, 5A2-SC8 and 3A5-SC14, and formulated them into

LNPs. The latter, with an alkyl tail length of 14 carbons compared to 8 carbons in 5A2-SC8 and differing in hydrophobic branching, exhibited distinct serum protein binding properties, leading to surface enrichment of albumin but a lack of ApoE, which facilitated uptake by Kupffer cells. In hepatocellular carcinoma treatment experiments, 5A2-SC8 LNPs effectively delivered RNA to hepatocytes, prolonging survival in MYC-driven liver cancer mouse models, whereas 3A5-SC14 LNPs showed limited efficacy, highlighting the critical role of ionizable amino lipid chemical structures in liver targeting (Figs. 6(a) and 6(b)). Su et al. [70] conducted a series of experiments, designing a library of ionizable cationic lipids (nAcx-Cm) with degradable cores. Through orthogonal optimization in ovarian cancer cell lines and *in vivo* studies, they found that the branching and tail chain types of nAcx-Cm lipids influenced LNP-mRNA performance, with multi-branched single-tail lipids exhibiting higher mRNA delivery efficiency. Adjusting LNP components revealed that 3-Comp LNPs, devoid of cholesterol and phospholipids, could control targeted mRNA accumulation and translation in the liver and lungs, while cholesterol removal reduced liver accumulation, enabling effective lung targeting (Figs. 6(c) and 6(d)).

Parrett et al. [71] constructed luciferase mRNA plasmids containing varying numbers and positions of miR-122 binding sites. By incorporating miR-122 binding sites into mRNA, they leveraged RNA interference mechanisms to regulate liver-targeted expression, thereby mitigating off-target expression in the liver during non-liver tissue treatments. Gao et al. [72] investigated the role of PEGylation in lipid nanoparticle-mediated mRNA delivery to the liver (Figs. 7(a) and 7(b)). They discovered that simply altering the terminal groups of PEGylated lipids from methoxy to carboxyl or amino groups, as in DSPE-COOH LNPs and DSPE-NH2 LNPs, significantly enhanced liver delivery. This effect was attributed to accelerated dePEGylation rates and enhanced LNP-cell interactions facilitated by the modified terminal groups (Figs. 7(c) and 7(d)).

4.2 Lung targeting

4.2.1 *Physiological characteristics of the lung*

The lung, with its vast surface area (approximately 70–100 m^2), ultrathin epithelial barrier (0.2–0.5 μm), abundant blood supply, and avoidance of first-pass metabolism, offers unique advantages for drug delivery [73]. These physiological characteristics provide ideal conditions for efficient drug absorption and localized action, yet the lung's complex structure also poses significant challenges. For instance, the air-blood barrier, composed of alveolar epithelium, basement membrane, and capillary endothelium, facilitates rapid absorption of small-molecule drugs (e.g., bronchodilators), but the delivery of large-molecule drugs (e.g., proteins) often requires the aid of nanocarriers to achieve effective permeation [74]. The mucus layer, consisting of mucins and water, can prolong drug retention time, but its high viscosity impedes drug diffusion, particularly posing a significant barrier to the delivery of macromolecular drugs and nanoparticles [75]. Ciliary motion, which propels the mucus layer toward the throat, forms the "mucociliary clearance mechanism". While this mechanism aids in the removal of foreign particles, it also rapidly clears drug particles deposited on the respiratory surface, thereby shortening drug action duration. Besides, pulmonary surfactant, a phospholipid-protein complex covering the alveolar surface, not only reduces surface tension and prevents alveolar collapse but also promotes drug diffusion and absorption across the alveolar surface. Leveraging this property, biomimetic surfactant-based nanocarriers have been developed to enhance drug delivery efficiency [76]. Additionally, alveolar macrophages, as a critical component of the pulmonary immune system, can clear foreign particles and pathogens, but their phagocytic activity toward nanoparticles may lead to drug degradation or inactivation [77].

4.2.2 *Lung organ-selective targeting strategies*

Inhalation delivery, a method of administering drugs or vaccines

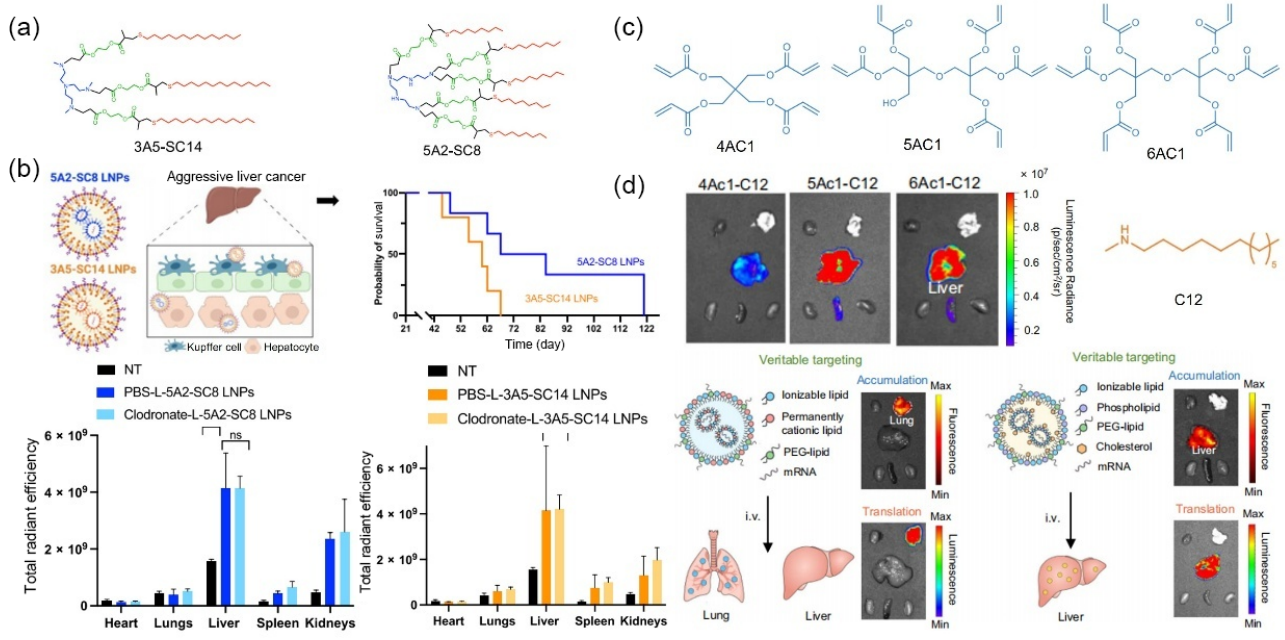

Figure 6 (a) Molecular structure, (b) carrier construction, survival curves and targeting of 5A2-SC8 and 3A5-SC14 in mice. Reproduced with permission from Ref. [69], © American Chemical Society 2022. (c) Structure, (d) targeting situation of three nAcx-Cm targeting molecules and changes of targeted organs with or without cholesterol. Reproduced with permission from Ref. [70], © Su, K. X. et al. 2024.

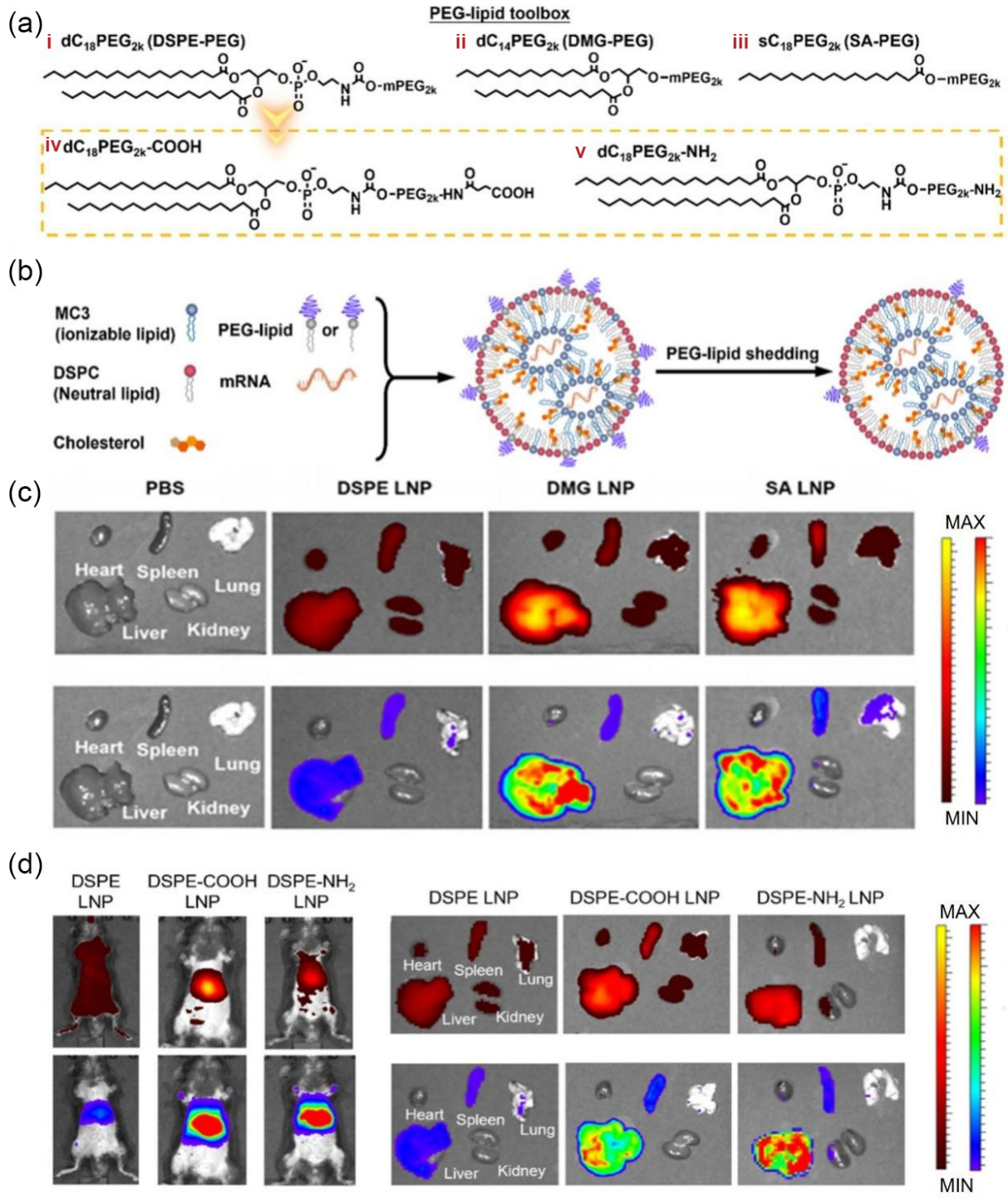

Figure 7 (a) The structure of different PEGs. (b) LNP construction diagram. (c) Biological distribution of different LNPS (Dir). (d) Effects of different PEG ends on biological distribution DiR fluorescence (top) and Fluc bioluminescence (bottom). Reproduced with permission from Ref. [72], © American Chemical Society 2025.

through the respiratory tract to target the lungs or systemic circulation, offers significant advantages such as direct action on the target site and reduced systemic side effects [78]. In the field of RNA therapeutics, inhalation delivery has demonstrated considerable potential. For instance, Liu et al. [79] conducted a series of experiments in which they developed a charge-assisted stabilization (CAS) strategy to prepare CAS-LNPs, which maintain stability during nebulization and efficiently deliver mRNA to the lungs. In studies on COVID-19 vaccines and cancer vaccines, the delivery of relevant mRNA via CAS-LNPs showed remarkable efficacy in inducing immune responses and inhibiting tumor metastasis, providing a critical foundation for the development of inhalable mRNA vaccines and therapies (Figs. 8(a) and 8(b)).

In addition to inhalation delivery, significant progress has been made in intravenous injection-based drug delivery, leveraging endogenous targeting strategies.

The research of Qiu and his colleagues [16] shows that the *in vivo* targeting specificity of lipid nanoparticles is intricately linked to

their chemical structure, primarily mediated through the regulation of the "protein corona" composition. Research has demonstrated that minimal alterations in the LNP tail linker can drastically alter organ tropism: O-series LNPs, containing an ester bond, tend to enrich ApoE on their surface, which mediates liver targeting via interaction with the low-density lipoprotein receptor on hepatocytes. In contrast, N-series LNPs, featuring an amide bond, preferentially adsorb coagulation-related proteins, notably fibrinogen. This distinct protein corona promotes the retention and uptake of LNPs by the pulmonary vasculature endothelium, enabling efficient lung targeting. Furthermore, on the foundation of organ targeting (e.g., the lungs), fine-tuning the headgroup structure of the lipids allows for precise modulation of cellular subtype specificity. Different headgroups facilitate the adsorption of unique sets of plasma proteins recognizable by specific receptors on pulmonary endothelial cells, epithelial cells, or macrophages, thereby directing LNP delivery to particular cell populations. This mechanism, wherein chemical structure dictates protein corona formation, which in turn dictates both organ and cellular selectivity, provides a crucial theoretical foundation for the rational design of delivery systems for precision medicine (Fig. 8(c)). Li et al. [80], through high-throughput screening, developed an LNP structure capable of efficient delivery and gene editing in the lungs. The lead formulation, RCB-4-8, is a sophisticated four-component system comprising a novel biodegradable ionizable lipid (also named RCB-4-8, featuring a headgroup-linker-tail structure with ester/carbonate bonds for enhanced biodegradability), a helper phospholipid (DOTAP, which replaced the initially used DOPE to improve pulmonary cell internalization and mucus retention), cholesterol, and a PEG-lipid (DMG-PEG2000). This optimally designed LNP, formulated via microfluidic mixing, demonstrated superior mRNA encapsulation, efficient endosomal escape, and potent transfection in lung epithelial cells, including club and ciliated cells (Fig. 8(d)).

Chen et al. [81] developed a class of crown-like biodegradable ionizable lipids based on a metal coordination chemistry design strategy. These lipids feature a core crown ether-amino headgroup that can coordinate with specific metal ions, thereby systematically modulating the *in vivo* targeting behavior of lipid nanoparticles. Studies demonstrate that coordination with ions such as zinc can redirect the tropism of lipid nanoparticles from the liver to the lungs, enabling highly efficient protein expression and gene editing in pulmonary epithelial cells. This mechanism aligns with the process where cationic lipids attract vitronectin and other proteins to form a protein corona that specifically targets the lungs, thereby offering new design principles for cationic lipids in endogenously targeted LNP systems (Fig. 9(a)).

Based on the SORT technology, Fei et al. [82] successfully developed a novel three-component simplified targeted LNP through systematic streamlining of lipid composition. The core of this strategy lies in eliminating non-essential auxiliary components from traditional LNPs, constructing a minimal functional unit composed solely of an ionizable lipid, a PEG lipid, and a targeting lipid. The study confirmed that simply adjusting the type of targeting lipid (cationic, anionic, or neutral) can precisely program the organ targeting specificity of LNPs, enabling targeted delivery to the lungs, spleen, or liver, which aligns with previous research findings [30]. This simplified LNP platform not only significantly enhances the delivery efficiency and targeting specificity of mRNA but also substantially reduces formulation complexity, providing a new pathway for LNP development characterized by strong versatility and high efficiency (Figs. 9(b) and 9(c)).

4.3 Spleen targeting

4.3.1 Physiological characteristics of the spleen

The spleen, as the largest secondary lymphoid organ in the human body, plays a pivotal role in immunity, hematopoiesis, and blood storage, with its unique physiological characteristics holding significant implications for drug delivery. Structurally, the spleen is composed of white pulp, red pulp, and the marginal zone. The white pulp contains T-cell and B-cell zones, which govern cellular and humoral immunity, respectively; the red pulp is responsible for blood filtration and the clearance of senescent red blood cells; and the marginal zone serves as a reservoir for various immune cells [83]. These structural features make the spleen a critical site for immune responses and provide unique targets and environments for drug delivery. From a functional perspective, the spleen is capable of initiating immune responses, defending against pathogens through cellular and humoral immune mechanisms, while also clearing senescent red blood cells, storing blood, and contributing to hematopoiesis under specific conditions [84].

4.3.2 Spleen organ-selective targeting strategies

In the field of drug delivery, numerous studies have focused on enhancing the targeting efficiency and therapeutic efficacy of drugs in the spleen. For instance, Wang et al. [85] developed a nucleic acid delivery carrier based on metal-organic frameworks (MOFs), encapsulating plasmids within nanoscale zeolitic imidazolate frameworks (ZIFs). Leveraging passive targeting, these nanoparticles accumulated in the spleen, with experiments demonstrating high transfection efficiency *in vitro*, primarily through clathrin-mediated and caveolae-mediated endocytosis. *In vivo*, 46% of the nanoparticles accumulated in the spleen, significantly surpassing liposomes, successfully delivering plasmids to extrahepatic organs such as the spleen for protein synthesis and inducing immune responses (Figs. 10(a) and 10(b)). Ren et al. [86] synthesized a series of ionizable lipids with varying head and tail group combinations, formulating them into LNPs. Through *in vitro* and *in vivo* experiments, they found that lipids with branched tail groups (e.g., A28-C6B2) significantly enhanced selective mRNA delivery to the spleen, achieving efficient mRNA expression in the spleen and effectively targeting mRNA delivery to antigen-presenting cells, offering potential applications for immunotherapy (Figs. 10(c) and 10(d)).

Liu et al. [87] designed and synthesized ionizable cholesterol analogs, incorporating them as a fifth component into traditional commercial LNPs. Their research demonstrated that adjusting the proportion of this component enabled targeted mRNA delivery to the spleen and lungs, with the 0315-Ergo–40% formulation achieving up to 95% delivery efficiency to the spleen (Figs. 11(a) and 11(b)). Jiang et al. [88] developed reactive oxygen species (ROS)-responsive poly(β-amino ester) (PBAE) nanoparticles, 93-TKA10-19, which were validated *in vivo* to specifically deliver mRNA to antigen-presenting cells in the spleen, effectively expressing mRNA and inducing a Th1-biased immune response (Figs. 11(c) and 11(d)).

In contrast to liver-targeting LNPs enriched with ApoE and lung-targeting LNPs enriched with vitronectin (Vtn), mass spectrometry analysis reveals that the most enriched protein in spleen-targeting SORT LNPs is β2-glycoprotein I (β2-GPI), accounting for up to 20.1% of the corona composition—a 125-fold enrichment over its level in plasma. This finding is further supported by the work of

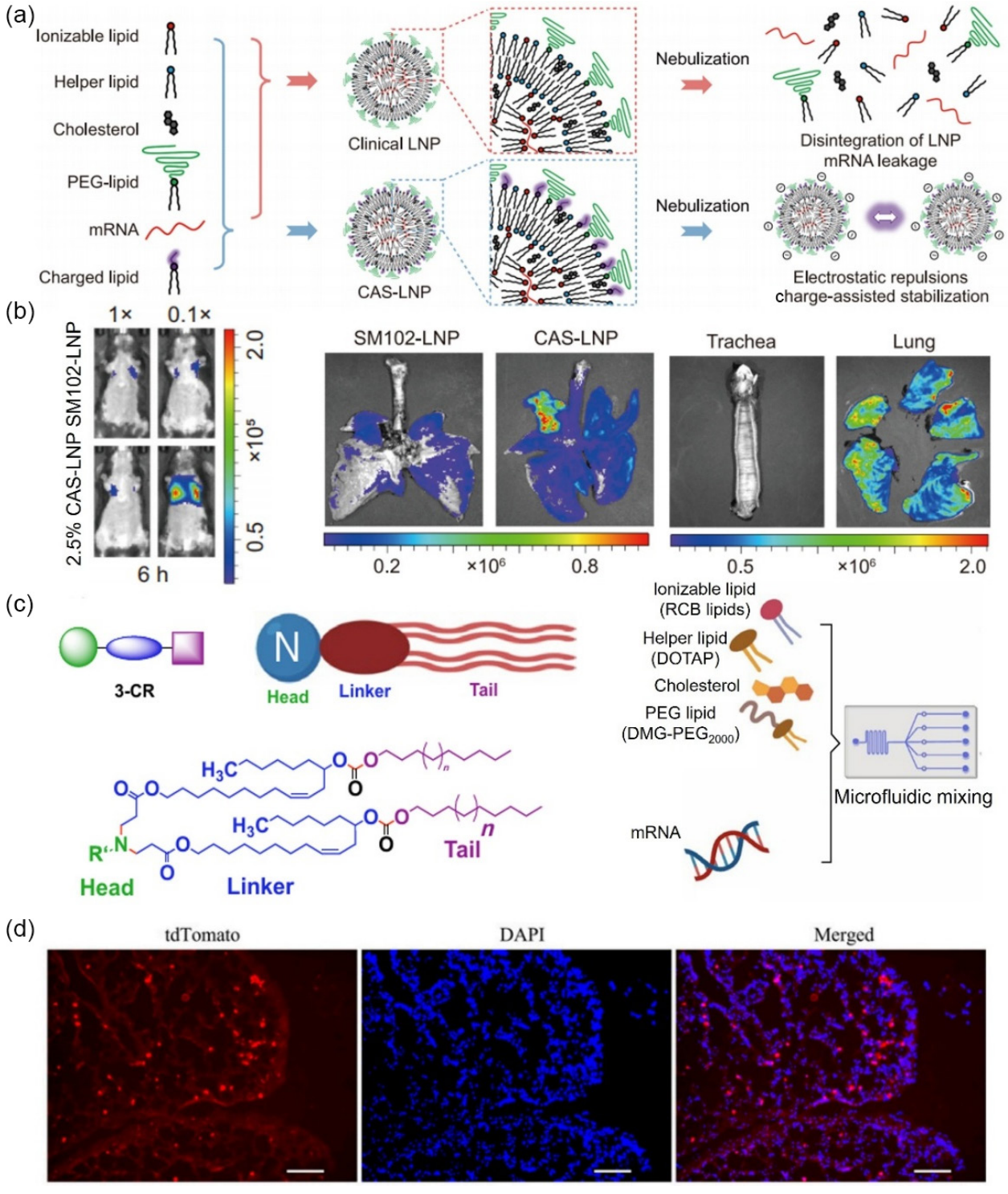

Figure 8 (a) LNP designed by Liu et al. (b) *In vivo* delivery and organ *in vitro* images. Reproduced with permission from Ref. [79], © Liu, S. et al. 2024. (c) Schematic diagram of ionizable lipids by Li et al. Reproduced with permission from Ref. [80], © Li, B. W. et al. under exclusive licence to Springer Nature America, Inc 2023. (d) Fluorescence images of lung sections. Reproduced with permission from Ref. [16], © This article is distributed under Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND) 2022.

Isaac et al. [89], who focused on modifying the auxiliary components of LNPs by completely replacing cholesterol with structurally similar endogenous corticosteroids (such as corticosterone and progesterone), leading to the development of a novel class of endogenous corticosteroid-derived LNPs. This design significantly alters the *in vivo* fate of LNPs, effectively redirecting them from predominant liver accumulation to the spleen, achieving remarkable spleen selectivity as high as 97%–99%. Mechanistic studies reveal that this splenic targeting is not mediated by traditional ligand–receptor interactions but stems from an endogenous protein corona reprogramming mechanism: the corticosteroid-modified LNPs specifically adsorb β2-GPI in the

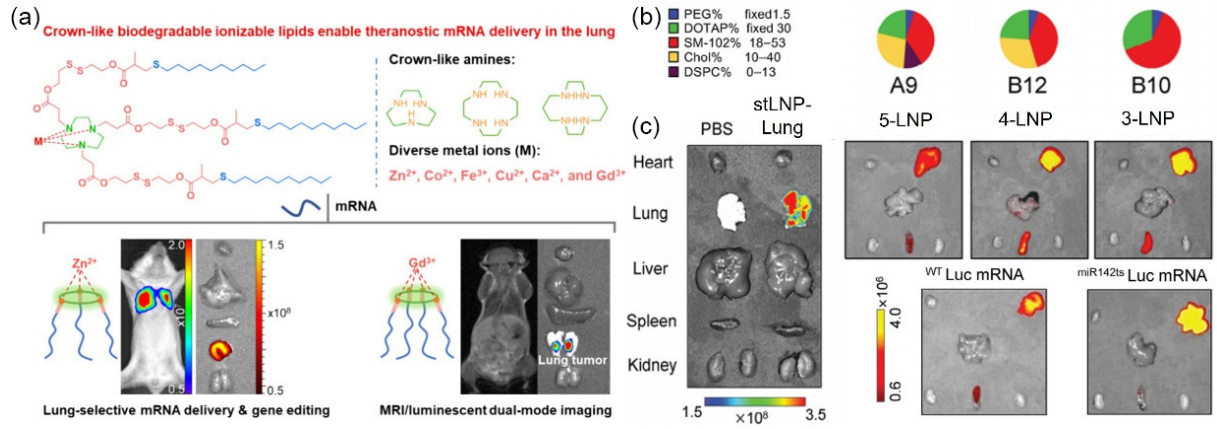

Figure 9 (a) Structural design of CBILs and mouse fluorescence imaging and organ images *in vitro*. Reproduced with permission from Ref. [81], © American Chemical Society 2024. (b) LNP design and (c) *in vitro* organ images by Fei et al. Reproduced with permission from Ref. [82], © Wiley-VCH GmbH 2024.

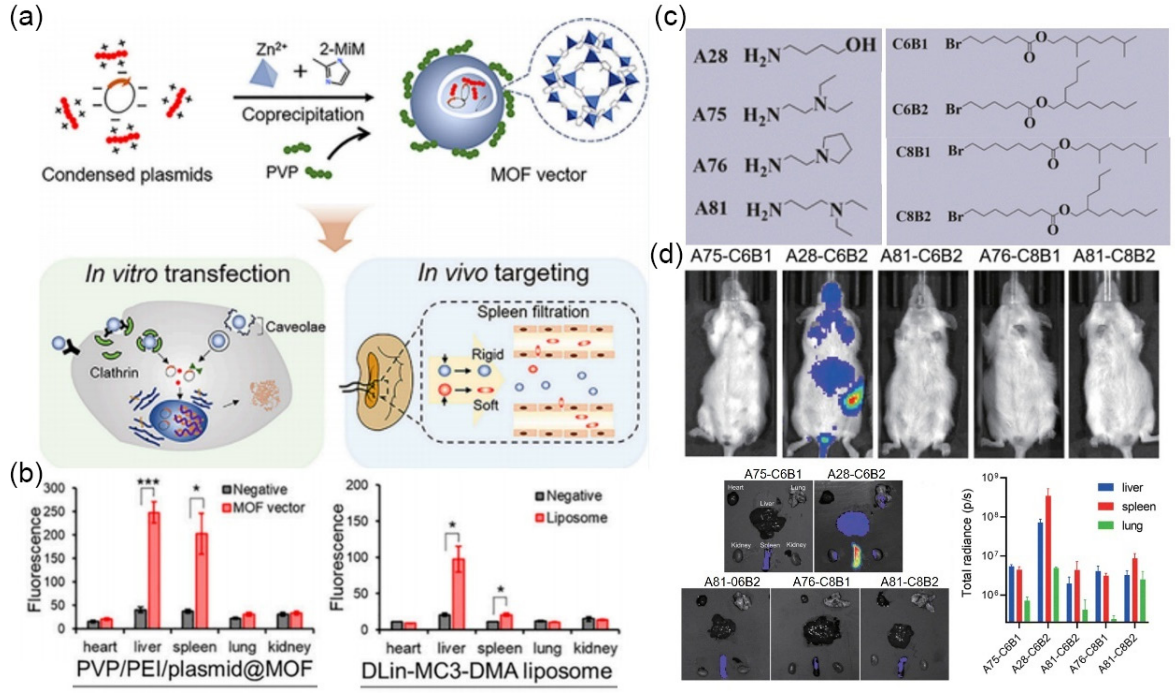

Figure 10 (a) Schematic diagram of spleen targeting nucleic acid vector based on MOFs, (b) targeting situation (compared with Dlin-MC3-DMA liposome) and (c) various ionizable liposome structures. Reproduced with permission from Ref. [85], © American Chemical Society 2024. (d) *In vivo* imaging system (IVIS) imaging of mice after intravenous LNP injection and *in vitro* images, and mRNA expression quantification of major organs of mice treated with LNP. Reproduced with permission from Ref. [86], © The Royal Society of Chemistry 2024.

systemic circulation, which acts as an "endogenous navigation signal" promoting efficient uptake by splenic antigen-presenting cells (such as dendritic cells). Notably, this strategy demonstrates significant platform versatility, enabling liver-to-spleen redirection in LNPs composed of various clinically validated ionizable lipids (e.g., MC3 and ALC-0315), thereby offering a universal new approach for developing spleen-targeted mRNA therapies for immunotherapy, vaccination, and gene editing.

Simultaneously, inspired by "comb-like polymers", Xue et al. [90] innovatively designed a "dendron-like" ionizable lipid featuring a polyamine head and multiple branched alkyl tails. This unique multi-arm branched structure not only enhances mRNA encapsulation and endosomal escape efficiency but, more importantly, alters the surface properties of the LNPs, enabling them to specifically adsorb key proteins associated with hematopoiesis and transport—such as integrin α2b (Itga2b)—*in vivo*. This forms a distinctive protein corona that endogenously navigates the LNPs to the spleen and facilitates efficient transfection of red pulp macrophages (RPM). The underlying mechanism involves the adsorption of the key protein Itga2b, which is predominantly expressed on the surface of platelets and megakaryocytes. This directs the LNPs to the spleen—an organ rich in platelets and macrophages—via a platelet-mediated mechanism.

4.4 Targeting of other organs

In addition to the liver, lungs, and spleen, significant progress has also been made in targeting strategies for other organs. Rampado et al. [91] increased the molar percentage of the helper lipid DSPC in LNPs, which, upon intravenous injection, demonstrated natural targeting to the colon in both healthy and colitis-afflicted mice. This

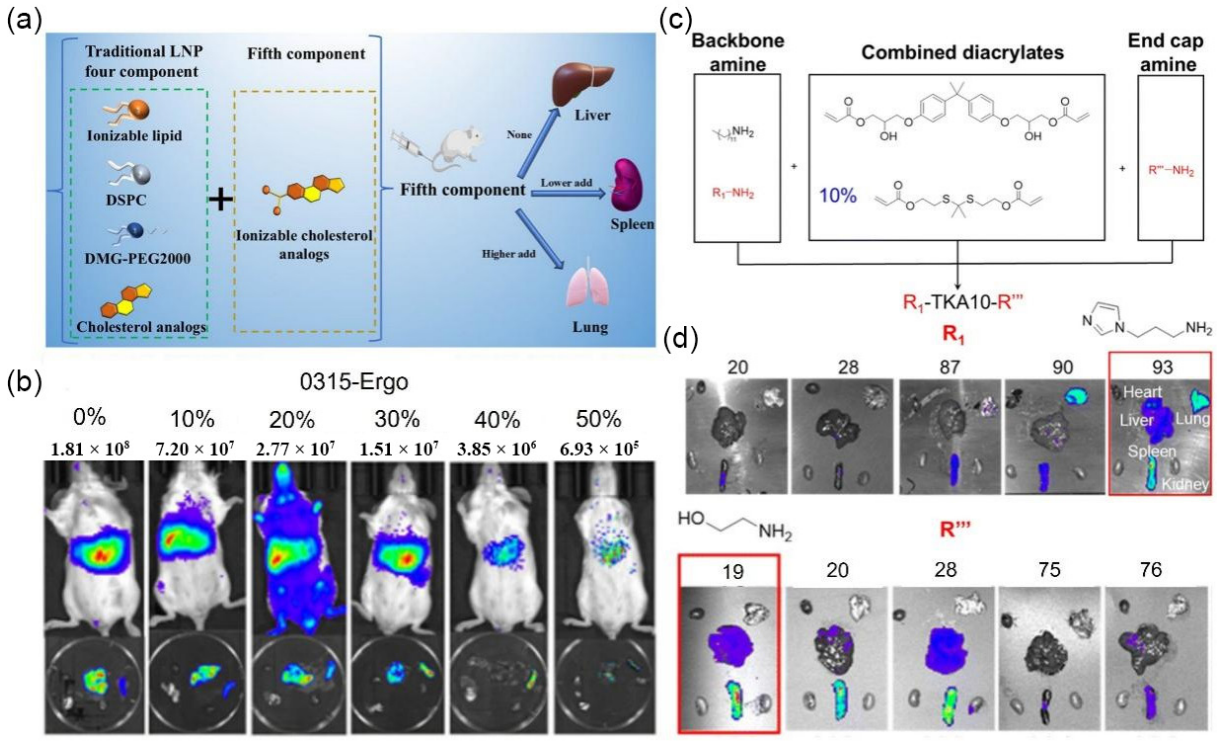

Figure 11 (a) LNP schematic diagram designed by Liu et al., and (b) *in vivo* delivery results. Reproduced with permission from Ref. [87], © American Chemical Society 2025. (c) Schemes for backbone and end cap amine in PBAEs. (d) The targeting ability of different backbone and end cap amine. Reproduced with permission from Ref. [88], © The Royal Society of Chemistry 2025.

approach significantly enhanced colonic mRNA expression under inflammatory conditions while reducing off-target accumulation in the liver and spleen. Treatment of colitis mice with 30-n-LNPs carrying interleukin-10-encoding mRNA effectively reduced levels of key inflammatory cytokines (Figs. 12(a) and 12(b)). Eygeris et al. [92] investigated thiophene-containing ionizable lipids (Thio-lipids), synthesizing 47 such lipids and formulating them into LNPs. Experiments revealed that lipid 20b enabled LNPs to transfect the liver and spleen, while lipid 29d facilitated transfection in the lungs and spleen. Notably, lipid 20b demonstrated efficient retinal mRNA delivery in both mice and non-human primates, successfully transfecting photoreceptors and retinal pigment epithelial cells without acute toxicity, offering a novel approach for mRNA-based treatment of retinal diseases (Figs. 12(c) and 12(d)).

Liu et al. [93] synthesized zwitterionic phospholipidated polymers (ZPPs) through zwitterionic phospholipidation of cationic polymers. *In vivo* studies showed that intravenous injection of ZPPs effectively delivered mRNA to the spleen and lymph nodes, with PA6-4P14 inducing high mRNA expression in the spleen and various lymph nodes (e.g., iliac, axillary, and mesenteric lymph nodes) while transfecting multiple immune cell types, providing a potential strategy for cancer immunotherapy and vaccine development (Figs. 13(a) and 13(b)). Vaidya et al. [94] optimized siRNA-selective organ-targeting lipid nanoparticles (siRNA SORT LNPs), which delivered functional siRNA to extrahepatic tissues such as the kidneys in mice, achieving significant silencing of tissue-enriched endogenous targets. This approach resulted in a 60% silencing rate of endogenous targets in the kidneys, with a dual-dosing regimen at 48-h intervals increasing the target gene silencing rate to 73% (Fig. 13(c)).

Notably, under the challenge of numerous neurological disorders, brain targeting has gradually become a key focus and a major challenge in LNP research. The primary difficulties in delivering LNPs to the brain include the following: after intravenous injection, the accumulation of LNPs in the liver limits the amount of drug that reaches the blood-brain barrier (BBB), with over 80% of the injected dose accumulating in the liver [95]; the limited penetration capability of LNPs across the BBB results in very low delivery efficiency (< 1% of the injected dose) [96]; additionally, protein corona adsorption introduces further interference. Han et al. [97] designed a peptide-functionalized lipid nanoparticle (pLNPs) platform by modifying the LNP surface with four targeting peptides (RVG29, T7, AP2, and mApoE) via click chemistry to achieve systemic mRNA delivery to the brain (Fig. 14(a)). Their study demonstrated *in vitro* that peptide functionalization significantly enhances transfection efficiency in BBB endothelial cells and neurons while reducing liver accumulation. Tong et al. [98] systematically investigated the influence of polyethylene glycol-lipid (PEG-lipid) anchor chain length (C14, C16, C18) as a key design parameter on the performance of LNPs for brain-targeted siRNA delivery (Fig. 14(b)). They found that longer PEG-lipid anchor chains (such as DSPE-PEG or DSG-PEG with C18) significantly prolong the blood circulation half-life of LNPs, reduce liver uptake, and effectively increase LNP accumulation in brain tissue by enhancing efflux efficiency and transcytosis in BBB endothelial cells. In an orthotopic glioblastoma model, LNPs with longer anchor chains exhibited stronger tumor accumulation and more efficient siRNA-mediated gene silencing. Mor Sela and colleagues [99] developed a modular and predictable brain-targeted mRNA delivery system by designing a series of PEG-lipid conjugates modified with small molecules known to interact with the BBB (such as glucose,

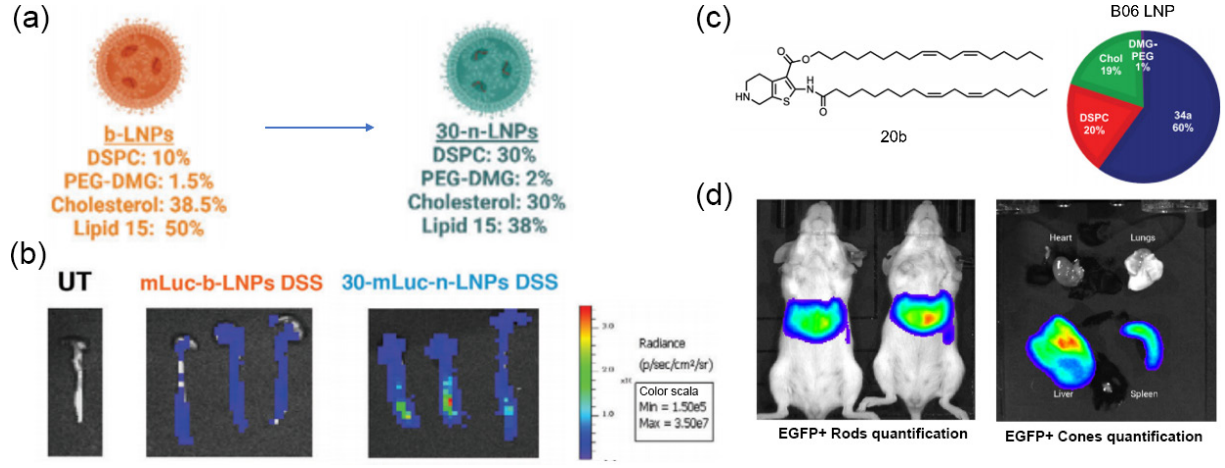

Figure 12 (a) LNP component optimization, (b) colonic stereofluorescence images by Rampado et al. Reproduced with permission from Ref. [91], © Rampado, R. et al. Advanced Science published by Wiley-VCH GmbH 2024. (c) Lipid 20b structure and group allocation ratio. (d) The targeting ability of 20b LNP to the lung and the delivery of specific cells in the retina. Reproduced with permission from Ref. [92], © Eygeris, Y. et al. Published by PNAS 2024.

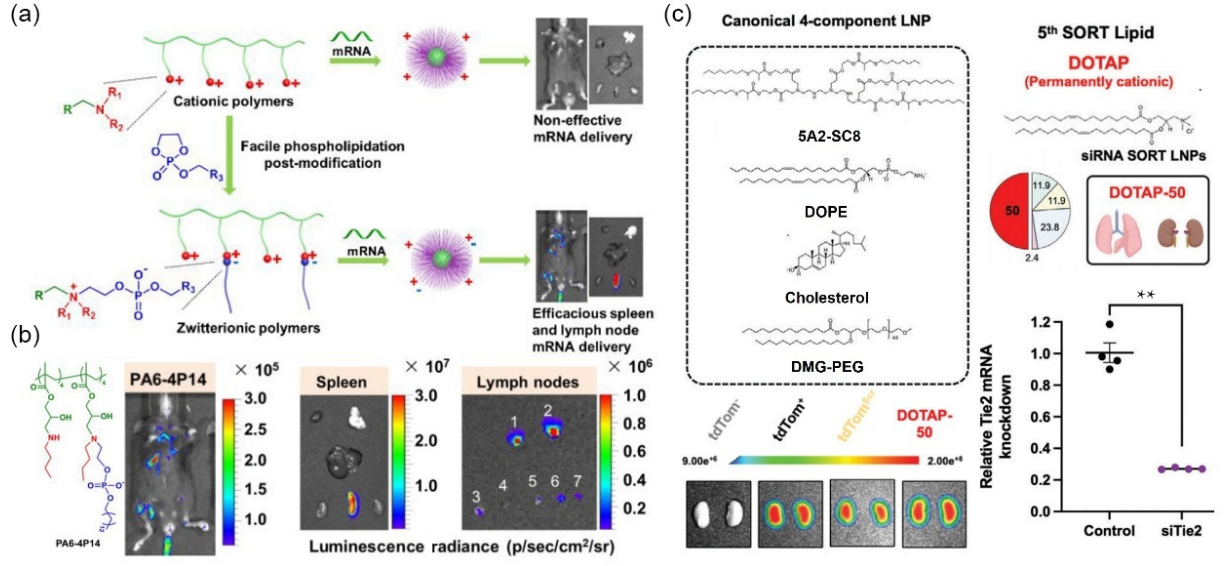

Figure 13 (a) Structure of zwitterionic phospholipidated polymers. (b) I*n vivo* delivery, and fluorescence images of organs *in vitro*. Reproduced with permission from Ref. [93], © American Chemical Society 2021.(c) LNP designed by Vaidya et al. and knockdown of targeted genes in the kidney. Reproduced with permission from Ref. [94], © Vaidya, A. et al. Advanced Materials published by Wiley-VCH GmbH 2024.

nicotine, acetylcholine, etc.) and integrating them into LNPs (Fig. 14(c)). The study further employed a graph neural network (GNN) AI model to predict the BBB permeability of these small molecules, demonstrating strong agreement between computational predictions and experimental data.

4.5 Precise targeting of specific cells and organelles

Recent years have witnessed remarkable advancements in cellular and organelle-targeted delivery technologies for disease therapeutics. Hofstraat et al. [100] developed an apolipoprotein nanoparticle (aNP) platform leveraging natural lipoprotein transport mechanisms, constructing a library of 72 aNPs through optimization of phospholipid, cholesterol, tricaprylin, and ionizable lipid MC3 formulations, with aNP18 identified as a potent silencer of lysosomal-associated membrane protein 1 (LAMP1). This carrier achieves specific gene silencing (e.g., LAMP1 and CCR2) in myeloid cells and hematopoietic progenitors via apolipoprotein A1-mediated binding to surface receptors, effectively reducing immunosuppressive monocyte infiltration in tumor models (Figs. 15(a) and 15(b)).

Meanwhile, Y. Xu et al. [101] engineered a core framework comprising cationic lipids (DOTMA and DDAB), helper lipid DOPE, and cholesterol (CHO), electrostatically and hydrophobically loaded with tumor-specific neoantigens and cholesterol-conjugated adjuvant (CHO-CpG). Following intravenous administration, the system preferentially accumulates in the spleen and tumor tissues, then targets antigen-presenting cells (APCs) such as dendritic cells (DCs) and macrophages via CD205 receptor-mediated endocytosis. This dual-action strategy activates systemic immune responses through splenic DCs while promoting M1 macrophage polarization within tumors to remodel immunosuppressive microenvironments (Figs. 16(a)–16(c)). X. Lian et al. [102] developed a series of LNPs with bone marrow-homing capability. Their core strategy involves incorporating 20 mol% of covalent lipid species (e.g., NHS ester-based lipids) as a fifth component into the classical four-component LNP

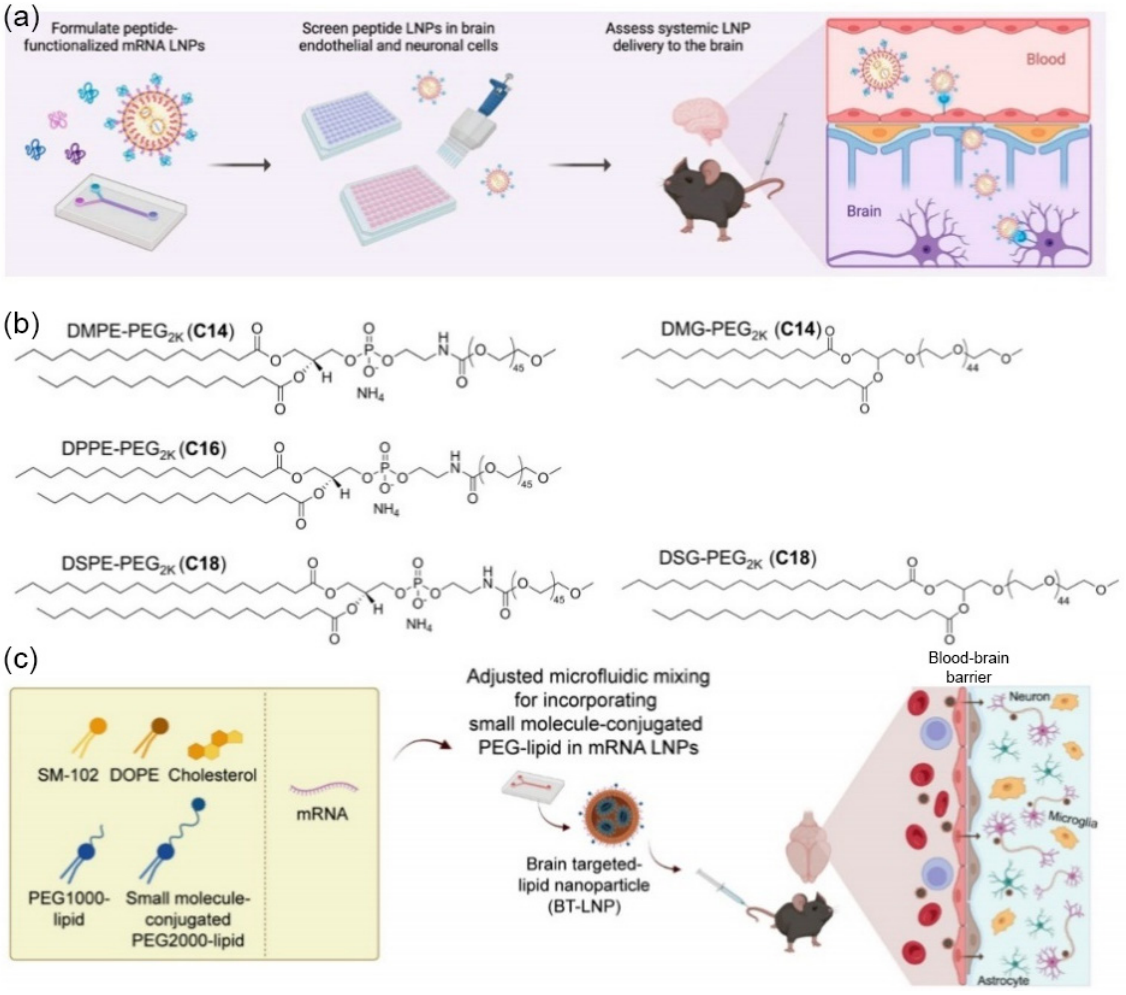

Figure 14 (a) Process of engineering and validating targeted LNPs for brain delivery following systemic administration. Reproduced with permission from Ref. [97], © American Chemical Society 2024. (b) Chemical structure of five different PEG-lipids. Reproduced with permission from Ref. [98], © Acta Materialia Inc. Published by Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies 2025. (c) mRNA LNPs were formulated with a BBB-interacting small molecule-conjugated PEG-lipid using optimized microfluidic mixing to enable BBB crossing. Reproduced with permission from Ref. [99], © Sela, M. et al. Published by American Chemical Society 2025.

formulation, endowing the LNPs with potent bone marrow targeting ability (Fig. 16(d)). Enrichment of ApoE in the LNP surface protein corona enables this delivery system to efficiently and broadly transport mRNA to at least 14 distinct cell types in the bone marrow, including healthy and diseased hematopoietic stem cells, progenitor cells, B cells, T cells, macrophages, and leukemia stem cells. In a sickle cell disease mouse model, the system mediated CRISPR/Cas9 and base editor-mediated editing of disease-causing genetic loci, while in an aggressive acute myeloid leukemia model, it achieved Cre recombinase-mediated gene deletion in leukemia stem cells.

5 Existing challenges and clinical applications

5.1 Approved drugs and progress in clinical trials

Since the Food and Drug Administratioin (FDA) approval of Onpattro, the first LNP-based siRNA drug, in 2018, lipid-based delivery strategies have experienced rapid clinical advancement. In 2021, mRNA vaccines targeting COVID-19, such as the LNP-based mRNA vaccine BNT162b2 developed jointly by Pfizer and BioNTech, also received FDA approval. Similar to mRNA-1273, BNT162b2 utilizes ionizable lipid nanoparticles to deliver mRNA encoding the SARS-CoV-2 spike protein, demonstrating approximately 95% continued efficacy in Phase III clinical trials and inducing robust immune responses.

In the realm of clinical translation of cationic lipid nanoparticles, BioNTech SE has demonstrated significant technological leadership. Its dual-platform approach, comprising FixVac (fixed antigen vaccine) and iNeST (individualized neoantigen-specific therapy), both based on lipid nanoparticle-mediated mRNA delivery, has propelled multiple drug candidates into Phase II clinical trials. These include BNT111 (NCT04526899) targeting melanoma-associated antigens, BNT113 (NCT03418480, NCT04534205) for HPV16-positive solid tumors, BNT115 (NCT04163094) as an ovarian cancer-specific vaccine, and individualized neoantigen vaccines BNT116 (NCT05142189 and NCT05557591) and BNT122 (NCT04813627 and NCT04486378). These advancements underscore the efficacy of cationic lipid nanoparticles in navigating the complex tumor microenvironment for targeted delivery.

Concurrently, other enterprises have achieved groundbreaking

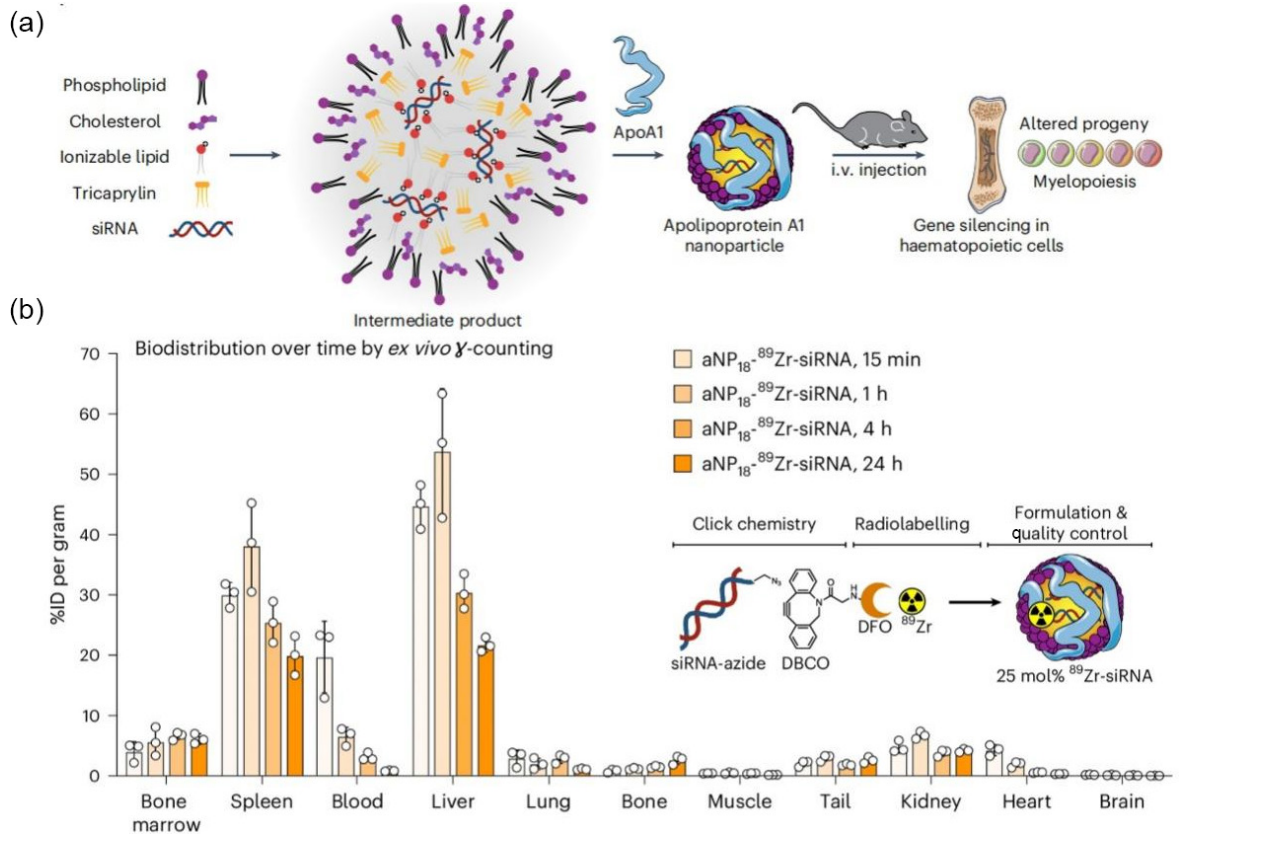

Figure 15 (a) LNP design and silencing of target genes in specific cells by Hofstraat et al. (b) Biological distribution of LNP after different time of intravenous administration. Reproduced with permission from Ref. [100], © Hofstraat, S. R. J. et al. 2025.

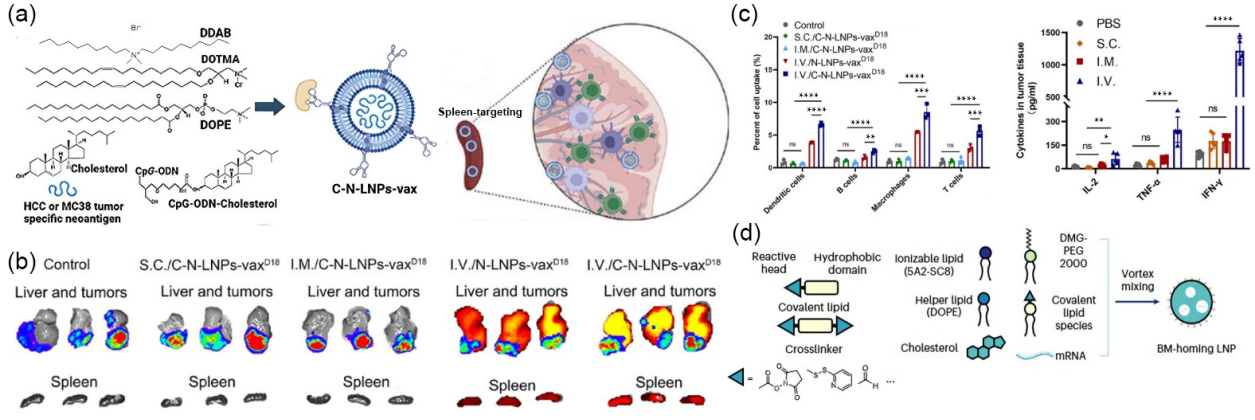

Figure 16 (a) C-N-LNPs-vax targets tumor and spleen antigen-presenting cells. (b) The efficient targeting ability of C-N-LNPs-vaxD18 in the spleen and tumor tissues through i.v. injection. (c) Uptake of C-N-LNPS-Vax by the same immune cells and significantly increased levels of cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2). Reproduced with permission from Ref. [101], © Xu, Y. et al. Advanced Science published by Wiley-VCH GmbH 2025. (d) Design of LNP vectors targeting the bone marrow. Reproduced with permission from Ref. [102], © Lian, X. et al. under exclusive licence to Springer Nature Limited 2024.

progress in LNP-mediated delivery. Moderna Inc's COVID-19 vaccine mRNA-1273 (NCT04470427), utilizing SM-102 cationic lipid-based complexes, demonstrated rapid immune responses via intramuscular administration and secured emergency use authorization. Its pipeline further encompasses mRNA vaccines targeting influenza (mRNA-1440, NCT03076385; mRNA-1851, NCT03450443), and Zika virus (mRNA-1893, NCT04064905), all advancing to Phase I/II trials through LNP technology. CureVac developed rabies vaccine CV7202 (NCT03713086) and COVID-19 vaccine CVnCoV (NCT04652102), the latter of which validated the stability and immunogenicity of LNP-delivered mRNA in Phase II/III trials. Translate Bio and MiNA Therapeutics Limited expanded LNP applications to genetic disorders: MRT5005 (NCT03375047) employs inhaled LNPs to deliver cystic fibrosis transmembrane conductance regulator (CFTR) mRNA for cystic fibrosis, while MTL_501 (NL-OMON51314) utilizes siRNA-loaded LNPs targeting the CEBPA gene for hepatocellular carcinoma. Additionally, Dicerna Pharmaceuticals Inc.'s DCR-HBVS (NCT03772249), leveraging LNPs to deliver siRNA targeting HBV genes, offers novel therapeutic avenues for hepatocellular

Table 1 Representative LNP clinical trials[a]

Name	Clinical trial indentifer	Sponsoring institution	Indication	Therapeutic mechanism	Phase
BNT111	NCT04526899	BioNTech RNA Pharmaceuticals GmbH	Malignant melanoma stage III/IV	Programmed cell death protein 1 inhibitor	II
BNT113	NCT04534205 NCT03418480	BioNTech RNA Pharmaceuticals GmbH	Squamous cell carcinoma and other tumors	Human papillomavirus E6/E7 protein modulator	II
BNT116	NCT05557591	BioNTech	Non-small cell lung cancer metastatic	Programmed cell death protein 1 inhibitor	II
BNT122	NCT03289962	BioNTech RNA Pharmaceuticals GmbH	Transitional cell carcinoma and other tumors	/	II
mRNA-1273	NCT05119855 NCT05249829	Moderna Inc.	COVID-19	COVID19 spike glycoprotein modulator	Approved
mRNA-1440	NCT03076385	Moderna Inc.	Influenza H10N8	/	I
mRNA-1851	NCT03345043	Moderna Inc.	Influenza H7N9	/	I
mRNA-1893	NCT04917861	Moderna Inc.	Zika virus infection	/	II
CV7202	NCT03713086	CureVac NV	Rabies virus infection	/	I
CVnCoV	NCT04652102	CureVac NV	COVID-19	COVID19 spike glycoprotein modulator	II/III
MRT-5005	NCT03375047	Translate Bio MA Inc.	Cystic fibrosis	CFTR gene modulator	II
MTL-501	NL-OMON51314	MiNA Therapeutics Limited	Hepatocellular carcinoma	CCAAT enhancer binding protein alpha gene stimulator	II
DCR-HBVS	NCT03772249	Dicerna Pharmaceuticals Inc.	Hepatitis B	/	I
ALN-TTR02	NCT01960348	Alnylam Pharmaceuticals Inc.	Transthyretin amyloid cardiomyopathy, familial amyloid polyneuropathy	Amyloid protein deposition inhibitor, transthyretin (TTR) gene inhibitor	Approved
MTS-105	NCT06689540	METiS Therapeutics Inc.	Hepatocellular carcinoma	CD3 modulator, glypican-3 modulator	I
YOLT-201	NCT06539208	Yoltech Therapeutics Co., Ltd.	Familial amyloid polyneuropathy, transthyretin amyloid cardiomyopathy	/	II

[a]Pharnex Dataverse. (n.d.). *Pharmaceutical industry datasets*. Retrieved January 30, 2026, from https://data.pharnexcloud.com/.

carcinoma and hepatitis B.

These multifaceted clinical trials, encompassing a spectrum of therapeutic indications spanning oncology, infectious diseases, genetic disorders, and metabolic conditions, not only underscore the versatility of LNP-based delivery systems but also reveal their formidable potential in biomedicine through diverse administration modalities—including intravenous, intramuscular, inhalational, and intratumoral routes—thereby exemplifying their capacity to address complex medical challenges with precision and adaptability (Table 1).

5.2 Immunogenicity and biocompatibility

Notably, lipid components of nanoparticles may elicit immunogenicity and biocompatibility concerns through multiple mechanisms. For instance, PEGylated lipids can activate the complement system, inducing hypersensitivity reactions (e.g., anaphylactoid symptoms or complement activation-related pseudoallergy (CARPA) syndrome), while repeated administration of PEGylated nanoparticles may trigger accelerated blood clearance (ABC) phenomena due to anti-PEG antibody production, leading to rapid elimination of subsequent doses, significantly reduced drug bioavailability, and heightened risk of adverse effects [103, 104]. Furthermore, cationic and ionizable lipids may stimulate the secretion of proinflammatory cytokines (e.g., IL-6, TNF-α) and ROS, potentially via complement system activation or Toll-like receptor (TLR)-mediated innate immune signaling [105–108]. Cytotoxicity of lipid materials remains a critical issue, as evidenced in animal models where LNPs have induced hepatopulmonary injury through lipid toxicity or proinflammatory factor release [105, 106, 109, 110]. To enhance biocompatibility, research has shifted toward developing biodegradable lipids (e.g., ester bond-modified lipids) [111, 112] and PEG alternatives (e.g., polysorbates, poly(hydroxypropyl methacrylamide)) [103, 104], aiming to mitigate immunogenicity and improve safety profiles. Antigen presentation pathways and immune cell activation patterns further underscore the intricate interplay between lipid composition and immunological outcomes.

5.3 Complexity of *in vivo* pharmacokinetics and biodistribution

The formulation of LNPs must overcome multiple physiological barriers *in vivo*, encompassing extracellular obstacles (e.g., nuclease degradation and mononuclear phagocyte system (MPS) clearance) and intracellular challenges (e.g., endosomal escape and cytoplasmic release). As mRNA is highly susceptible to degradation by nucleases in physiological fluids, LNPs must provide robust protection. To achieve therapeutic efficacy, LNP-mRNA systems must evade interception by MPS and clearance via glomerular filtration, successfully reaching target tissues and undergoing cellular internalization by target cells; physicochemical properties such as particle size and surface charge critically influence their *in vivo* behavior, thereby modulating pharmacokinetics and biodistribution [113, 114]. For instance, PEGylated lipids reduce MPS recognition and renal filtration clearance [115], while adjusting lipid composition ratios enables organ-selective distribution, as exemplified by delivery systems designed for spleen or lung

targeting [16, 17, 81, 86].

However, studies have revealed that successful targeted accumulation of LNPs in specific organs does not necessarily ensure a corresponding enhancement in mRNA transfection efficiency. Research by Voke et al. [116] demonstrates that upon entering the biological environment, LNPs rapidly form a protein corona on their surface, the composition of which significantly impacts subsequent delivery efficiency. For instance, apolipoprotein E (ApoE) mediates efficient uptake of LNPs by hepatocytes, increasing cellular internalization by five-fold, yet mRNA expression levels show no corresponding increase and may even be limited due to enhanced lysosomal co-localization. Similarly, vitronectin (VTN) promotes LNP adhesion to the cell membrane, enhancing apparent uptake signals, but leads to an approximately 50% reduction in mRNA expression; meanwhile, the presence of C-reactive protein (CR) can cause a drastic decline in expression by up to 90%. These findings indicate that the protein corona may compromise functional mRNA delivery at critical stages by altering the intracellular trafficking pathway of LNPs—particularly by promoting lysosomal routing and inhibiting endosomal escape.

To address this challenge, the following strategies can be considered: optimizing LNP surface properties to minimize adsorption of detrimental proteins (e.g., VTN, CR); rationally modulating lipid composition and the pK_a of ionizable amines to enhance endosomal escape efficiency; or employing protein pre-coating strategies to actively direct favorable intracellular transport routes. For example, by adjusting lipid structures or introducing specific shielding molecules, it is possible to regulate the corona composition to some extent, thereby improving endosomal escape and cytoplasmic release efficiency [70, 80, 117].

In addition to the protein corona, the *in vivo* fate of LNPs is co-regulated by a variety of complex factors. Different administration routes profoundly influence their biodistribution and metabolic kinetics: Following intravenous injection, LNPs predominantly accumulate in the liver via apolipoprotein-mediated receptor recognition pathways, while a subset migrates through lymphatic vessels to secondary lymphoid organs (e.g., spleen, lymph nodes). This dual distribution pattern endows them with unique advantages in gene editing and systemic immune activation [118–121]. In contrast, localized administration (e.g., intramuscular, intradermal injection) leverages active uptake by tissue-resident APCs, such as dendritic cells, to induce localized immune responses and propagate systemic antigen signaling. However, pharmacokinetic profiles are markedly influenced by tissue microenvironmental factors: The low metabolic activity of muscle tissue prolongs LNP retention ($t_{1/2}$ > 24 h) [122, 123], whereas the dense extracellular matrix of the dermis may restrict nanoparticle diffusion [14, 124]. Notably, the intensity of immune responses elicited by localized administration correlates closely with APC subtype distribution—for instance, the potent antigen-presenting capacity of $CD103^+$ DCs in the dermis enhances $CD8^+$ T cell activation, offering critical design insights for vaccine development [118–120]. These findings underscore that rational selection of administration routes necessitates comprehensive consideration of target organ characteristics, therapeutic objectives, and immunomodulatory requirements to achieve spatiotemporally controlled precision delivery.

6 Conclusions

In summary, this review has systematically elucidated the mechanistic foundations and design principles of selective organ-targeting lipid nanoparticles (SORT LNPs), with a particular focus on the pivotal role of the protein corona in dictating organotropism. The core insight lies in the rational manipulation of nanoparticle physicochemical properties—such as lipid composition, surface charge, and the inclusion of SORT molecules—to actively recruit specific endogenous proteins (e.g., ApoE for liver targeting, vitronectin for lungs, β2-glycoprotein I for spleen). This endogenous targeting strategy represents a paradigm shift from traditional ligand-dependent approaches, leveraging the body's natural transport systems to achieve precise organ- and even cell-specific delivery. The interplay between nanoparticle design, protein corona formation, and subsequent receptor-mediated cellular uptake forms a coherent "design-function" framework that enables spatiotemporal control over biodistribution.

Looking forward, the integration of emerging technologies holds immense promise for advancing the SORT platform. Artificial intelligence and machine learning can accelerate the rational design of next-generation ionizable lipids and LNP formulations by predicting their protein corona signatures and *in vivo* fate, thereby reducing reliance on empirical screening. Furthermore, the development of novel biodegradable and biocompatible materials will be crucial for mitigating immunogenicity concerns, such as anti-PEG immunity and cytokine activation, while maintaining targeting precision. These innovations should be coupled with a deeper investigation into the intracellular trafficking of corona-nanoparticle complexes, specifically how corona dynamics influence endosomal escape and functional nucleic acid delivery—a critical bottleneck highlighted herein. Ultimately, bridging the translational gap requires robust cross-species correlation models and clinical validation to ensure that the promising organotropism observed in preclinical models translates into safe and effective targeted therapies in humans. By converging mechanistic understanding with intelligent design, SORT LNPs are poised to usher in a new era of precision nanomedicine for treating cancer, genetic disorders, and immune-related diseases.

Data availability

Not applicable.

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Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

Y. Z. F.: Conceptualization, data curation, visualization, writing – original draft. Y. Z.: Data curation. J. X. H., F. H. W. L., and G. L.: Data curation, visualization. B. W., Q. C., and J. B. S.: Funding acquisition, project administration, resources, supervision, writing – review & editing. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Informed consent

Not applicable.

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Not applicable.

Use of AI statement

During the preparation of this work, the authors used deepseek in order to refine the language expression. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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