RESEARCH PAPER

Recent Advances in the Updates of Dendrimers in Drug Delivery Systems

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ABSTRACT

Dendrimers, highly branched and monodisperse macromolecules, have garnered significant interest as advanced nanocarriers in drug delivery due to their unique structural and physicochemical properties. Their precisely controlled architecture, abundant surface functional groups, and high drug-loading capacity enable effective encapsulation and targeted delivery of a wide range of therapeutic agents. Recent advances in dendrimer chemistry have focused on improving biocompatibility, stimuli-responsive release, and site-specific targeting through surface modification with ligands and smart moieties. This review comprehensively examines the latest innovations in dendrimer design, drug encapsulation techniques, and functionalization strategies. Key applications in cancer therapy, gene delivery, infectious disease management, and treatment of neurological and inflammatory disorders are highlighted. Furthermore, the integration of dendrimers into hydrogel and nanogel matrices offers promising platforms for sustained and localized drug release. The review also discusses clinical translation challenges including scalable synthesis, regulatory hurdles, and safety concerns. Finally, the emerging role of artificial intelligence in accelerating dendrimer development and optimizing drug delivery systems is explored. Future perspectives emphasize the need for multidisciplinary collaboration to overcome existing barriers and harness the full therapeutic potential of dendrimer-based nanomedicines.

Keywords: Dendrimers, Drug Delivery, Targeted Therapy, Gene Therapy, Nanogels, Hydrogels, Artificial Intelligence, Nanomedicine, Stimuli-Responsive Release, Clinical Translation.

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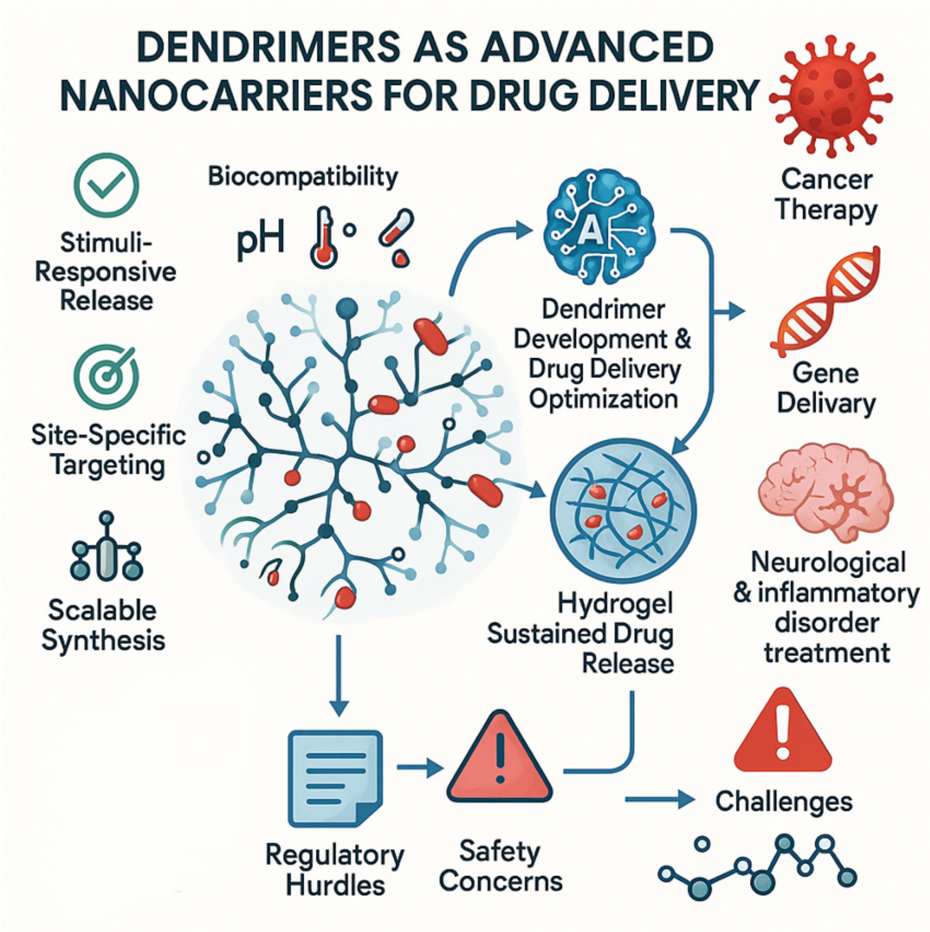
Graphical abstract



1. Introduction

Dendrimers represent a distinctive and versatile class of synthetic, nanoscale polymers that exhibit a highly branched, tree-like architecture. This unique structural design consists of a central core, repetitive branching units (referred to as generations), and numerous surface functional groups. Such an architecture allows precise control over molecular size, shape, polarity, solubility, and reactivity. These characteristics grant dendrimers exceptional suitability for a wide range of biomedical applications, with drug delivery being one of the most extensively studied.The multivalent nature of dendrimers—where multiple functional groups can be presented simultaneously—offers an unparalleled advantage for conjugating therapeutic agents, imaging moieties, targeting ligands, and other bioactive compounds. Furthermore, their internal cavities can encapsulate small molecules through hydrophobic, electrostatic, or hydrogen bonding interactions [1]. These capabilities enable dendrimers to serve both as carriers and protectants of therapeutic agents, improving solubility, pharmacokinetics, and overall therapeutic efficacy.Over the past two decades, significant advancements have been made in dendrimer synthesis, allowing for precise control over their generation size and surface functionality. Polyamidoamine (PAMAM), polypropylene imine (PPI), and poly(L-lysine) dendrimers are among the most widely investigated due to their biocompatibility and ease of functionalization. However, challenges such as cytotoxicity—primarily attributed to cationic surface charges—and poor biodegradability in some dendrimer types have prompted extensive research into surface engineering strategies [2]. Modifications including PEGylation, acetylation, and ligand conjugation have been employed to improve dendrimer safety and target-specific delivery.

Current trends in dendrimer research focus on integrating stimuli-responsive elements (pH, redox, temperature), optimizing targeted delivery via surface ligand attachment, and combining dendrimers with other nanocarriers such as liposomes and hydrogels for synergistic effects. Additionally, dendrimers are being increasingly applied in emerging therapeutic areas such as gene therapy, immunomodulation, and personalized medicine [3].

Table 1 shows a review that aims to present a comprehensive overview of recent advances in dendrimer-based drug delivery systems, highlighting innovations in design, drug encapsulation, targeting mechanisms, and clinical translation. Special attention is given to application areas including cancer, genetic disorders, infectious diseases, and neurological conditions. Furthermore, the integration of artificial intelligence (AI) in dendrimer design and optimization is discussed as a cutting-edge direction for future research [4].

Table 1 : recent adavances in dendimers

Aspect	Recent Advances	Details
Structure & Design	Janus dendrimers, click chemistry, hybrid systems	Enhanced functionality, bifunctional surfaces, modular construction
Drug Loading & Release	Stimuli-responsive systems	pH-, temperature-, redox-, and enzyme-responsive dendrimers for controlled drug release
Targeting Strategies	Ligand-conjugated dendrimers	Antibodies, peptides, folate, aptamers for site-specific delivery
Cancer Therapy	Combination therapy, immunotherapy loading	Co-delivery of chemo drugs and immune agents, targeted delivery to tumor microenvironment
Gene Delivery	PEGylated and cationic dendrimers	Enhanced transfection efficiency, reduced cytotoxicity
Infectious Disease	Antiviral and antibacterial dendrimers	SARS-CoV-2 inhibition, MRSA targeting with multivalent interactions
Neurological Disorders	BBB-penetrating dendrimers	Functionalized for brain targeting (e.g., Alzheimer's, Parkinson's)
Inflammatory Diseases	Anti-inflammatory drug carriers	Targeted delivery to inflamed tissues, macrophage-targeting dendrimers
Hydrogel/Nanogel Integration	Dendrimer-loaded hydrogels for sustained release	Injectable hydrogels for localized and extended drug delivery
Clinical Translation	Dendrimer-based drugs in trials (e.g., VivaGel®, DEP® docetaxel)	Progress in safety, pharmacokinetics, and therapeutic efficacy
AI & Computational Design	AI-driven dendrimer optimization, QSAR modelling	Predictive modeling of drug loading, release, and toxicity
Scalability & Manufacturing	Green synthesis, solvent-free approaches	Environmentally friendly, scalable production methods
Toxicity & Biocompatibility	Surface modification (PEGylation, acetylation)	Reduced toxicity, improved circulation time and cell compatibility
Regulatory Pathways	Standardization and	Increasing interest in

	guideline development	clear regulatory frameworks for nanomedicine

2. Structural Features and Drug Encapsulation

Dendrimers are characterized by their highly organized, symmetrical architecture composed of three fundamental components: a central core, repeated branching units (generations), and a peripheral shell of functional groups. This well-defined structure allows for precise control over size, shape, molecular weight, and surface chemistry, which distinguishes dendrimers from traditional linear polymers and other nanocarriers [5]. The internal cavities created by the branching layers provide ample space for encapsulating small drug molecules through non-covalent interactions such as hydrogen bonding, hydrophobic interactions, and van der Waals forces.Simultaneously, the abundance of surface functional groups allows for the covalent or electrostatic attachment of therapeutic agents, imaging probes, targeting ligands, and solubilizing moieties [6]. This dual capability—internal encapsulation and surface conjugation—enables dendrimers to carry both hydrophilic and hydrophobic drugs, enhancing their versatility as drug delivery systems.Recent advances in dendrimer synthesis and functionalization have further refined their physicochemical properties. Researchers can now tailor the size, charge density, hydrophilicity, and degradation profile of dendrimers to optimize pharmacokinetics, minimize toxicity, and control drug release rates. For instance, modifying the terminal groups with polyethylene glycol (PEG) or other biocompatible polymers has been shown to reduce cytotoxicity and extend systemic circulation time. In addition, dendrimers can be designed to respond to physiological stimuli such as pH, temperature, or enzymatic activity enabling site-specific and controlled drug release.These structural and functional advantages make dendrimers highly effective nanocarriers for improving drug solubility, enhancing bioavailability, and achieving targeted therapeutic outcomes, all of which are critical factors in the development of next-generation drug delivery platforms [7].

3. **Targeted Drug Delivery and Stimuli-Responsive Systems**

One of the most valuable features of dendrimers in drug delivery systems is their highly functionalizable surface, which enables precise and selective therapeutic targeting [8]. By modifying dendrimer surfaces with specific targeting ligands such as antibodies, peptides, folic acid, or aptamers, these nanocarriers can recognize and bind to overexpressed receptors or specific biomarkers on diseased cells. This active targeting approach enhances the accumulation of therapeutic agents at the intended site while minimizing off-target effects and systemic toxicity.In addition to targeting ligands, dendrimers can be engineered to incorporate stimuli-responsive moieties that allow for controlled and site-specific drug release[9]. These functional groups respond to internal stimuli—such as pH variations in tumor microenvironments, elevated levels of glutathione (redox), or overexpressed enzymes and external stimuli like temperature or light. For example, pH-sensitive dendrimers can remain stable at physiological pH but release their cargo in acidic tumor or endosomal environments, thereby improving therapeutic efficiency [10]. Integrating targeting and stimuli-responsive functionalities in dendrimers represents a synergistic strategy that ensures both high selectivity and temporal control over drug release. Such intelligent delivery systems hold significant promise for personalized medicine by tailoring treatment to specific disease profiles and individual patient conditions [11].

a. Cancer Therapy

Dendrimers are widely investigated for cancer therapy due to their ability to selectively deliver chemotherapeutic drugs to tumor cells while minimizing damage to healthy tissues. Their surfaces can be functionalized with targeting ligands like folic acid, transferrin, or peptides that recognize overexpressed receptors on cancer cells, enabling enhanced tumor-specific uptake [12]. Furthermore, dendrimers can be engineered to release drugs in response to tumor-specific stimuli such as acidic pH or high intracellular glutathione (GSH) levels, improving intracellular drug release. Redox-sensitive dendrimers, for example, remain stable in circulation but degrade in the reductive tumor microenvironment, allowing site-specific drug action. Recent developments include multifunctional dendrimers for combined drug delivery and imaging (theranostics). These intelligent systems offer improved therapeutic indices, reduced systemic toxicity, and enhanced patient outcomes, positioning dendrimers as a cornerstone in the evolution of nanomedicine for precision cancer therapy [13].

b. Gene Therapy and Genetic Disorders

Gene therapy requires safe and efficient delivery systems for nucleic acids, and dendrimers—particularly cationic ones like PAMAM and PPI—have shown substantial promise. These dendrimers can form stable complexes with DNA, siRNA, or mRNA via electrostatic interactions, protecting them from enzymatic degradation and facilitating cellular uptake. However, early generations exhibited cytotoxicity due to high surface charge [14]. To address this, surface modifications such as PEGylation, acetylation, or ligand conjugation have been employed to improve biocompatibility without compromising transfection efficiency. Recent studies report dendrimers achieving efficient gene delivery in vitro and in vivo, with applications in treating genetic disorders such as cystic fibrosis, spinal muscular atrophy, and hemophilia. Additionally, dendrimers allow co-delivery of genes and small-molecule drugs, enabling combination therapies [15]. These advances underline dendrimers' potential as customizable, non-viral vectors offering safety, precision, and multifunctionality in genetic medicine.

c. Infectious Disease Management

Dendrimers offer significant advantages in managing infectious diseases due to their capacity to encapsulate and stabilize antiviral, antibacterial, and antifungal agents. Their nanoscale architecture allows them to cross biological barriers and deliver drugs directly to infected cells or tissues, improving therapeutic efficacy and reducing systemic toxicity. For viral infections like HIV and COVID-19, dendrimer-based formulations enhance drug solubility and protect active compounds from degradation. Notably, VivaGel®, a dendrimer-based antiviral gel, has demonstrated effectiveness against sexually transmitted infections [16]. In tuberculosis, dendrimers improve drug delivery to intracellular reservoirs like macrophages. Additionally, surface modification with pathogen-targeting ligands or charge optimization enhances selectivity. With increasing drug resistance, dendrimers are being explored as platforms for co-delivery of antimicrobial agents and adjuvants [17]. Their ability to combine therapeutic delivery with immunomodulation marks dendrimers as innovative tools in the fight against infectious diseases.

d. Anti-Inflammatory and Autoimmune Therapies

Dendrimers offer a promising platform for targeted delivery of anti-inflammatory drugs, particularly in the treatment of chronic inflammatory and autoimmune diseases. Systemic administration of corticosteroids or NSAIDs often leads to undesirable side effects; dendrimer-based systems help mitigate this by enabling localized and sustained release of therapeutic agents at inflamed sites. Functionalization with specific ligands allows dendrimers to accumulate in inflamed tissues or immune cells [18]. For example, dendrimer-N-acetylcysteine conjugates have shown significant reduction of inflammation in models of rheumatoid arthritis and inflammatory bowel disease. Additionally, dendrimers can modulate immune responses by delivering siRNA or immunosuppressive agents directly to immune cells, minimizing systemic immunosuppression. Advances in stimuli-responsive dendrimers further enable release of drugs in response to oxidative stress or enzymatic activity associated with inflammation. These targeted and responsive systems demonstrate the potential of dendrimers to revolutionize therapy for inflammatory and autoimmune conditions.

e. Neurological Disorders

The treatment of neurological disorders is challenging due to the blood-brain barrier (BBB), which restricts drug access to the central nervous system (CNS). Dendrimers offer a unique solution, as they can be engineered to cross the BBB and deliver neurotherapeutics directly to affected regions. Surface modification with ligands such as transferrin, lactoferrin, or glucose enhances BBB penetration via receptor-mediated transport. Dendrimers have been successfully used to deliver small molecules, peptides, and nucleic acids in models of Alzheimer's disease, Parkinson's disease, and glioblastoma [19]. They also enable sustained drug release and reduced systemic exposure, minimizing side effects. In addition, dendrimers have anti-inflammatory and neuroprotective properties, further supporting their use in CNS disorders. Studies have shown promising results in animal models, and some formulations are progressing toward clinical evaluation. These advancements establish dendrimers as powerful tools for the targeted and effective treatment of complex neurological diseases [20].

f. Ocular and Pulmonary Therapies

Dendrimers are increasingly utilized for localized treatment in ocular and pulmonary conditions, offering improved bioavailability and reduced systemic side effects. In ophthalmology, dendrimer-based eye drops, gels, and inserts enhance drug retention and penetration across ocular barriers, improving the treatment of glaucoma, uveitis, and dry eye disease. Their mucoadhesive properties and ability to control release rates ensure prolonged therapeutic action. In pulmonary therapy, dendrimers enable aerosol-based delivery of antibiotics, anti-inflammatory agents, or antivirals directly to the lungs [21]. This is especially beneficial in diseases like asthma, COPD, tuberculosis, and cystic fibrosis, where localized action is essential. Inhalable dendrimer formulations can also encapsulate poorly soluble drugs, improving their efficacy. Advances in biocompatible and biodegradable dendrimers further support their clinical translation in respiratory and ocular medicine. These delivery systems offer precision, reduced dosing frequency, and enhanced patient compliance.

4. Gene Delivery Applications

Dendrimers have emerged as powerful non-viral vectors for gene delivery due to their well-defined architecture, high degree of surface functionality, and biocompatibility. Unlike viral systems, dendrimers exhibit low immunogenicity and minimal insertional mutagenesis, making them safer for therapeutic use. Their cationic surface facilitates strong electrostatic interactions with negatively charged nucleic acids such as plasmid DNA, siRNA, miRNA, or mRNA, forming nanoscale complexes known as dendriplexes [22]. These complexes not only protect genetic material from enzymatic degradation but also enhance cellular uptake and transfection efficiency. One of the key innovations in this field is the development of dendrimer-based hybrid systems that integrate dendrimers with lipids, peptides, or other polymers to improve biostability, targeting, and endosomal escape. These hybrids combine the strengths of multiple nanocarriers to overcome the limitations of single-component systems. Furthermore, dendrimers have been successfully engineered for the co-delivery of gene-editing tools, such as the CRISPR-Cas9 system. By encapsulating or complexing both Cas9 protein and guide RNA, dendrimers provide a compact and efficient platform for in vivo genome editing. Dendrimer-based delivery systems have been evaluated in a variety of disease models, including cancer, genetic disorders, and neurological diseases. Functionalization with targeting ligands such as antibodies or aptamers has enhanced tissue-specific delivery and reduced off-target effects [23]. Additionally, surface modifications like PEGylation and acetylation have significantly improved their safety and circulation time. With their customizable architecture and multifunctional capabilities, dendrimers represent a highly adaptable and promising platform for safe, efficient, and targeted gene therapy.

4. **Dendrimer-Based Hydrogels and Nanogels**

Integration of dendrimers into hydrogel and nanogel matrices represents a significant advancement in the design of multifunctional drug delivery platforms. These composite systems combine the nanoscale precision and functional versatility of dendrimers with the structural and physicochemical advantages of hydrogels and nanogels. Dendrimer-based hydrogels are formed through covalent or physical crosslinking between dendrimers and polymeric networks, allowing for controlled architecture and tunable drug loading. Such systems offer several benefits, including sustained and localized drug release, high biocompatibility, adjustable degradation rates, and mechanical strength suitable for diverse biomedical applications. The high water content of hydrogels ensures a moist environment, beneficial for wound healing, while dendrimer functional groups can be tailored to encapsulate or conjugate therapeutic agents such as antibiotics, anticancer drugs, or growth factors [24]. In cancer therapy, dendrimer-loaded hydrogels have been used for localized, intratumoral drug release, minimizing systemic toxicity. In tissue engineering, they provide scaffolding that supports cell attachment and proliferation, while delivering regenerative cues. Nanogels, on the other hand, offer injectable, stimuli-responsive formulations that can release their payloads in response to pH, temperature, or enzymatic changes in the pathological microenvironment. Moreover, these systems can be engineered with targeting moieties and imaging agents for theranostic applications. Ongoing research focuses on optimizing these hybrid structures for enhanced stability, precision, and clinical translation [25]. Overall, dendrimer-based hydrogels and nanogels represent a promising frontier in personalized medicine, offering precise spatial and temporal control over therapeutic delivery.

5. Clinical Translation and Challenges.

While dendrimers have demonstrated remarkable potential in preclinical studies for drug delivery, their translation into clinical applications remains limited. Several significant challenges must be addressed to enable widespread clinical adoption. One major hurdle is the scalable synthesis of dendrimers with consistent quality and reproducibility. The complex, multistep synthesis procedures often result in batch-to-batch variability, which complicates regulatory approval and manufacturing. Regulatory pathways for dendrimer-based therapeutics are also not well established, as these nanomaterials possess unique physicochemical and biological properties that differ from traditional small molecules or biologics [26]. This creates difficulties in defining appropriate characterization standards, toxicity assessments, and quality control measures. Furthermore, long-term safety data are scarce, and concerns about dendrimer accumulation, biodegradability, and immunogenicity persist, necessitating extensive in vivo studies.Despite these challenges, a few dendrimer-based products, such as VivaGel®, have successfully advanced to clinical trials and even market approval. VivaGel® is a dendrimer-based antiviral gel developed for prevention of sexually transmitted infections, exemplifying the clinical feasibility of dendrimer platforms. Encouragingly, ongoing research focuses on improving dendrimer design to enhance biodegradability and reduce toxicity [27]. overcoming manufacturing and regulatory challenges, alongside thorough safety evaluations, will be critical to unlocking the full clinical potential of dendrimer-based drug delivery systems. Continued interdisciplinary collaboration and innovation are essential to accelerate their transition from bench to bedside.

7. AI in Dendrimers

Artificial intelligence (AI) and machine learning (ML) are transforming the field of dendrimer research by accelerating the design, optimization, and application of dendrimer-based drug delivery systems. Traditional dendrimer development involves labor-intensive synthesis and experimental testing, which can be time-consuming and costly. AI-driven computational approaches enable the rapid prediction of dendrimer properties, drug-binding affinities, and biological interactions, significantly streamlining the development pipeline [28]. Machine learning models analyze large datasets from experimental and simulation studies to uncover structure-activity relationships (SARs), identifying key molecular features that influence drug encapsulation efficiency, release kinetics, and targeting capabilities. These insights guide the rational design of dendrimers with optimized size, charge, and surface functionality tailored for specific therapeutic applications.AI also facilitates optimization of formulation parameters, such as drug loading capacity, stability, and stimuli-responsiveness, enabling the development of smart, controlled-release systems. Moreover, deep learning algorithms can predict dendrimer biocompatibility and toxicity profiles, enhancing safety assessments early in the design process.Beyond design, AI assists in identifying novel therapeutic targets and predicting synergistic drug combinations for dendrimer-mediated delivery, expanding their applicability across various diseases. Integration of AI with experimental workflows accelerates discovery and reduces resource consumption, promoting personalized and precision medicine.In summary, AI-powered tools represent a paradigm shift in dendrimer research, offering unprecedented capabilities to design sophisticated nanocarriers efficiently and effectively, thus enhancing the translational potential of dendrimer-based therapeutics [30].

8. Challenges and Future Directions

Despite significant progress, several key challenges must be addressed to fully realize the potential of dendrimers in drug delivery. Ensuring biocompatibility and minimizing cytotoxicity remain critical, particularly for clinical applications requiring repeated or long-term administration. Achieving highly efficient targeted delivery combined with stimuli-responsive release mechanisms also poses challenges, as it requires precise control over dendrimer surface chemistry and responsiveness to complex biological environments. Another major barrier is the complexity of dendrimer synthesis, which often involves multiple steps, expensive reagents, and difficult purification processes. Simplifying and streamlining synthesis pathways is essential to enable scalable manufacturing and reduce production costs. Standardization of protocols will also enhance batch-to-batch reproducibility, a crucial requirement for regulatory approval [31]. Future research directions include the development of hybrid dendrimer systems that combine the advantages of dendrimers with other nanomaterials, such as liposomes or polymers, to improve stability, targeting, and multifunctionality. Personalized nanomedicine approaches, leveraging patient-specific biomarkers and AI-driven design, promise to enhance therapeutic efficacy and safety. Moreover, integrating dendrimer-based delivery platforms with digital health technologies could enable real-time monitoring of drug release and disease progression, facilitating precision therapy. Advances in scalable manufacturing and regulatory science will be necessary to translate these innovations into clinical reality.

In conclusion, multidisciplinary efforts combining chemistry, biology, engineering, and data science are vital to overcoming current limitations and advancing dendrimer drug delivery toward widespread clinical adoption.

9.Conclusion

Dendrimers have emerged as highly versatile and promising nanocarriers in drug delivery systems, owing to their well-defined, tree-like architecture, multivalency, and tunable surface functionalities. These unique structural features enable efficient drug encapsulation, targeted delivery, and stimuli-responsive release, making dendrimers suitable for a wide range of therapeutic applications including cancer, gene therapy, infectious diseases, and neurological disorders. Advances in dendrimer-based hydrogels, nanogels, and hybrid systems further expand their utility in localized and sustained drug release. Integration of artificial intelligence accelerates rational dendrimer design and optimization, enhancing translational potential. However, challenges such as biocompatibility, scalable synthesis, regulatory hurdles, and long-term safety remain barriers to clinical translation. Addressing these issues requires sustained interdisciplinary collaboration across chemistry, nanotechnology, biology, and computational sciences. With ongoing innovation and integration of personalized medicine and digital health tools, dendrimer-based therapeutics hold great promise for advancing precision drug delivery and improving patient outcomes.

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