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Dendrimer-based nanoplatforms for enhanced mRNA delivery: From rational structural design to formulation strategies

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ABSTRACT

Development of safe and efficient mRNA delivery systems remains challenging. Dendrimers have emerged as promising mRNA carriers due to their unique advantages, including high nucleic acid condensation efficiency, nuclease protection capability, enhanced cellular uptake and endosomal escape capability mediated by proton sponge effect. However, their clinical applications are often limited by cytotoxicity and suboptimal size. Surface functionalization strategies, including targeting ligand modification or polyethylene glycol modification, can effectively mitigate their cytotoxicity while improving bioavailability and circulation stability. Furthermore, to address rapid systemic clearance of small-sized dendrimers, advanced nanostructures such as nanoclusters, core-shell tecto dendrimers, nanogels, and hybrid systems have been developed to enhance the gene delivery efficiency. Ionizable amphiphilic Janus dendrimers are also promising materials for mRNA delivery applications. This review systematically examines mRNA therapeutic applications in gene editing, cancer therapy, anti-inflammation therapy and infectious disease treatment using dendrimer-based vectors. Current challenges and future directions for optimizing dendrimer-based mRNA therapeutics are also briefly discussed.

1. Introduction

Messenger RNA (mRNA) therapeutics are emerging as a promising modality for treating a wide spectrum of diseases, owing to their customizable design, favorable safety profile, and rapid manufacturing scalability [1]. These therapeutics employ synthetic mRNA to direct *in vivo* production of target proteins, which may function either as therapeutic agents or as immunogens to stimulate immune responses [2]. mRNA therapeutics aiming to address genetic disorders have numerous applications in cancer immunotherapy and vaccine for infectious diseases [3]. Compared to DNA, mRNA does not integrate into the host genome, significantly reducing the risk of permanent genetic alterations and offering a safer therapeutic profile [4]. Through the precise production of functional proteins, mRNA can be applied to replace the deficient proteins in diseases such as cystic fibrosis [5]. In cancer immunotherapy, mRNA encoding tumor-associated antigens (TAAs) or immunomodulators can elicit potent tumor-specific immune responses [6]. Furthermore, the rapid production capacity and modular nature of mRNA platforms facilitate prompt adaptation to novel pathogens and viral variants, as evidenced by the accelerated development of COVID-19 vaccines [7,8]. This highlights the revolutionary capabilities of mRNA-based therapeutic approaches [9].

Although mRNA therapeutics hold promises to tackle diverse diseases, their clinical translation remains to be challenging. The susceptibility of mRNA to enzymatic degradation (notably by extracellular RNases) makes it difficult for preparation and storage of mRNA-based therapeutic reagents [10–12]. Another major hurdle lies in the efficient cellular mRNA delivery. The polyanionic nature of mRNA creates electrostatic repulsion against similarly negatively charged cell membranes, impeding mRNA cellular internalization. Furthermore, following cellular uptake, successful endosomal/lysosomal escape of mRNA becomes essential to enable cytoplasmic release for ribosomal translation into functional proteins [13]. In addition, the targeting of mRNA formulations for specific tissue or cells remains a pivotal challenge for improved bioavailability and therapeutic efficacy [14]. Additionally, mRNA vaccines and therapeutics may provoke immune responses, potentially leading to inflammation and other adverse effects [6]. Therefore, balancing the immune response and therapeutic effect is crucial for the development of mRNA therapeutics [15].

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To address the challenges associated with mRNA therapeutics, various nanoparticulate systems have been developed, including lipid nanoparticles (LNPs) [14], proteins [16], polymers [17] and hybrid carriers [18,19]. Conventional LNPs are typically composed of ionizable lipids, phospholipids, or polyethylene glycol (PEG)-lipid conjugates, and function synergistically to encapsulate mRNA to facilitate its cellular uptake and promote its endosomal escape through the ionization of lipids in the acidic endosomal environment [14]. Protamine, a protein vector, can also electrostatically assemble with mRNA to generate nanocomplexes (NCs) with enhanced stability [20]. Polymer-based delivery systems exhibit considerable promise for mRNA therapeutics due to their structurally tunable architectures and capacity for functional customization [21]. Commonly used polymers for mRNA delivery include polyethyleneimine (PEI), polyesters, poly(amino acids), dendrimers (*e.g.*, poly(amidoamine), PAMAM), and natural polymers (*e.g.*, chitosan) [10,17,21–24].

The clinical translation of mRNA therapeutics is critically dependent on safe and efficient delivery systems. To date, LNPs have emerged as the most clinically advanced non-viral vector, as demonstrated by the success of COVID-19 mRNA vaccines. Despite these remarkable successes, LNPs often suffer certain limitations, including inflammatory responses related to the ionizable lipids, the requirement for strict cold-chain storage, the complexity in further surface functionalization, and the batch-to-batch variability [10]. These limitations have motivated efforts to either improve LNP performance or develop novel delivery vectors. Among the various alternative platforms, dendrimers represent a highly attractive candidate for mRNA delivery. Dendrimers are synthetic, monodisperse, hyperbranched macromolecules with a well-defined architecture, consisting of a central core, interior layers (generations), and numerous peripheral functional groups. Compared to LNPs, dendrimers possess advantages including precise and tunable nanoscale structure and abundant surface functional groups that can be conjugated with targeting ligands, PEG chains or other moieties to modulate pharmacokinetics and specificity. In addition, certain dendrimers, such as PAMAM, possess intrinsic proton-buffering capacity that can facilitate mRNA endosomal escape *via* the known “proton sponge” effect [25,26].

This review systematically examines the use of dendrimer-based nanoplatforms in terms of fundamental structural and physicochemical properties, modification strategies and composite formulations to mitigate toxicity while enhancing targeting specificity and bioavailability of the delivered genes, especially mRNAs. We also introduce the recent advances in ionizable amphiphilic Janus dendrimers (IAJDs) for mRNA delivery. Furthermore, we critically analyze therapeutic applications of mRNA in gene editing, cancer therapy, anti-inflammation therapy, and infectious disease treatment (Fig. 1). Finally, we delineate current challenges and propose future research directions to advance dendrimer-based mRNA delivery systems.

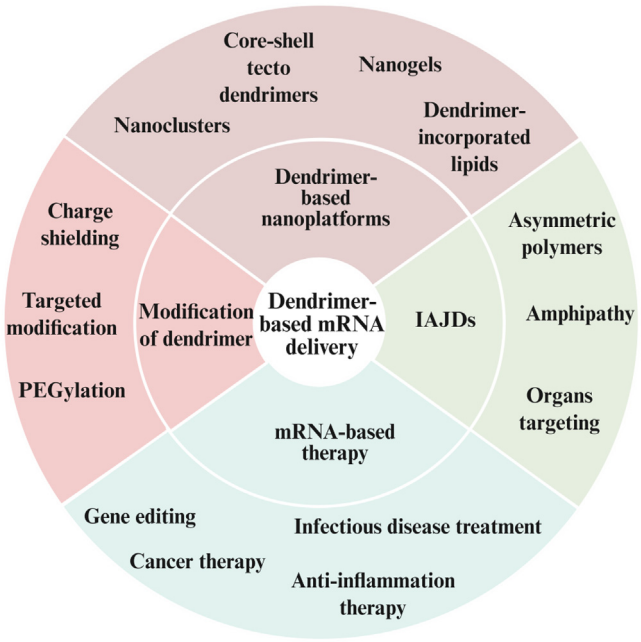


Fig. 1. Dendrimer modification strategies, dendrimer-based formulations, and IAJDs for mRNA-based therapeutics.

2. Structure and physicochemical properties of dendrimers

Dendrimers are branched, symmetrical macromolecules with a defined layered structure. They have a central core from which multiple branches or dendrons extend, giving them a tree-like architecture. This structure is built up through stepwise synthetic methods, either a convergent or divergent approach that results in well-organized and monodisperse molecules with a precise size and shape (Fig. 2) [27,28]. Dendrimers possess internal cavities capable of encapsulating diverse drugs. With a characteristic nanoscale dimension (1–10 nm), they exhibit typical NP properties such as high surface-to-volume ratio. Their surface functional groups (*e.g.*, amines or hydroxyl) enable both drug loading and multifunctional modifications, including antifouling coatings, fluorescent labeling, targeting ligand conjugation, antibody attachment, and enzyme immobilization [29].

The solubility of dendrimers is a critical physicochemical property primarily determined by their structural composition and surface groups. Dendrimers with amide backbones (e. g., PAMAM) typically exhibit high aqueous solubility, whereas those containing aromatic moieties (e. g., phosphorus dendrimers) demonstrate surface functional group-dependent water solubility [30]. Surface modifications with hydrophilic groups (amino, hydroxyl, carboxyl, sulfo, or phosphate) significantly enhance their hydrophilicity, while those with hydrophobic or other functionalities (alkyl chains, phenyl or cholesterol) have diminished water solubility [28]. In general, hydrophilic modifications serve to enhance the colloidal stability and biocompatibility of dendrimers, whereas hydrophobic modifications primarily augment their loading capacity for hydrophobic drugs and promote cellular internalization [31–33]. The mitigation of cytotoxicity is mediated by two key strategies: 1) reducing the surface charge density of the dendrimer by chemical modification; 2) employing targeted modifications to promote its specific accumulation at the target site, consequently minimizing off-target effects on healthy tissues. Dendrimers display remarkable thermal and chemical stability, making them versatile for a range of biomedical applications. To further optimize their solubility and biocompatibility while ensuring formulation stability, dendrimers are often conjugated with PEG. Such chemical modifications not only prevent aggregation but also enhance their performance for drug delivery applications [34]. The structural architecture and surface chemistry of dendrimers collectively govern their physicochemical behavior, biological compatibility, functional bioactivity, and nucleic acid delivery efficiency.

Cationic dendrimers with terminal cationic groups (*e.g.*, primary amines) can efficiently complex mRNA through electrostatic interaction to achieve a high loading efficiency [35–37]. The created dendrimer-mRNA polyplexes have enhanced cellular internalization ability *via* electrostatic attraction to negatively charged cell membranes. Meanwhile, dendrimers with multiple surface groups can be tailored through precise chemical modifications, thus having improved biocompatibility, targeting specificity, enhanced cellular uptake efficiency, controlled drug release kinetics, and prolonged systemic circulation [38,39]. These attributes make dendrimers highly effective in mRNA delivery with improved efficacy and reduced side effects. Following cellular internalization, dendrimers rich in tertiary amines exhibit pH-responsive buffering capacity under an acidic condition, thereby facilitating mRNA lysosomal escape *via* the known “proton sponge” effect for subsequent protein translation. Despite the advantages of dendrimers in mRNA delivery,

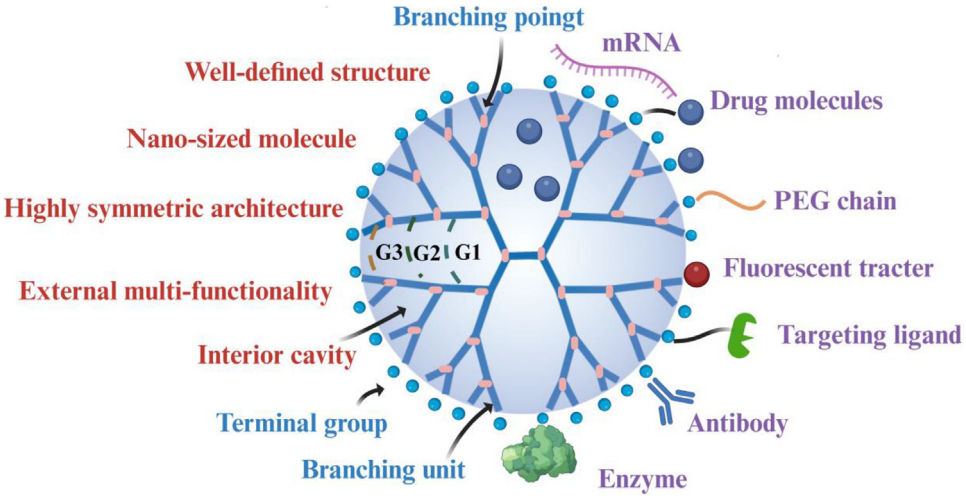


Fig. 2. Structural characteristics, tunable surface functionality, and multi-payload encapsulating capacity of dendrimers. G1, G2, and G3 indicate generation 1, 2, and 3 dendrimers, respectively. PEG denotes polyethylene glycol.

high-generation dendrimers often exhibit significant cytotoxicity at high doses, owing to their dense surface amine groups. Furthermore, a more comprehensive study is required to detail the metabolic pathways of dendrimers *in vivo*.

3. Dendrimer modification strategies for desired gene delivery

Dendrimers demonstrate distinct advantages over conventional nanocarriers for mRNA delivery, exhibiting promising preclinical efficacy in therapeutic applications including prophylactic vaccines and cancer immunotherapy. However, their clinical applications are limited by dose-dependent cytotoxicity. The cytotoxicity of dendrimers is typically associated with their generation-dependent surface amine charge density. Generally, higher-generation dendrimers exhibit greater cytotoxicity, whereas lower-generation dendrimers have reduced toxicity [29,40]. Comprehending the mechanisms underlying dendrimer-induced cytotoxicity is essential for desired gene delivery applications. Firstly, cationic dendrimers compromise plasma membrane integrity, which impairs cellular functions and reduces cell viability. After cellular uptake, dendrimers further induce organelle damage, particularly in lysosomes and the endoplasmic reticulum, ultimately triggering cell apoptosis. Such cytotoxic effects typically occur within hours post-transfection of dendrimers [41]. Ongoing research aims to optimize dendrimer structures and surface chemistries to reduce the surface charge density, thus mitigating their cytotoxicity while enhancing their efficacy of mRNA delivery. Dendrimer surfaces can be chemically modified through diverse strategies (*e.g.*, acetylation, PEGylation, or hydroxylation) to improve biocompatibility and stability (Fig. 3). Additionally, the incorporation of specific ligands (such as folate (FA) or Arg-Gly-Asp (RGD) peptide) enables targeted delivery to cells or tissues, thereby enhancing delivery efficiency and minimizing off-target effects [42]. The strategies utilized to modify dendrimers for improved gene (mRNA) delivery can be summarized in Table 1.

Table 1
Summary of dendrimer-based structural design for gene (mRNA) delivery.

Design strategy	Surface modification	Performances	Refs.
Charge shielding	Hydroxylation	Reduced cytotoxicity	[29]
	Amino acid modification (lysine, arginine, or histidine)	Reduced cytotoxicity Enhanced mRNA condensation efficiency and endosome escape capability	[44]
	Hydrophobic moiety	Promoted membrane interaction and cellular internalization	[45]
	Fusogenic group	Enhanced endosome escape capability	[45]
Targeting ligand modification	FA ligand	Tumor targeting	[48]
	Mannose	DC targeting	[49]
PEGylation modification	PEGylation	Minimized nonspecific uptake by the RES	[51]

3.1. Charge shielding modification of dendrimers

The cytotoxicity of dendrimers is largely attributed to their high surface charge density, making charge shielding an effective strategy for reducing cytotoxicity [41]. Additionally, excessive positive surface charge on dendrimers leads to nonspecific adsorption of negatively charged proteins, which can interfere with their interactions with cell membranes, reduce cellular uptake, and accelerate clearance by the reticuloendothelial system (RES) in the bloodstream [43]. Hydroxylated PAMAM (PAMAM-OH) dendrimers exhibit significantly lower cytotoxicity toward 293T cells than amine-terminated PAMAM with the same generation [29]. In addition, the incorporation of arginine residues and imidazole groups can reduce the cytotoxicity of dendrimers and enhance their capability to escape from endosomes [44].

When modified by lysine, PAMAM dendrimers demonstrate enhanced mRNA condensation and delivery efficiency with reduced cytotoxicity through decreased surface amine density. Incorporation of hydrophobic moieties further improves the stability of dendrimers, promoting membrane interaction and cellular internalization. Further functionalization with fusogenic groups significantly enhances their endosomal escape capability. The optimized dendriplexes demonstrate superior *in vitro* mRNA delivery and transfection performance compared to commercial jetPEI® reagents [45]. Despite being widely used as a cationic polymer transfection reagent for delivering various nucleic acids (*e.g.*, DNA, mRNA, siRNA), the jetPEI® exhibits pronounced cytotoxicity and can trigger inflammatory responses and organ toxicity. In summary, these strategies together improve the overall performance of dendrimer-based mRNA delivery systems by reducing cytotoxicity, enhanced stability and improved cellular uptake (Fig. 4).

3.2. Targeting ligand modification of dendrimers

Dendrimers can be surface modified with specific ligands (e. g., mannose, antibodies, or FA), thus enabling active targeting to target cells or tissues [46,47]. Recent studies have demonstrated that G5 dendrimers modified with FA and gold NPs (AuNPs) display significantly enhanced mRNA loading and delivery efficiency (Fig. 5). The FA-modified

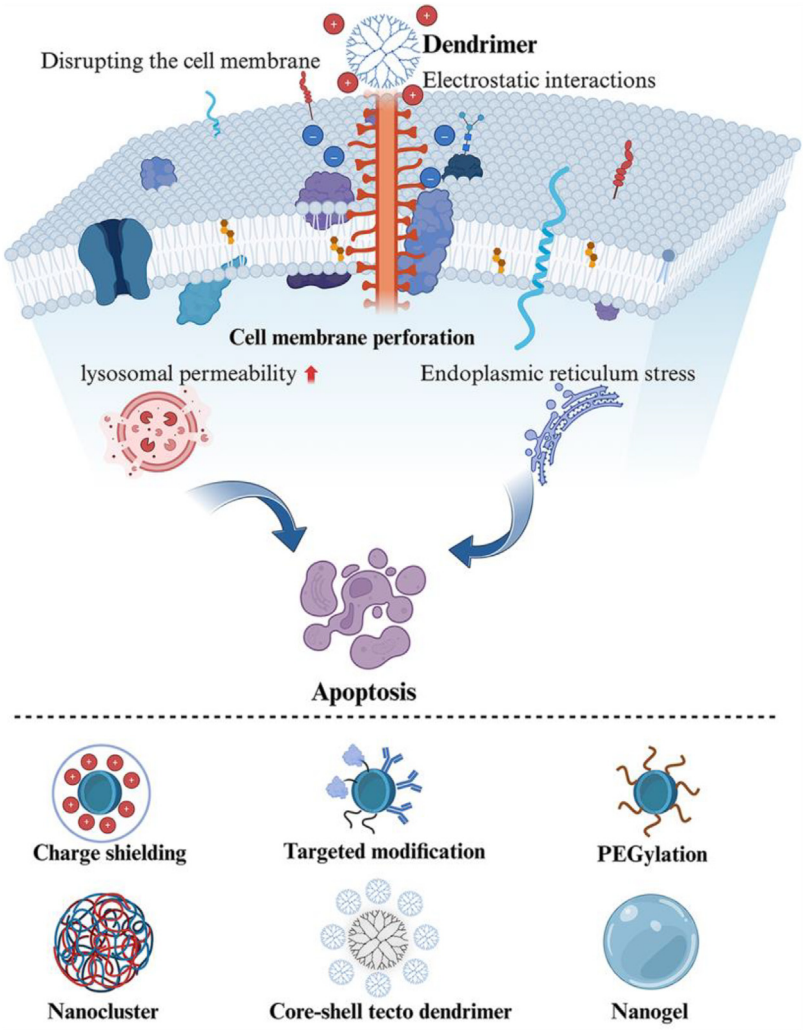


Fig. 3. Cytotoxic effects of dendrimers on cellular membranes, lysosomes, and endoplasmic reticulum, with corresponding strategies to reduce dendrimer toxicity while enhancing mRNA delivery efficiency.

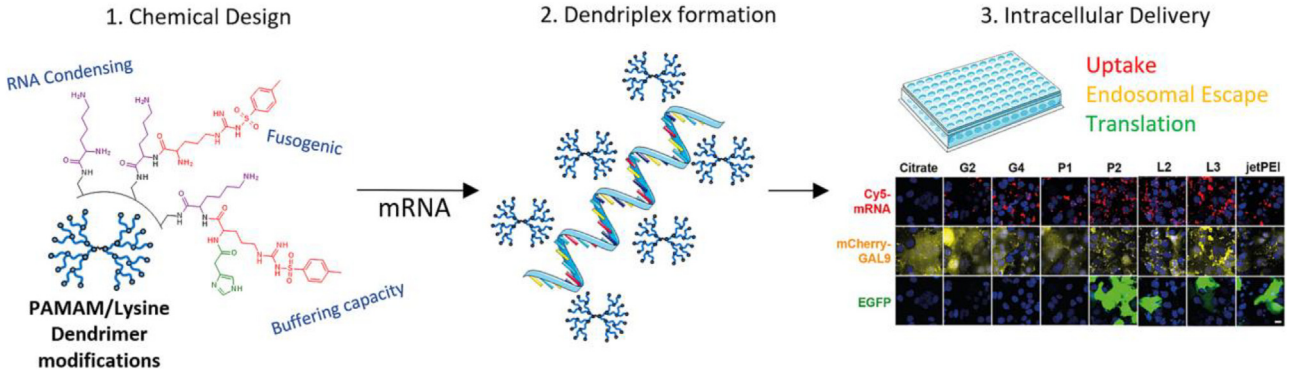


Fig. 4. Structural modifications of PAMAM and lysine dendrimers through diverse functional groups enhance their RNA-condensing ability, membrane fusion properties, and proton buffering efficiency. Reproduced with permission from ref [45]. Copyright 2023, Elsevier B. V.

dendrimer-AuNPs complexed with mRNA can target FA receptors on cancer cell surfaces, facilitating endocytosis and subsequent release of mRNA within the cytoplasm, thus triggering the expression of the target protein [48].

Mannose has been extensively studied as a targeting ligand that has high affinity to mannose receptor (CD206) overexpressed on dendritic cells (DCs). In our recent work, we developed mannose- and 1,3-propanesultone-functionalized dendrimer-entrapped AuNPs (Au DENPs) using G5 PAMAM dendrimers (abbreviated as MDNP, Fig. 6) [49]. The resulting MDNP had a hydrodynamic diameter of 266.3 nm and a positive zeta potential of 22.2 mV, exhibiting favorable colloidal stability, excellent cytocompatibility, and efficient YTHDF1

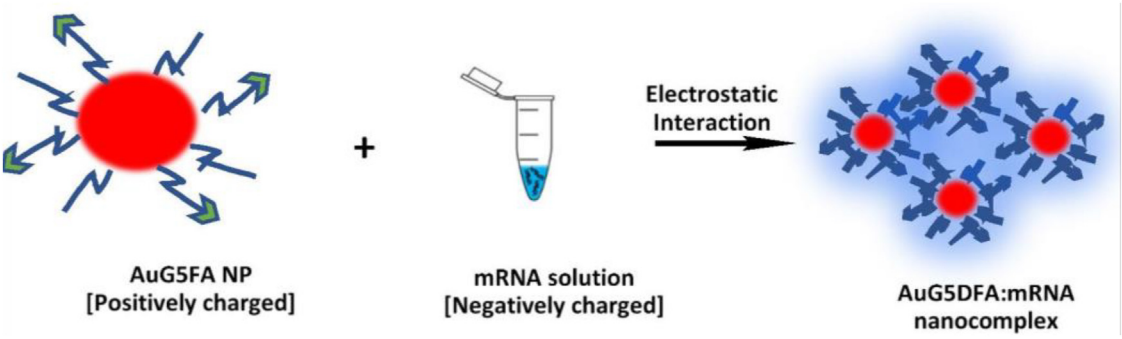


Fig. 5. FA-modified G5 PAMAM-grafted AuNPs for mRNA condensation. Reproduced with permission from ref [48]. Copyright 2021, MDPI.

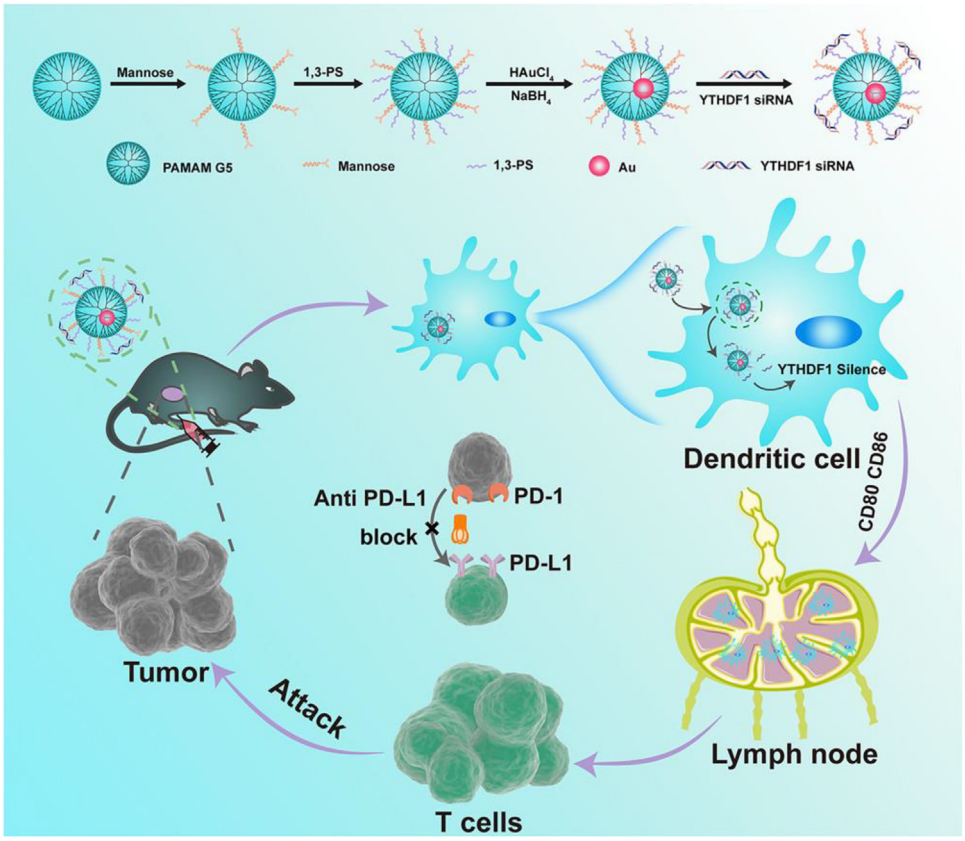


Fig. 6. Synthesis of MDNP and its mechanism in delivering YHDF1 siRNA to DCs to promote DCs maturation for enhanced antitumor immunotherapy. Reproduced with permission from ref [49]. Copyright 2021, American Chemical Society.

siRNA (siYTH) compaction capacity. Notably, cellular internalization efficiency of MDNP/siYTH in DCs was enhanced by 1.5-fold compared to mannose receptor-blocked control group, demonstrating the potential of mannose-mediated targeting for DC-specific gene delivery. The strategy of mannose-conjugated dendrimers may be further extended for targeted mRNA delivery to DCs.

3.3. PEGylation modification of dendrimers

PEGylation modification of dendrimers is known to improve their biocompatibility and prolong their blood circulation time by evading rapid immune clearance. PEGylation also minimizes non-specific interactions, thus increasing the safety and effectiveness of mRNA delivery [50]. For instance, Niu and colleagues developed an innovative drug delivery system by covalently coupling celastrol, a natural molecule with potent antitumor activity, to PEG-functionalized dendrimers. This PEGylated nanocarrier demonstrated significantly improved tumor-targeting specificity, prolonged tumor retention time, and superior tissue penetration depth compared to antibody-modified formulations [34].

Surface functionalization with PEG can effectively minimize nonspecific uptake by the RES, thereby enhancing the accumulation of dendrimers at target sites. In our earlier work [51], a novel nanoplatform based on Au DENPs using G5 PAMAM dendrimers as templates was developed to co-deliver dexamethasone and a microRNA-155 inhibitor (miR-155i). The system was constructed through amide bond conjugation of Dex-PEG-COOH to the dendrimer surface, while miR-155i was loaded *via* electrostatic interaction. The resulting polyplexes exhibited favorable physicochemical characteristics, including a positive surface charge (16–26 mV) and desired hydrodynamic size (175–230 nm). These nanocarriers demonstrated excellent biocompatibility and achieved efficient miR-155i delivery to lipopolysaccharide (LPS)-stimulated alveolar macrophages (Fig. 7).

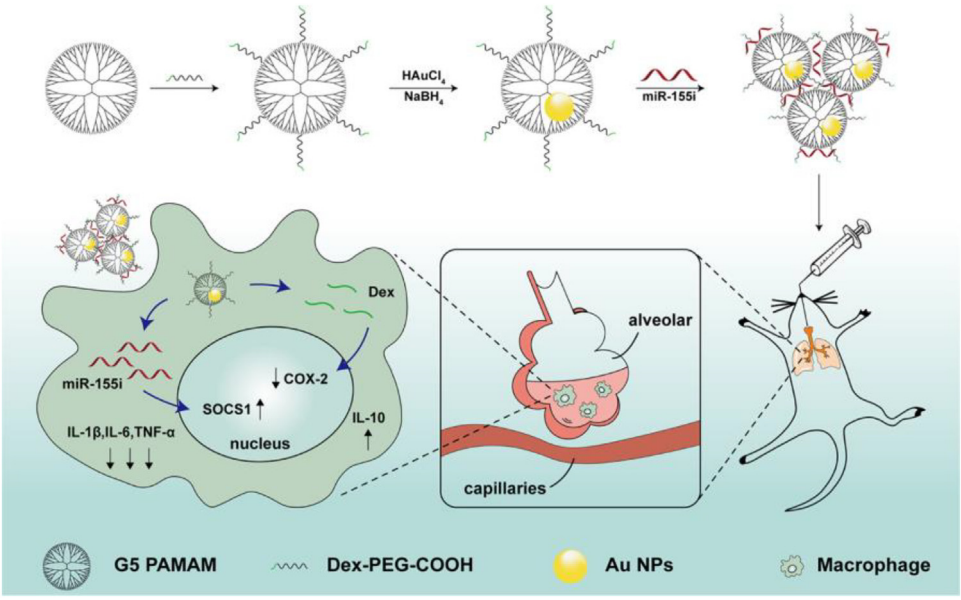


Fig. 7. Synthesis of $(Au^0)_{25}$-G5.NH_2-(PEG-Dex) complexed with miR-155i for combined chemo-gene therapy of acute lung injury (ALI). Reproduced with permission from ref [51]. Copyright 2021, American Chemical Society.

4. Dendrimer-based nanoplatforms for gene delivery applications

The surface modified dendrimers demonstrate numerous advantages with reduced cytotoxicity, prolonged blood circulation, and targeting specificity, which are desirable for gene delivery applications although some of the strategies have not been adopted for gene delivery, in particular mRNA delivery. In another aspect, due to the relatively small size (usually less than 20 nm), single dendrimers exhibit a relatively short residence time in the body, resulting in limited accumulation and retention at targeted sites and low therapeutic bioavailability [52]. To address this challenge, several dendrimer nanoplatforms based on multiple dendrimers or dendrimer aggregates have been developed, including dendrimer nanoclusters (DNCs) [53,54], core-shell tecto dendrimers (CSTDs) [55,56], and dendrimer nanogels (DNGs) [57]. These dendrimer nanoplatforms possess a particle diameter generally considered to be optimal (in the range of 20–200 nm) for amplifying the enhanced permeability and retention (EPR) effect, thereby promoting accumulation and penetration within tumor or inflammatory tissues. Furthermore, the formation of these nanostructures consumes primary amine groups on the PAMAM dendrimers, which reduces the overall zeta potential of the nanoplatform. This charge reduction decreases nonspecific protein adsorption, prolongs systemic circulation time, and helps balance gene loading efficiency with cytotoxicity. Additionally, specific surface modifications (*e.g.*, PEGylation and ligand conjugation) on the dendrimer nanoplatform can further extend the *in vivo* circulation time and enhance targeted gene delivery efficacy [53], thereby offering a range of promising opportunities for mRNA delivery applications (Table 2).

4.1. Dendrimer nanoclusters (DNCs)

DNCs can be synthesized using low-generation dendrimers in order to avoid the use of expensive high-generation dendrimers (G4 or above). In our recent work [53], a DNC platform based on G3 PAMAM dendrimers was developed *via* chemical crosslinking by 4,4′-dithiodibutryic acid (DA). The resulting DNCs exhibit a hydrodynamic diameter of 219.3 nm with excellent colloidal stability under physiological conditions, and can form stable polyplexes with the tumor suppressor p53 gene while maintaining favorable cytocompatibility. Notably, the DNC/pDNA polyplexes displayed significantly enhanced gene delivery efficiency in cancer cells, which is 2.3-fold and 2.1-fold greater than single monodisperse G3 and G5 PAMAM dendrimers, respectively. This substantial improvement highlights the advantages of the nanocluster architecture for mRNA delivery applications (Fig. 8) [53]. Furthermore, the DNC/pDNA polyplexes exhibited superior tissue penetration depth and enhanced growth suppression compared to its monomeric dendrimer counterpart, likely due to the amplified EPR effect.

4.2. Core-shell tecto dendrimers (CSTDs)

CSTDs are a class of highly structured nanocarriers composed of a central dendrimer core covalently or non-covalently surrounded by peripheral dendrimer units, forming a core-shell architecture [56]. CSTDs with a larger dimension than single dendrimer counterparts can be designed to be stimuli-responsive for controlled drug/gene release, which cannot be achieved using conventional single-generation dendrimers, making them promising candidates for targeted drug/gene delivery applications [58].

CSTDs have been developed for delivery of different genetic materials. In our previous work, AuNP-loaded CSTDs were fabricated using lactobionic acid (LA)-functionalized G5 PAMAM dendrimers entrapped with AuNPs as cores and phenylboronic acid (PBA)-conjugated G3 dendrimers as shells linked *via* dynamic phenylborate ester bonds, which are responsive to both reactive oxygen species (ROS) and pH [59]. These dual ROS- and pH-responsive Au-CSTDs can effectively deliver a CRISPR/Cas9 plasmid to disrupt the PD-L1 gene in cancer cells, enabling immune checkpoint blockade-based tumor immunotherapy. In another work [58], pH-sensitive G5@G3 CSTDs with terminal amines were constructed through host-guest molecular recognition. The system consisted of benzimidazole-modified G3 PAMAM dendrimers as shells and β-cyclodextrin-functionalized G5 PAMAM dendrimers as cores (Fig. 9). These G5@G3 CSTDs exhibit a hydrodynamic size of 256 nm and a surface potential of 35.90 mV, and can form polyplexes with negatively charged CD47 siRNA and chemotherapeutic agent doxorubicin (DOX). The G5@G3/DOX/CD47 siRNA exhibited superior tumor accumulation compared to individual G3 or G5 dendrimers, likely attributable to the magnified EPR effects mediated by their optimized particle size. Following cellular internalization by tumor cells, the polyplexes simultaneously induced CD47 gene silencing and DOX-mediated immunogenic cell death. This dual-action mechanism promoted the up-

Table 2
Summary of representative dendrimer-based formulations for gene (mRNA) delivery.

Dendrimer formulations	Formation strategies	Applications	Refs.
DNCs	Covalent crosslinking	Enhanced EPR and p53-pDNA delivery	[53]
CSTDs	G5 PAMAM core and G3 PAMAM shell through supramolecular recognition or boronic ester bonding	Enhanced EPR and CD47 siRNA delivery	[58,59]
DNGs	Self-crosslinking	Enhanced EPR	[52]
	Crosslinking with other crosslinkers	Enhanced EPR	[66]
	Crosslinking with other polymers	Enhanced EPR and p53-pDNA delivery	[57]
	Incorporating dendrimers onto preformed polymer NGs	Charge-mediated enhanced transport	[43]
	Assembly of dendrimers with proteins	Enhanced EPR	[67]
Dendrimer-like lipids	dLNP systems	Enhance luciferase (Luc) mRNA, mCherry mRNA, FAH mRNA, Cas9 mRNA, sgRNA, and donor DNA delivery	[68–70]

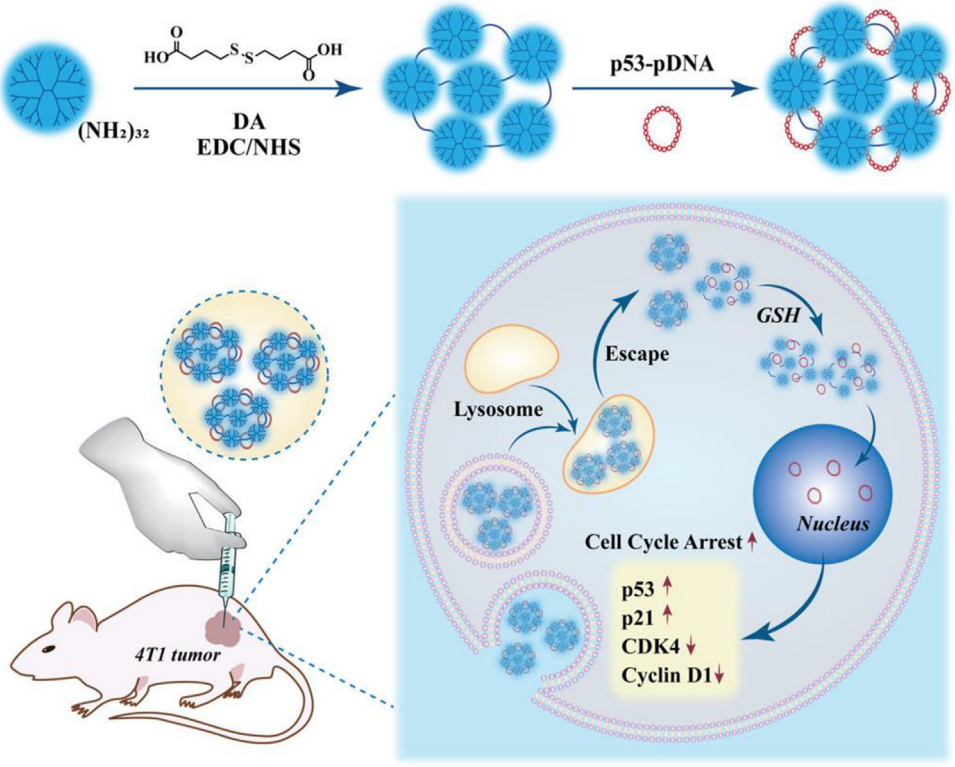


Fig. 8. Preparation of G3-DA NCs/pDNA-p53 polyplexes for cancer gene therapy. GSH represents glutathione. Reproduced with permission from ref [53]. Copyright 2021, American Chemical Society.

regulation of "eat-me" signals (*e.g.*, calreticulin exposure) and downregulation of CD47 ("don't-eat-me" signal), thereby facilitating macrophage-mediated phagocytosis, and promoted DC maturation and cytotoxic T lymphocyte-mediated tumor cell elimination when combined with anti-CTLA-4. The coordinated immune activation and direct cytotoxicity significantly potentiated antitumor efficacy.

4.3. Dendrimer nanogels (DNGs)

Polymeric NGs with a size of typically 50–200 nm, characterized by three-dimensional network structure, high water content, and excellent fluidity, offer promising alternatives for gene delivery [60]. By varying the monomers and crosslinkers, stimuli-responsive NGs can be designed to adapt to the tumor microenvironment for enhanced tumor delivery [61]. These formulations can be engineered as controlled drug delivery platforms to improve the bioavailability of mRNA-based therapeutics. Furthermore, these NG systems can be incorporated with dendrimers to show both features of NGs and dendrimers [62], thereby displaying improved utility for mRNA delivery applications. Furthermore, the inherent stability of the DNGs may significantly enhance their efficacy for *in vivo* mRNA delivery [52]. In our recent work [63], three types of mannose-functionalized stimuli-responsive DNGs based on G3 PAMAM dendrimers were synthesized through differential crosslinking strategies for mEGFP delivery applications. These formulated DNGs demonstrated excellent colloidal stability and superior cytocompatibility compared to the commercial lipidic agent Lipo8000^{TM}, and achieved a high transfection efficiency for both mEGFP and pEGFP in DCs comparable to the commercial Lipo8000^{TM} agent.

Owing to their exceptional biocompatibility, structural flexibility, deformability, high drug loading capacity, and controllable release kinetics, DNGs have emerged as promising vectors for gene therapeutics [57]. DNGs can be synthesized through either dendrimer crosslinking or chemical incorporation of dendrimers with other co-monomers using specific crosslinkers [64]. Under an inverse microemulsion conditions, dendrimers can serve as macromonomers for NGs synthesis when reacted with external crosslinkers [65]. For instance, our team crosslinked G3 PAMAM dendrimers with N,N'-bis(acryloyl) cystamine *via* Michael addition in a reverse microemulsion system. The resulting DNGs exhibit a uniform diameter of ~86 nm and good colloidal stability. By further incorporating AuNPs, gadolinium, the targeting peptide RGD, and the

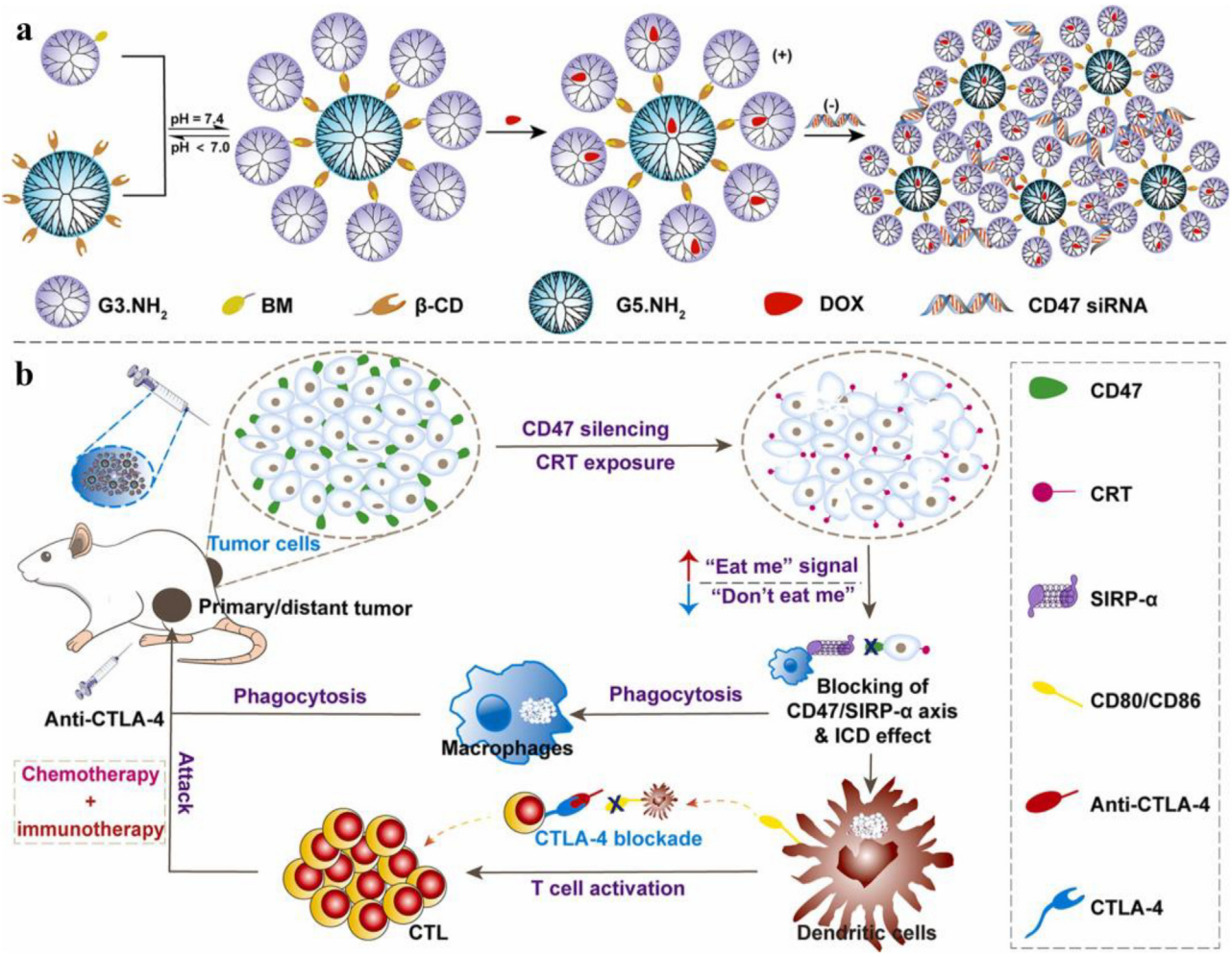


Fig. 9. Fabrication of G5@G3 PAMAM complexes co-delivering DOX and CD47 siRNA for augmented chemoimmunotherapy of breast cancer. (a) Schematic illustration of the G5@G3 CSTD nanoplatform loaded with DOX and CD47 siRNA. (b) Proposed mechanism of tumor suppression through G5@G3-mediated DOX/CD47 siRNA co-delivery combined with CTLA-4-mediated immune checkpoint blockade. Reproduced with permission from ref [58]. Copyright 2024, Elsevier B. V.

antifouling agent 1,3-propanesultone (1,3-PS), the DNGs demonstrated more significantly enhanced targeted CT/MR dual-modal tumor imaging than single-generation dendrimer counterparts [66].

Besides, dendrimers can be self-crosslinked to form DNGs using dendrimers as both the monomer and crosslinker. In this case, no external crosslinkers are required. In our group's previous research [52], DNGs were developed by self-crosslinking of G3 PAMAM dendrimers modified with NHS-PEG-S-acetyl groups in a reverse microemulsion system. The resulting DNGs with a size of ~200 nm, were stable and demonstrated glutathione-responsive degradation due to the disulfide bond formed between dendrimers, and could be co-loaded with AuNPs and chemotherapeutic Toy for theranostics of a pancreatic tumor mouse model. In addition, G3 amine-terminated PAMAM dendrimers can be modified with copolymers of poly(N-vinylcaprolactam) (PVCL)-glycidyl methacrylate (GMA) and further crosslinked with un-modified G3 amine-terminated PAMAM dendrimers to form DNGs in an emulsion-free system (Fig. 10) [57]. After being taken up by cells, the developed G3-NGs can undergo self-triggered degradation into dendrimer fragments, resulting in controlled gene release and reduced cytotoxicity. The innovative design achieves an optimal balance between transfection efficiency and cytotoxicity. Compared to higher-generation dendrimers, the G3-NGs platform offers significantly improved p53-pDNA transfection efficiency and markedly reduced cytotoxicity and lower production costs.

Furthermore, DNGs can also be formed by incorporating dendrimers onto preformed polymer NGs. For instance, Pich *et al.* [43] developed a synthetic approach to first create poly(N-vinylcaprolactam-co-glycidyl methacrylate) (abbreviated as PVCL-GMA) NGs *via* precipitation polymerization, followed by surface conjugation of G2 PAMAM dendrimers through amine-epoxy coupling. This modification yielded NGs with a cationic surface and neutral core, promoting cellular uptake *via* charge-mediated transport.

Lastly, DNGs can be formed by assembly of dendrimers with proteins to form a biomimetic NG platform inspired by the glycopeptide architecture of extracellular matrix [67]. In this case, amine-terminated G5 PAMAM dendrimers were first conjugated with 3,4-dihydroxybenzaldehyde, and then assembled with bovine serum albumin to form the DNGs. The formed DNGs demonstrate exceptional biocompatibility and serve as an effective delivery platform for cyclophosphamide, showing high therapeutic effect for systemic sclerosis treatment.

4.4. *Dendrimer-like lipids*

Dendrimer-like lipid nanoparticles (dLNPs) represent an advanced class of delivery systems that integrate structurally defined dendrimers into conventional LNP frameworks. By combining these two components, dLNPs are engineered to leverage the benefits of both materials. In contrast to the heterogeneous composition of ionizable lipids in traditional LNPs, the dendrimer introduces a monodisperse and well-defined architecture, thereby enhancing structural homogeneity and im-

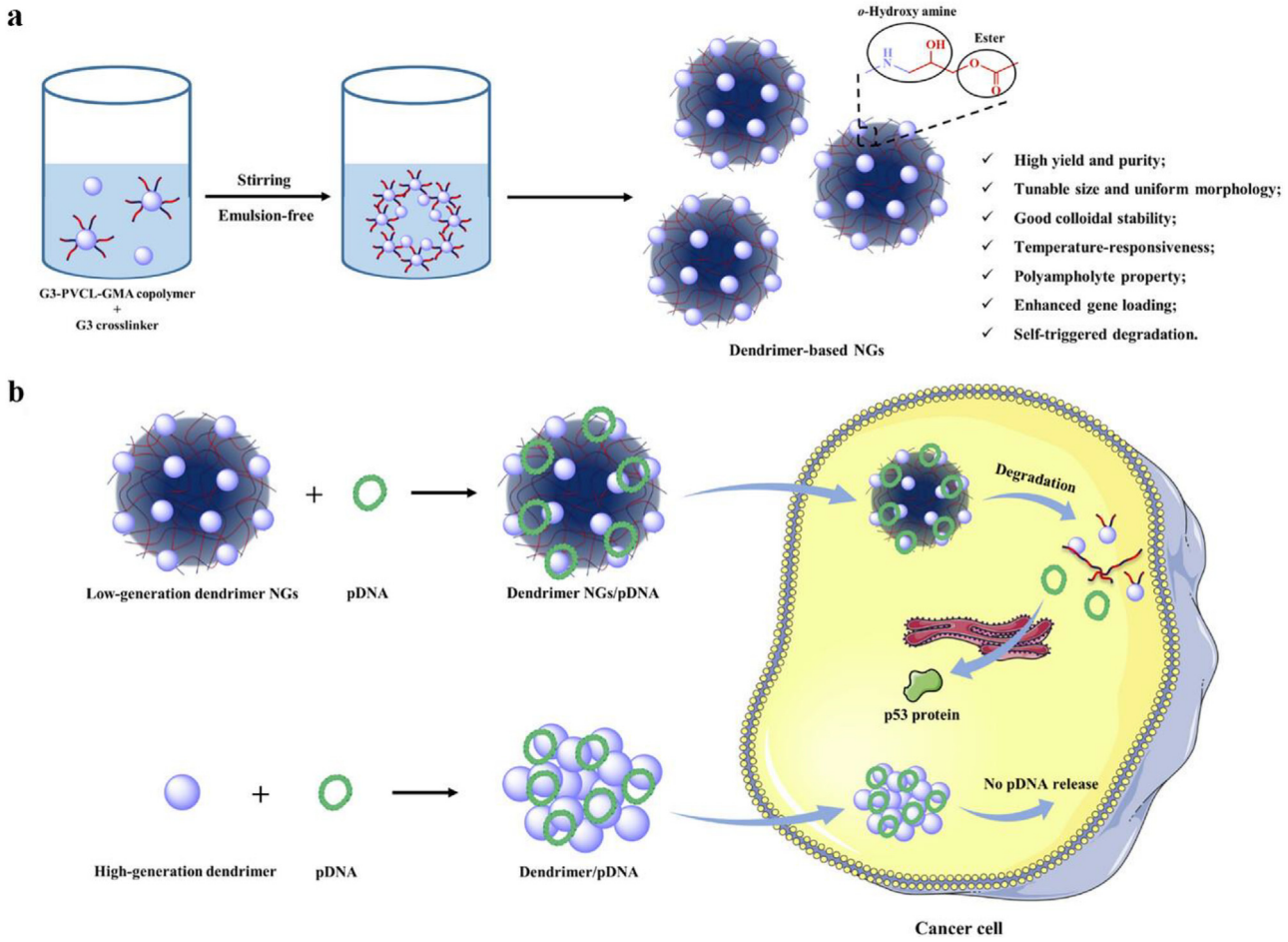


Fig. 10. (a) Preparation of DNGs using an emulsion-free method. (b) Schematic illustration of DNGs for highly efficient DNA delivery and gene therapy. Reproduced with permission from ref [57]. Copyright 2025, Wiley-VCH GmbH.

proving batch-to-batch consistency [71]. The multivalent cationic surface of the dendrimer facilitates more efficient and stable complexation with negatively charged mRNA *via* electrostatic interactions. Moreover, within dLNP systems, the dendrimer contributes to its intrinsic "proton sponge" effect, which promotes endosomal escape and enhances the efficiency of mRNA release into the cytoplasm [72]. Another key advantage lies in the abundant peripheral functional groups of the dendrimer, which serve as readily accessible conjugation sites. These allow for precise covalent attachment of targeting ligands, cell-penetrating peptides, or stealth polymers (*e.g.*, PEG) without disrupting the self-assembly of the lipid shell [25]. In summary, the strategic integration of dendrimers into LNPs aims to create a next-generation delivery platform that combines the high transfection efficiency and clinical maturity of LNPs.

A novel cationic dendrimer, 5A2-SC8, was developed as part of dLNPs for mRNA delivery (Fig. 11) [68]. Using a systematic orthogonal matrix design, the lipid composition of the NPs was optimized, resulting in a high loading capacity of fumarylacetoacetate hydrolase (FAH) mRNA. The study demonstrated that the optimized dLNPs successfully transfected over 44% of hepatocytes in the liver, leading to substantial expression of functional FAH protein.

Another dLNPs with a modular design featuring ionizable amine core, ester linkages, and alkyl-thiol peripheries were designed to replace the ionizable components in LNPs [69]. These dLNPs can co-encapsulate multiple nucleic acid components, including Cas9 mRNA, single-guide RNA (sgRNA), and donor DNA. The optimized dLNPs demonstrated over 92% encapsulation of the Cas9 mRNA. Additionally, a theranostic dLNPs system was developed by integrating PEGylated BODIPY dyes (PBD) for mRNA delivery and near-infrared imaging [70]. Through the optimization of component ratios, the system successfully facilitated efficient mRNA delivery, leading to the expression of functional proteins. Simultaneously, it enabled high-contrast imaging at the tumor site, providing a dual benefit of therapeutic and diagnostic capabilities *in vivo* (Fig. 12). By combining lipids, the dendrimer-lipid hybrids significantly improve the mRNA delivery efficiency, stability, and biocompatibility, making them highly effective carriers for therapeutic applications. In a recent study by Liu et al. [73], dendrimers were sequentially modified *via* ring-opening reaction with alkane epoxide and alkylated dioxaphospholane oxide, yielding phospholipidated and alkylated polymers (PAPs) with significantly higher mRNA delivery efficiency *in vivo* than their unmodified counterparts. Furthermore, these PAPs can be formulated into four-component LNPs, enabling selective mRNA expression in the lung and liver organs.

In summary, these structural modifications and nanoformulation strategies establish dendrimers as a highly promising mRNA delivery platform. Their tunable physicochemical properties enable both high transfection efficiency and enhanced biosafety, positioning dendrimer-based systems as clinically viable candidates for mRNA therapeutics in disease treatment.

5. Ionizable amphiphilic Janus dendrimers (IAJDs)-mediated mRNA delivery

IAJDs are a class of asymmetric dendrimers with both hydrophilic and hydrophobic functional units. The term "Janus" refers to their two-faced nature, where one side contains hydrophilic groups and the

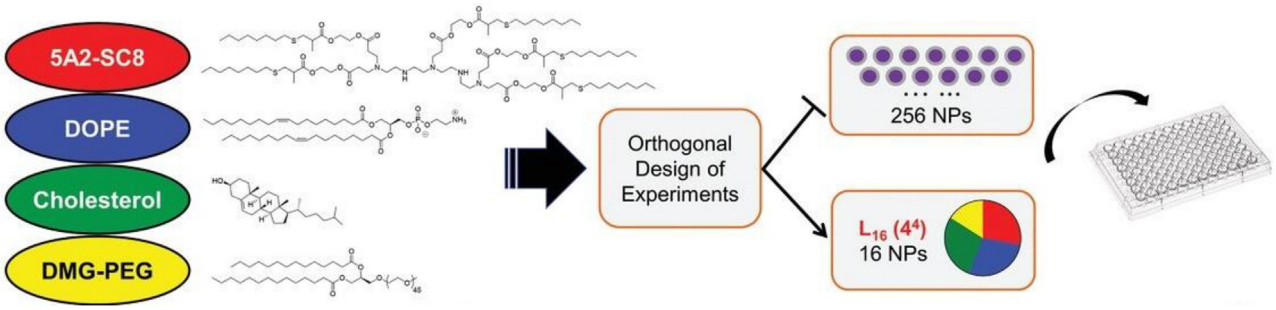


Fig. 11. Rational engineering of dLNPs enhances mRNA delivery efficiency. Reproduced with permission from ref [68]. Copyright 2018, Wiley-VCH GmbH.

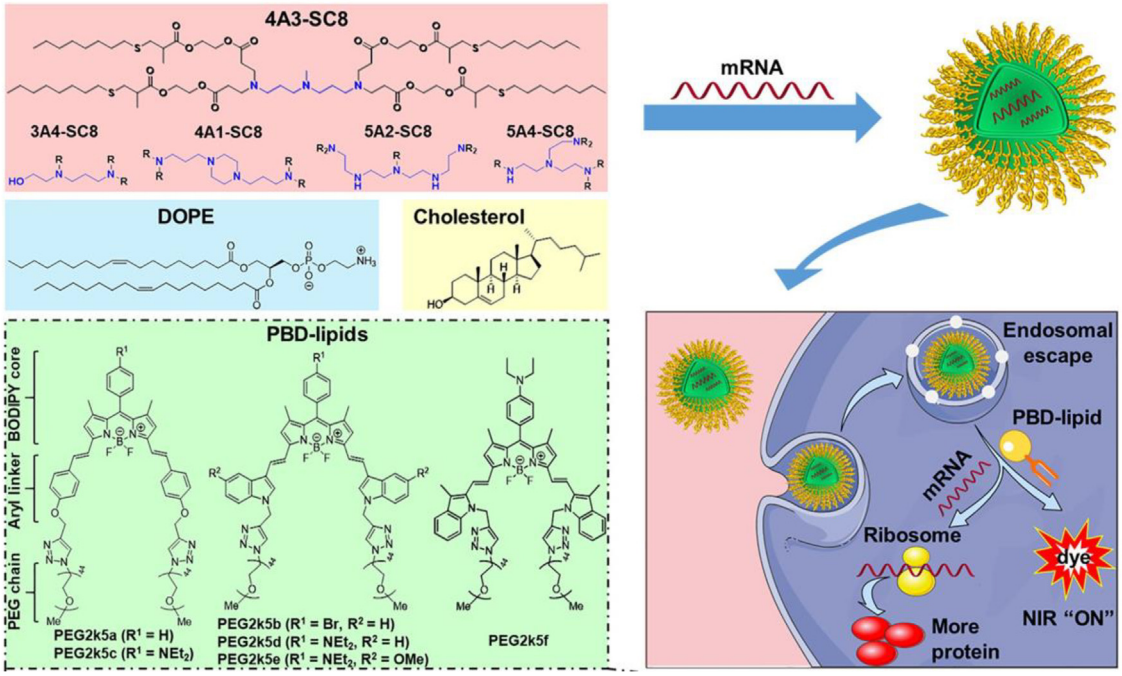


Fig. 12. Engineered dendrimer-based systems incorporating 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine, cholesterol, and PBD-lipid components for combined diagnostic and therapeutic mRNA delivery. Reproduced with permission from ref [70]. Copyright 2020, Elsevier B. V.

other contains hydrophobic groups [74]. This unique architecture allows them to self-assemble into ordered aggregates, such as dendrimersomes, in aqueous environments. Self-assembly of dendrimersomes for mRNA compaction can be readily achieved by direct injection of an IAJD ethanol solution into a citrate buffer containing mRNA. This process is driven by synergistic intermolecular interactions, including hydrophobic/hydrophilic forces, electrostatic interactions, and cation–π interactions [75]. The ionizable nature of IAJDs, which involves the incorporation of ionizable amines, enables them to effectively interact with anionic molecules like mRNA, facilitating their encapsulation, protection, and efficient delivery into cells. IAJDs have shown great promise in the targeted delivery of mRNA for gene therapy, where they enhance cellular uptake, endosomal escape, and overall delivery efficiency. Their modular design allows for tuning the molecular properties to optimize performance for specific therapeutic applications, making them a versatile tool in drug delivery and gene therapies [76].

Given the multiple advantages of IAJDs in gene delivery, researchers have recently explored their applications for mRNA delivery. For instance, Zhang *et al.* [75] developed six libraries consisting of 54 sequence-defined IAJDs using an accelerated modular-orthogonal synthesis method. These IAJDs were co-assembled with mRNA to form dendrimer NPs (DNPs) *via* a straightforward injection method. In contrast to traditional four-component LNPs that require microfluidic mixing for preparation, the formulated DNP platform is assembled from a single IAJD component using a simple injection method. To screen the prepared DNP formulations, firefly luciferase-encoding mRNA (Luc-mRNA) was utilized to evaluate their efficacy in mRNA delivery. *In vitro* testing revealed that 44 out of the 54 IAJDs (81%) demonstrated effective mRNA delivery capacity, with four showing superior performance compared to the Food and Drug Administration-approved D Linoleic acid-MC3-Dimethylamine (for short, MC3) control in four-component LNPs. And 31 of the DNPs (57%) achieved high mRNA delivery efficacy *in vivo*, with two achieving higher lung-targeted delivery efficiency than the MC3 control, which is particularly significant for organ-selective mRNA delivery (Fig. 13).

The IAJDs with different structures exhibit distinct organ-targeting specificities, which are of significant clinical importance for mRNA therapeutics. Zhang *et al.* [77] investigated the use of IAJDs for targeted mRNA delivery to various organs, including the lung, liver, spleen, and lymph nodes. The results showed that eleven IAJDs achieved organ-selective targeting specificity. Among them, IAJD 178(13/18) yielded the highest Luc-mRNA delivery efficiency in the spleen, whereas IAJD 155(11/EH) and IAJD 111(11/11) showed the highest efficacy in the lung. The study emphasized the importance of structural modifications, particularly the transition from ester to amide linkages between den-

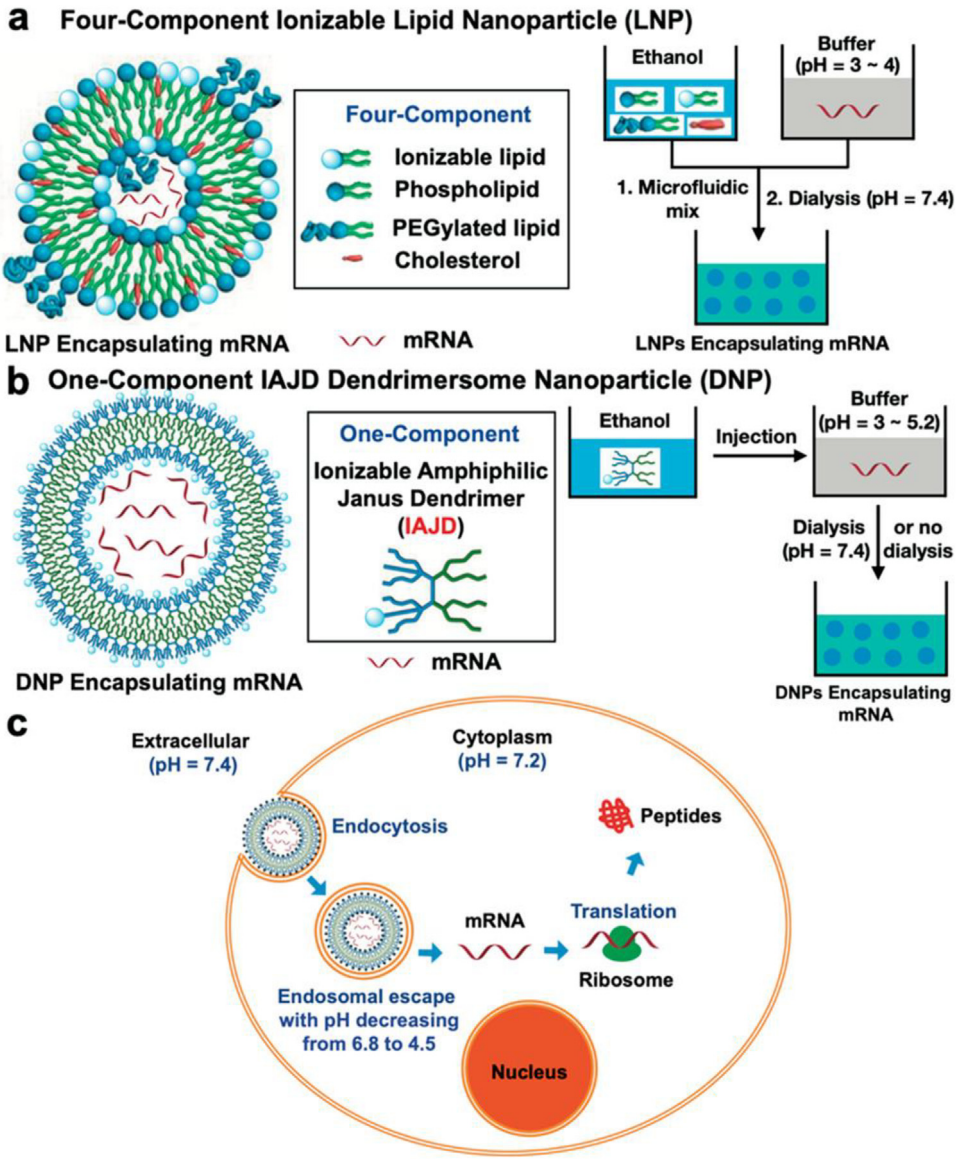


Fig. 13. Graphical depiction of (a) multicomponent LNPs for mRNA encapsulation and delivery; (b) one-component DNPs for mRNA delivery, and (c) comparative cellular internalization and payload release mechanisms of LNPs or DNPs. Reproduced with permission from ref [75]. Copyright 2021, American Chemical Society.

drimer components in enhancing mRNA delivery efficiency. Additionally, varying the length of the alkyl chains in the hydrophobic portion of the IAJDs was found to be useful to optimize mRNA delivery performance. Furthermore, a library of pentaerythritol-based IAJDs was synthesized by Lu *et al.* [78] using a three-step reaction, revealing an interesting result showing that IAJD 288 can effectively deliver mRNA in a nearly equal distribution to the spleen, liver, and lymph nodes. These findings suggest that such IAJDs could serve as simpler and more efficient synthetic alternatives than other viral and synthetic delivery systems for mRNA therapeutics.

Beyond the above IAJDs, another type of IAJDs, non-symmetric star-star ionizable amphiphilic Janus dendrimers (nsSS IAJDs) libraries have been synthesized using a modular-orthogonal approach. The libraries consist of 78 molecules based on 3,5-dihydroxy phenolic acid, incorporating methyl piperazine and hydroxyethyl piperazine as ionizable amines. The hydrophilic component of the IAJDs, determined by their ionizable amines and sequence structure, plays a crucial role in deciding the targeted organs. Specifically, the nsSS IAJDs with hydroxyethyl piperazine tend to target the spleen, while their methyl piperazine-modified counterparts are more effective for liver targeting. Furthermore, piperidine- and dimethylamine-conjugated nsSS IAJDs are particularly beneficial for targeting the lungs, highlighting the importance of amine selection in optimizing the delivery of mRNA to specific organs [79].

Furthermore, studies have revealed that structural isomers of IAJDs display varying efficiencies in mRNA delivery and targeting specificity to organs. For example, IAJD 178 exhibits the highest luciferase activity in the liver, whereas IAJD 308 shows the highest activity in the spleen (Fig. 14). These findings suggest that IAJDs possess considerable potential for targeted mRNA delivery with the ability to direct mRNA to specific organs [76].

6. Applications of dendrimer-mediated mRNA delivery

6.1. Gene editing

Dendrimer-mediated mRNA delivery has unlocked potential in novel therapeutic domains, particularly in gene editing, due to its enhanced stability, targeting capabilities, and low cytotoxicity. In this field, dendrimers are proving to be valuable delivery vehicles for mRNA-

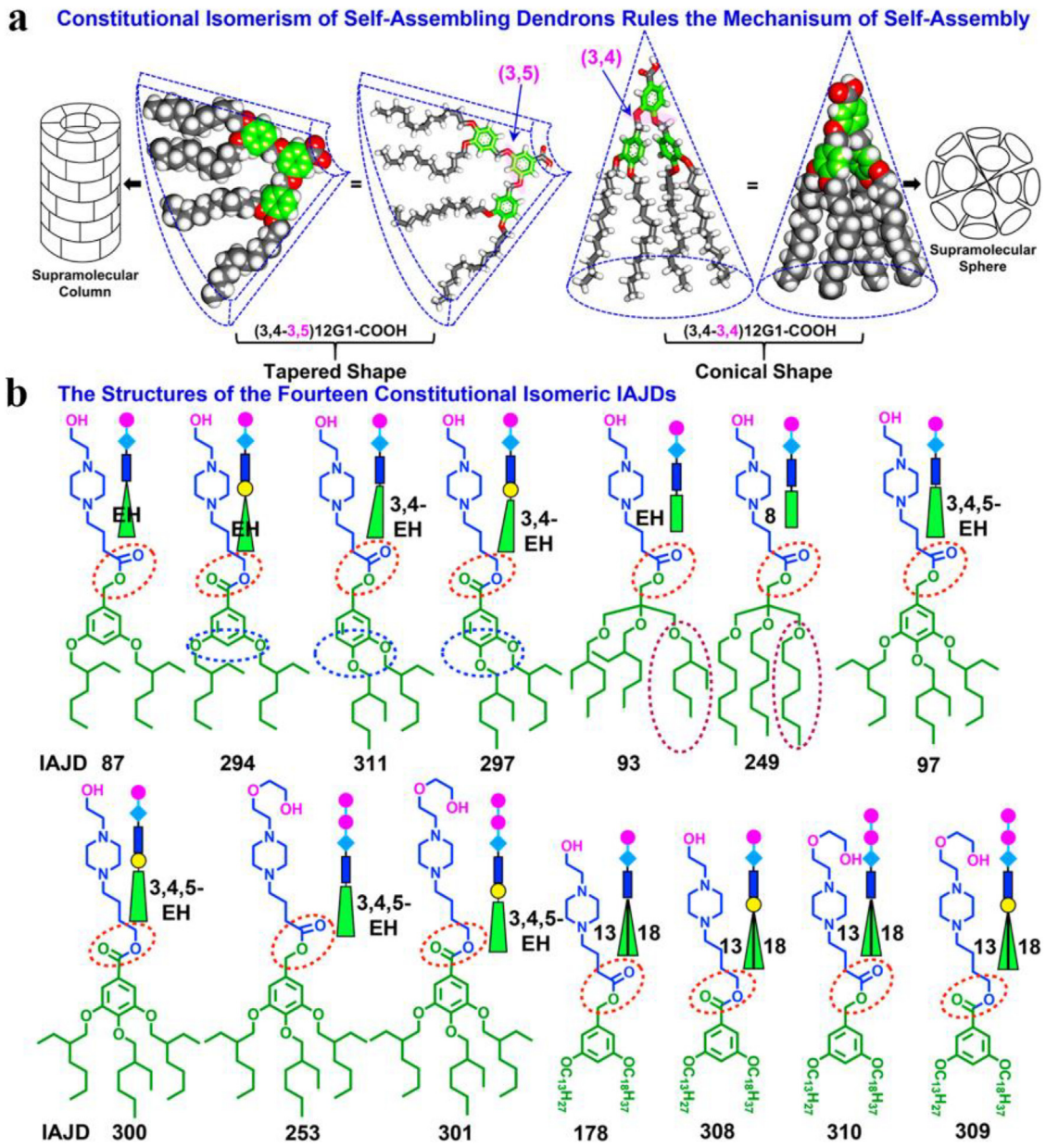


Fig. 14. (a) Stereochemical isomerism in dendron self-organization. (b) Structures of IAJDs containing ionizable amines attached *via* benzyl and benzoate esters to hydrophobic fragments. IAJD numbers and structures are also shown. Reproduced with permission from ref [76]. Copyright 2024, American Chemical Society.

encoded gene editing of enzymes like CRISPR-associated proteins (*e.g.*, Cas9) [62]. Siegwart and colleagues developed an all-nucleic-acid CRISPR/Cas9 delivery platform for precise genome editing. The system incorporates Cas9 mRNA, sgRNA, and single-stranded donor DNA (ssDNA) within dendrimer-incorporated 4A3-SC8 dLNPs, achieving high-efficiency HDR. Remarkably, this approach mediated gene editing in >91% of cultured cells with 56% HDR efficiency, while maintaining >20% HDR efficiency *in vivo* (Fig. 15) [69]. In contrast, the corresponding gene editing efficiency of LNPs was 90.3% in erythroid cells *in vitro* and 48.5% in murine bone marrow cells *in vivo*. These results indicate that the performance of dLNPs for *in vivo* editing still requires further optimization [80]. The highly customizable nature of 4A3-SC8 dLNPs enables effective transport of mRNA payloads to specific cellular compartments, facilitating precise gene editing at targeted sites. This precision is critical for treating genetic disorders, as it reduces non-specific editing while improving the treatment effectiveness of CRISPR-Cas9-based interventions, enabling safe and effective clinical applications in gene therapy.

6.2. Cancer therapy

Dendrimer-mRNA polyplexes can also be used as cancer therapeutics. Tumor suppressor dysfunction drives carcinogenesis and therapy resistance. Therefore, restoring the function of tumor suppressors represents a promising therapeutic strategy. Xiao *et al.* [81] developed C-X-C motif chemokine receptor 4 (CXCR4)-targeted dendrimer nanoparticles delivering p53 mRNA to reshape the immunosuppressive tumor microenvironment in a p53-deficient mouse hepatocellular carcinoma (HCC) model. Combined with anti-PD-1 antibody-mediated immune checkpoint blockade, this strategy enhanced antitumor immunity, suppressed cancer metastasis, and prolonged survival of tumor-bearing mice (Fig. 16).

6.3. Anti-inflammation therapy

Dendrimer-based nanoplatforms enable efficient delivery of mRNA encoding therapeutic proteins, facilitating immunomodulation to tackle

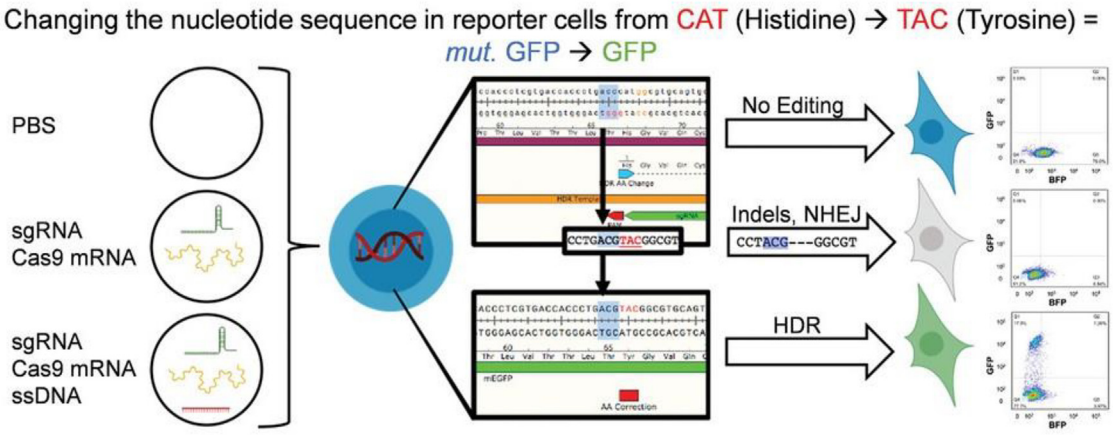


Fig. 15. HEK293 cells contain a single amino acid mutation in their green fluorescent protein (GFP) sequence that alters their fluorescence. Depending on the gene editing technique employed, the fluorescence can be eliminated (non-homologous end joining) or restored to native GFP (HDR). Reproduced with permission from ref [69]. Copyright 2021, Wiley-VCH GmbH.

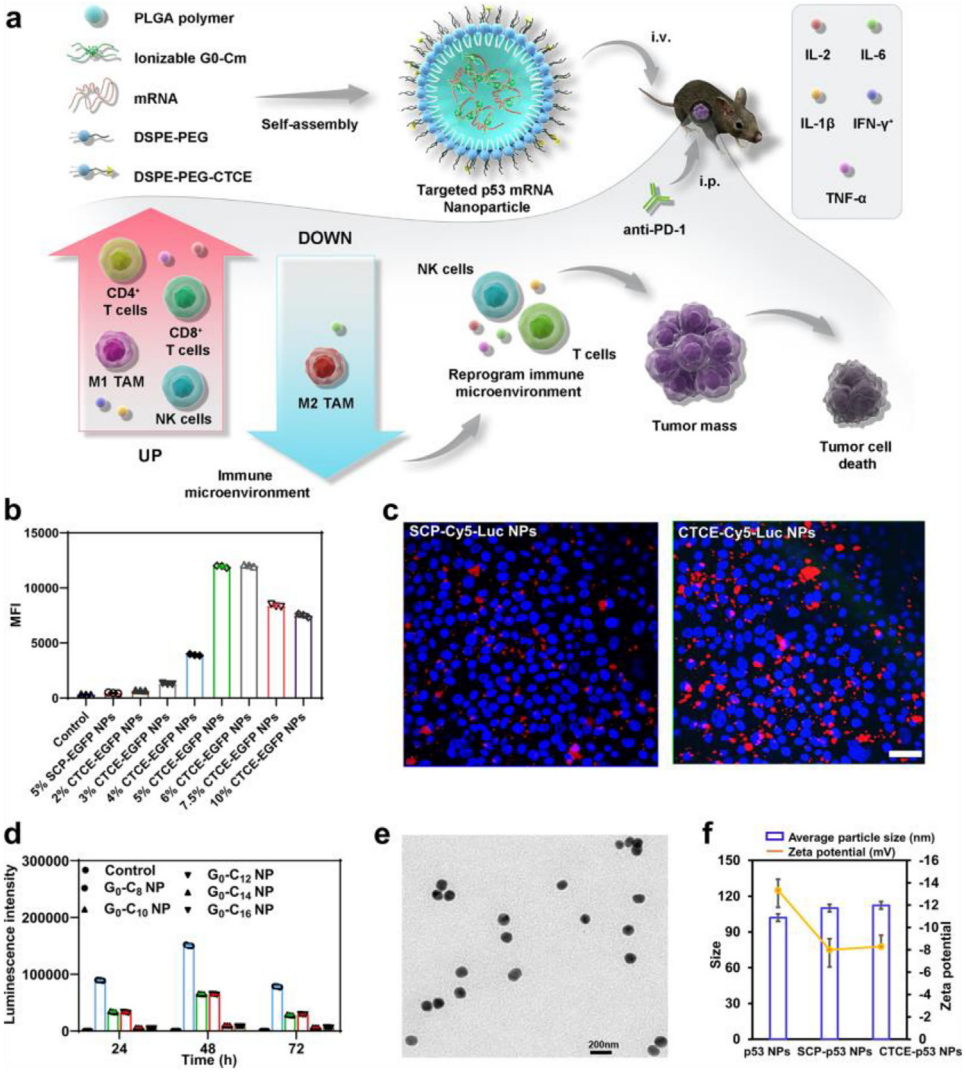


Fig. 16. Dendrimer-based NPs for p53 mRNA delivery to treat HCC. (a) Schematic of a combinatorial immunotherapy strategy employing CXCR4-targeted p53 mRNA nanoparticles and anti-PD-1 blockade to remodel the immunosuppressive microenvironment in p53-deficient HCC. (b) Cellular uptake in RIL-175 HCC cells of different NPs by flow cytometry. (c) Confocal microscopy of RIL-175 cells after 4 h incubation with different NPs. (d) Transfection efficiency of Luc-mRNA NPs formulated with different cationic lipid-like materials. (e) TEM image of CTCE-mRNA NPs. (f) Hydrodynamic size and zeta potential of different NPs. Reproduced with permission from ref [81]. Copyright 2022, Springer Nature.

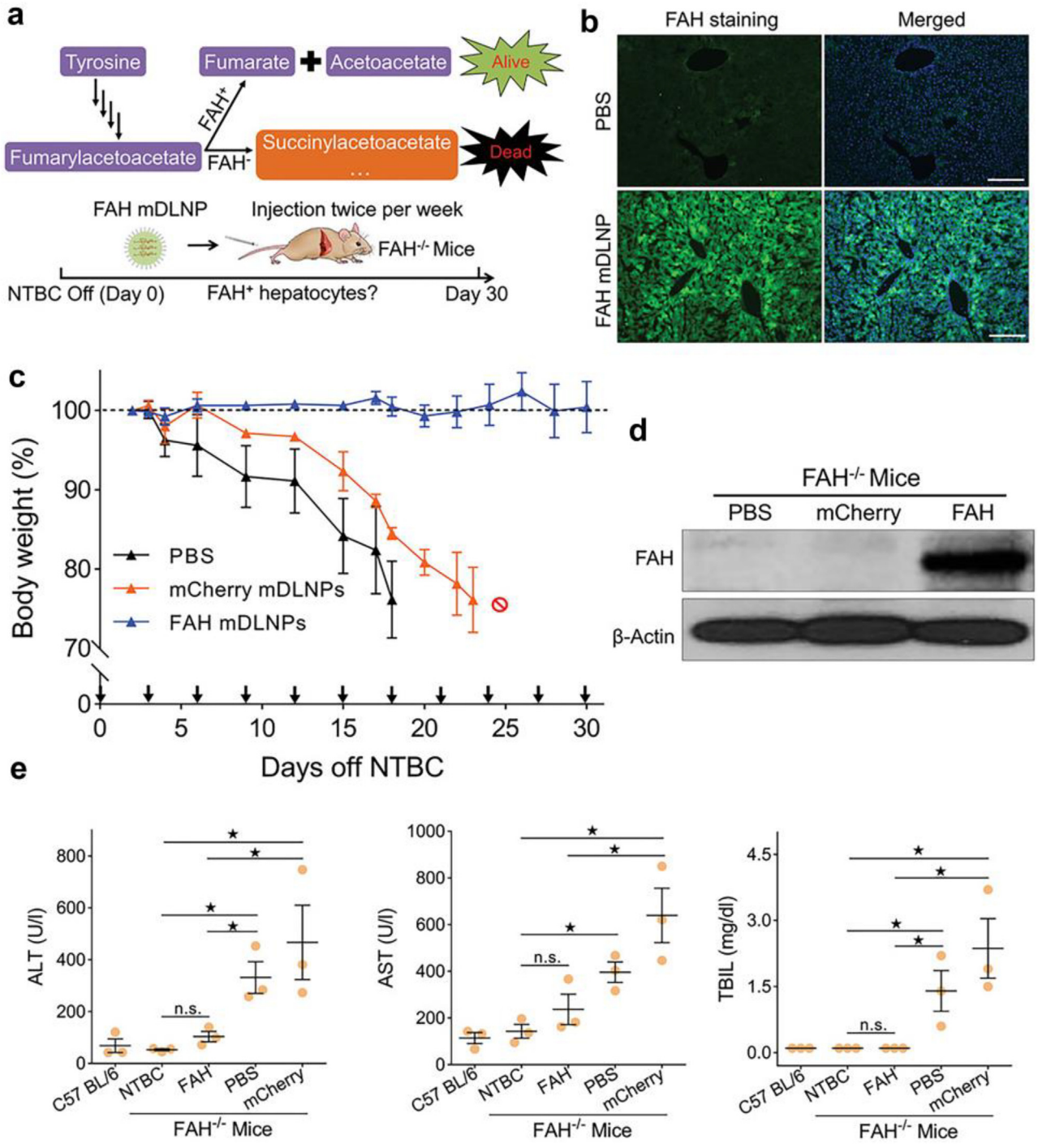


Fig. 17. Delivery of FAH mRNA complexed with dendrimer-incorporating dLNPs effectively rescued hepatobiliary functional markers in FAH knockout mice. (a) Schematic of the mRNA therapeutic regimen. (b) Immunofluorescence (IF) staining of liver sections from FAH−/− mice 6 h after injection of FAH mRNA-loaded dLNPs. (c) Body weight changes in FAH−/− mice over one month of treatment. (d) Western blot analysis of FAH expression in liver tissues at endpoint. (e) Serum levels of liver injury markers: ALT, AST, and TBIL. Reproduced with permission from ref [68]. Copyright 2018, Wiley-VCH GmbH.

inflammatory diseases. Children with FAH deficiency develop hepatorenal tyrosinemia type 1 (HT-1), a metabolic disorder characterized by liver failure, renal dysfunction, and neurological complications, often accompanied by secondary inflammation due to tissue damage. FAH mRNA-based protein replacement therapy is promising in treating HT-1. Cheng *et al.* [68] demonstrated that FAH mRNA-loaded dendrimer-incorporating 5A2-SC8 dLNPs restore functional FAH expression in FAH−/− mice, normalizing body weight and hepatic function, thereby mitigating secondary inflammatory damage (Fig. 17).

Dendrimer-based nanoplatforms can also deliver mRNA for immunoregulation in lung diseases. Recently, a pulmonary-targeted IAJD34 dendrimers delivered TGF-β mRNA to alveolar macrophages, transiently expressing TGF-β and mitigating bleomycin-induced lung injury in mice [72]. Furthermore, dendrimer-based mRNA delivery nanoplatforms can be applied to treat inflammation-associated ocular diseases. Cheng *et al.* [22] developed a library of fluorinated PAMAM dendrimers (FD) for Cas9 mRNA delivery. The lead candidate, FD17, demonstrated superior serum stability and endosomal escape capacity,

outperforming commercial transfection reagents such as Lipofectamine 3000 in mRNA delivery across diverse cell types. In a murine model of laser-induced choroidal neovascularization (CNV), intravitreal administration of FD17 complexed with Cas9 mRNA and vascular endothelial growth factor A (VEGFA)-targeting sgRNA achieved robust retinal pigment epithelium penetration. This enabled efficient VEGFA gene knockout, resulting in significant suppression of choroidal angiogenesis, vascular leakage, CNV lesion formation and associated pathological inflammation. These advances highlight the versatility of dendrimer platforms in mRNA-based therapeutics for anti-inflammation therapy.

6.4. Infectious disease treatment

In addition to therapeutic applications, mRNA vaccines demonstrate considerable potential for prophylactic interventions against infectious diseases. G1 PAMAM dendrimers modified with 2-tridecyloxirane were utilized to combine with PEG phospholipids and mRNA to prepare NPs through microfluidics [82]. This platform enabled rapid, contaminant-free production and elicited significant $CD8^+$ T cells and antibody responses after a single immunization, conferring a 100% survival rate following the lethal challenge with multiple virulent pathogens, notably Ebola virus, pandemic H1N1 influenza strains, and the protozoan parasite Toxoplasma gondii. These advancements demonstrate the versatility and promise of dendrimer-mediated mRNA vaccines, which offer a safer and more effective alternative than conventional therapeutics.

7. Conclusions and future perspectives

In conclusion, dendrimers have emerged as a promising platform for mRNA delivery, benefiting from advances in the design, synthesis, and application of dendrimer-based gene carriers. Their cationic nature enables efficient mRNA complexation through electrostatic interactions for intracellular mRNA delivery and subsequent ribosomal translation into functional proteins. Through surface-modification strategies such as surface shielding, targeting ligands, and PEGylation, dendrimers can be modified to have ameliorated cytotoxicity and improved mRNA transfection efficiency. Additionally, formulating dendrimers into different nanostructures (*e.g.*, NCs, CSTDs, or DNGs) not only reduces their cytotoxicity but also enhances their tissue penetration and retention. This structural optimization is beneficial for magnify the EPR effect associated with a desired particle size, thereby enhancing the efficacy of mRNA therapy. Further improvements in delivery efficiency can be achieved by integrating dendrimers with other materials, such as LNPs, to integrate both advantages of them. The designed mRNA-based therapeutics can be applied in gene editing, cancer therapy, anti-inflammation therapy and infectious disease treatment.

Dendrimer-mediated mRNA delivery systems have shown significant promise for therapeutic applications. However, the clinical translation of dendrimer-mediated mRNA delivery systems meets stringent regulatory requirements of safety, efficacy, and manufacturing consistency. Polycationic dendrimers may have certain cytotoxicity at a high dose. Consequently, it is necessary to modify dendrimers to balance the efficiency and safety for mRNA therapeutics. In addition, maintaining mRNA stability during formulation and ensuring efficient encapsulation within dendrimers necessitate rigorous optimization of dendrimer structures. Furthermore, incorporating stimuli-responsive elements enables controlled mRNA release in response to environmental triggers such as pH variations, redox conditions, light exposure, or ultrasonic waves, thereby achieving precise spatiotemporal mRNA delivery. The precise control over dendrimer-based mRNA therapeutics in size, shape, and charge distribution is crucial for scaling up production and ensuring batch consistency, which is essential for clinical translation.

Research on dendrimer-based mRNA delivery is still at an early stage, with many challenges to be addressed. First, although some of the dendrimer-based nanoformulations such as DNGs, DNCs, and CSTDs have been used for drug delivery or gene delivery applications, these dendrimer formulations have not been fully employed in mRNA delivery applications. Hence, it is vital to design different dendrimer systems to fully explore their mRNA delivery potential. Further investigations are also required to adapt these dendrimer designs for tissue-specific mRNA delivery to diverse organs, enabling precision treatment of various pathologies. Currently, LNPs dominate clinical mRNA delivery development but face inherent limitations, including notable cytotoxicity and instability. Combining phospholipids with dendrimers could lead to improved mRNA delivery. Furthermore, given the limited therapeutic efficacy of monotherapies, combinatorial approaches integrating mRNA-based treatment with different modalities of treatments warrant further exploration to achieve optimal outcomes. Additionally, rigorous efforts in mRNA screening are imperative. Only the synergy between well-selected mRNA cargos and highly efficient delivery vectors can maximize the treatment efficacy.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Xianghao Xiao: Writing – original draft. **Yiyang Jia:** Writing – original draft. **Mingwu Shen:** Supervision, Resources, Funding acquisition, Conceptualization. **Andrij Pich:** Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Xiangyang Shi:** Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Data availability

Data will be made available on request.

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