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Review article

DNA polymer conjugates: Revolutionizing neurological disorder treatment through targeted drug delivery

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ABSTRACT

Neurological disorders present a formidable challenge to modern medicine due to their complex etiology and limited treatment options. Traditional therapeutic approaches often struggle to penetrate the blood-brain barrier (BBB) effectively, hindering the delivery of drugs to the central nervous system (CNS). However, recent advancements in nanotechnology have opened new avenues for targeted drug delivery, among which DNA polymer conjugates have emerged as promising candidates. Various types of DNA polymer conjugation strategies have been developed, including covalent attachment, non-covalent assembly, and aptamer-mediated conjugation. Covalent attachment involves the direct bonding of drugs to DNA polymers, ensuring stable complexes capable of traversing the BBB. These DNA polymer conjugates exhibit multifaceted functionalities in the context of neurological disorders. They can enhance BBB permeability, enabling efficient transport of therapeutics into the CNS. Moreover, conjugates functionalized with targeting ligands can selectively bind to receptors overexpressed in diseased tissues, minimizing off-target effects. Additionally, DNA polymers provide a platform for the controlled release of drugs, optimizing their pharmacokinetics and improving therapeutic efficacy while reducing systemic toxicity. In conclusion, DNA polymer conjugates represent a promising paradigm in the treatment of neurological disorders, offering precise targeting, enhanced drug delivery, and reduced adverse effects. Continued research into the design and optimization of these conjugates holds immense potential for revolutionizing the management of various neurological conditions.

1. Introduction

Neurodegenerative disorders cover a broad spectrum of severe conditions characterized by increasing neuronal deterioration and dysfunction in the central nervous system [1]. Prominent among these disorders are Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [2]. Despite their distinct clinical presentations and underlying pathological mechanisms, these disorders share common features such as the accumulation of misfolded proteins, oxidative stress, inflammation, and neuronal loss, leading to cognitive decline, motor impairment, and ultimately, loss of independence and quality of life [3–5].

Despite extensive research efforts, treatment options for neurodegenerative disorders remain limited, with existing therapies primarily focused on symptomatic management rather than disease modification [6]. Current pharmacological interventions often provide only modest symptomatic relief and do not address the underlying neurodegenerative processes [7]. Moreover, many treatments are associated with adverse effects, and their efficacy may diminish over time as the disease progresses [8]. There is an urgent need for breakthrough therapeutic techniques that can prevent or slow disease development, preserve neuronal function, and improve patient's quality of life [9].

In recent years, DNA-polymer conjugation has emerged as a promising approach for the treatment of neurodegenerative disorders. This novel therapeutic strategy involves the conjugation of therapeutic DNA molecules with biocompatible polymers to enhance their stability, bioavailability, and targeted delivery to affected cells and tissues within the central nervous system [10]. DNA-based therapeutics offer several advantages, including the ability to target specific genes or pathways implicated in disease pathogenesis, modulate gene expression, and potentially reverse pathological processes underlying neurodegeneration [11–14]. By harnessing the unique properties of polymers, such as their biodegradability, biocompatibility, and tunable physicochemical properties, DNA-polymer conjugates can overcome barriers to cellular uptake and intracellular trafficking, thereby improving the efficacy and safety of therapeutic interventions [15,16].

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An essential feature of many drug delivery systems is their ability to be imaged or tracked within the body. DNA polymer conjugates leverage this capability to redefine treatment for neurological disorders. These advanced nanostructures merge the programmability of DNA with the versatile properties of polymers, enabling precise targeting and controlled release of therapeutic agents. Incorporating imaging agents allows real-time monitoring of drug distribution and effectiveness, promising to optimize treatment outcomes while minimizing side effects. Engineered to target specific brain regions or cell types (Table 1), DNA-polymer conjugates deliver therapeutic payloads precisely, reducing off-target effects and enhancing the therapeutic index of neurodegenerative disorder treatments. Additionally, they protect therapeutic DNA from degradation, extending circulation time in vivo. This innovative approach marks a significant stride towards personalized drug in neurology [10,17].

Furthermore, DNA-polymer conjugation represents a novel and versatile therapeutic approach for addressing the unmet medical needs of patients with neurodegenerative disorders. This review highlights, by combining the unique properties of DNA-based therapeutics with the advantages of polymeric drug delivery systems, this innovative approach holds great promise for achieving disease modification, neuroprotection, and improved clinical outcomes in patients suffering from Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other neurodegenerative disorders.

1.1. Rationale for DNA-polymer conjugation

DNA holds immense potential as a therapeutic agent due to its ability to encode genetic information and regulate cellular processes. In neuroprotection, DNA can be engineered to express specific proteins or RNA sequences, enabling targeted interventions in various neurological disorders. Additionally, DNA-based therapies offer the advantage of specificity, allowing precise modulation of cellular functions without causing widespread systemic effects [27,28]. Polymers play a critical role in enhancing DNA delivery and stability, particularly in the context of therapeutic applications [29]. One primary function of polymers is to protect DNA from enzymatic degradation and rapid clearance from the bloodstream. When DNA is administered alone, it is vulnerable to degradation by nucleases present in biological fluids, limiting its therapeutic efficacy DNA delivery involves several steps: condensation, introduction into the systemic circulation, targeted delivery to specific cells, cellular uptake, endosomal release, nuclear transport, and carrier/DNA polyplex unpacking before translation in eukaryotic cells (Fig. 1) [30].

However, when complexed with polymers, DNA molecules are encapsulated within protective structures that shield them from enzymatic attack, thereby increasing their stability and prolonging their circulation time in the body. Moreover, polymers can facilitate the efficient delivery of DNA to target cells by enhancing cellular uptake and intracellular trafficking. They can be engineered to possess properties that promote interaction with cell surface receptors or facilitate endosomal escape, overcoming barriers to efficient DNA delivery [31,32]. Additionally, polymers can provide structural support and control release kinetics, enabling sustained and controlled release of DNA payloads at the target site. By enhancing DNA stability and delivery, polymers significantly improve the therapeutic potential of DNA-based therapies for various diseases, including neurological disorders. Their versatile properties and tunable characteristics make polymers indispensable components in the development of effective DNA delivery systems for clinical applications [33,34].

The synergistic effects of DNA-polymer conjugates in neuroprotection stem from their combined mechanisms of action, which enhance therapeutic efficacy in treating neurological disorders. One key mechanism involves the polymer-mediated protection and delivery of DNA to target cells within the central nervous system [35,36]. Polymers encapsulate DNA, forming stable complexes that shield it from degradation by nucleases and enhance its circulation half-life, thereby prolonging its presence in the bloodstream and improving its bioavailability to neural tissues. Additionally, polymers can facilitate cellular uptake and endosomal escape of DNA, ensuring efficient delivery to target neurons or glial cells. Once internalized, the DNA payload encoded with therapeutic genes or RNA sequences exerts its neuroprotective effects by modulating cellular processes implicated in neurodegeneration, such as inflammation, oxidative stress, or apoptosis [37,38]. Furthermore, polymer conjugation can confer intrinsic neuroprotective properties to the conjugates themselves, such as antioxidant or anti-inflammatory activities, which synergistically enhance the therapeutic benefits beyond the DNA payload. Overall, the combined mechanisms of DNA and polymer action in conjugates offer a multifaceted approach to neuroprotection, providing targeted delivery, enhanced stability, and potent therapeutic effects, thus holding great promise for the treatment of neurological disorders [39,40].

Table 1
listing of polymers used for DNA conjugation for the treatment of neurodegenerative disorders, along with their application and action in cells.

Polymer	Neurodegenerative Disorder	Action in Cells	Application	References
Polyethyleneimine (PEI)	Alzheimer's Disease	Facilitates endosomal escape, enhances transfection	Delivery of therapeutic DNA encoding anti-amyloid antibodies to target amyloid plaques in the brain.	[18]
Poly (lactic-co-glycolic acid) (PLGA)	Parkinson's Disease	Biodegradable carrier, controlled release	Encapsulation of DNA encoding neurotrophic factors for sustained release to promote neuronal survival and function.	[19]
Poly (β-amino esters) (PBAEs)	Huntington's Disease	Biodegradable, pH-responsive drug release	Complexation with DNA encoding therapeutic RNA interference (RNAi) molecules to inhibit mutant huntingtin expression and reduce neurotoxicity.	[20]
Polyethylene glycol (PEG)	Amyotrophic Lateral Sclerosis (ALS)	Increases circulation time, reduces immunogenicity	Conjugation with DNA encoding growth factors to enhance motor neuron survival and delay disease progression.	[21]
Poly (propylene mine) (PPI)	Frontotemporal Dementia (FTD)	Enhances cellular uptake and endosomal escape	Delivery of DNA encoding protein-based therapies to target specific neuronal populations affected by FTD pathology.	[22]
Poly(L-lysine) (PLL)	Multiple System Atrophy (MSA)	Facilitates DNA condensation and protects from degradation	Coupling with DNA encoding heat shock proteins to enhance cellular proteostasis and mitigate protein aggregation associated with MSA	[23]
Poly (Lactic Acid) (PLA)	Creutzfeldt-Jakob Disease (CJD)	Biodegradable carrier for sustained release	Delivery of DNA encoding anti-prion agents to inhibit prion replication and propagation in the brain.	[24]
Polydimethylsiloxane (PDMS)	Charcot-Marie-Tooth Disease (CMT)	Provides flexibility and biocompatibility	Encapsulation of DNA encoding neurotrophic factors for localized delivery to peripheral nerves to promote axonal regeneration and improve motor function in CMT.	[25]
Poly (2-hydroxyethyl methacrylate) (PHEMA)	Prion Diseases	Hydrogel forming for controlled release	Surface modification with DNA encoding prion antibodies to capture and neutralize infectious prion particles in the central nervous system.	[26]

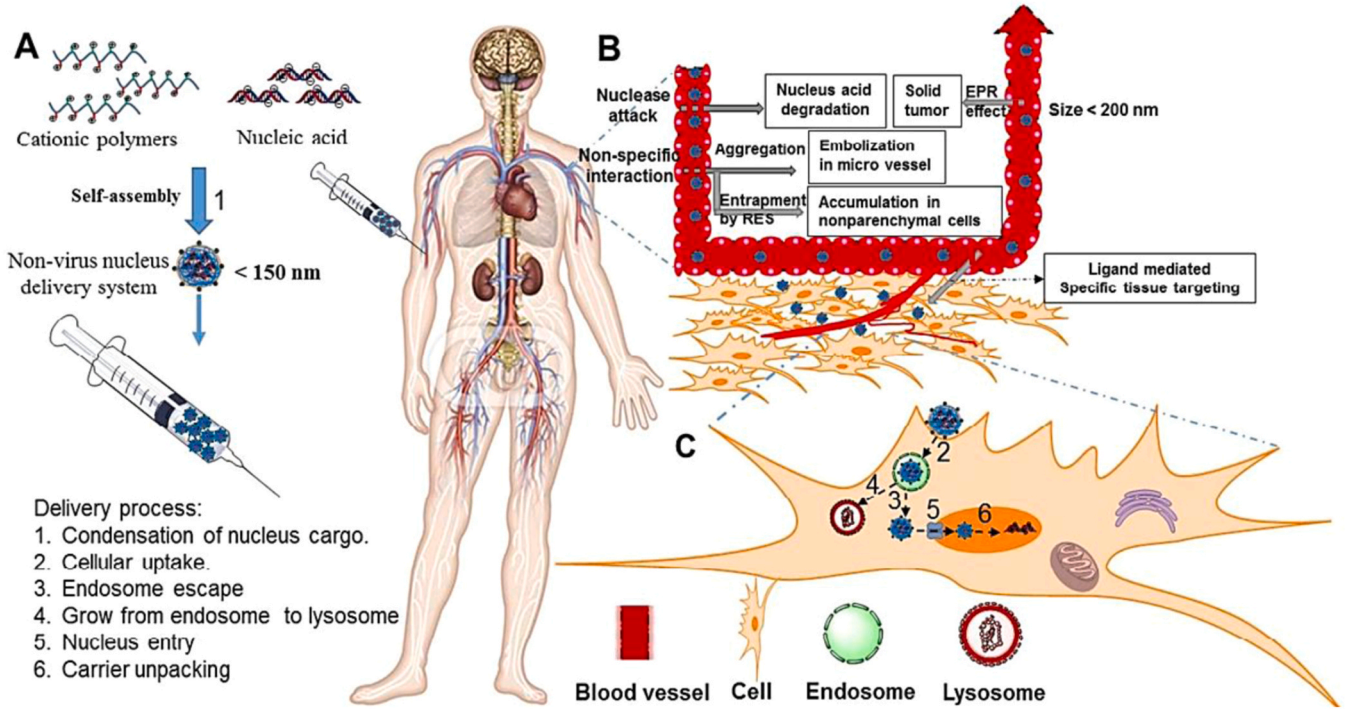


Fig. 1. Representation of the process and significant problems in gene delivery, from polycation/nucleic acid polyplex synthesis (A) circulation through the system (B); target tissue accumulation (B); and intracellular transport and nucleus unloading (C). Reproduced with permission from [30].

2. Types of DNA-polymer conjugation

Combining the unique properties of DNA and synthetic polymers has opened exciting possibilities in various fields like drug delivery and biosensing. This powerful approach involves the creation of DNA-polymer conjugates, which are essentially molecules where DNA

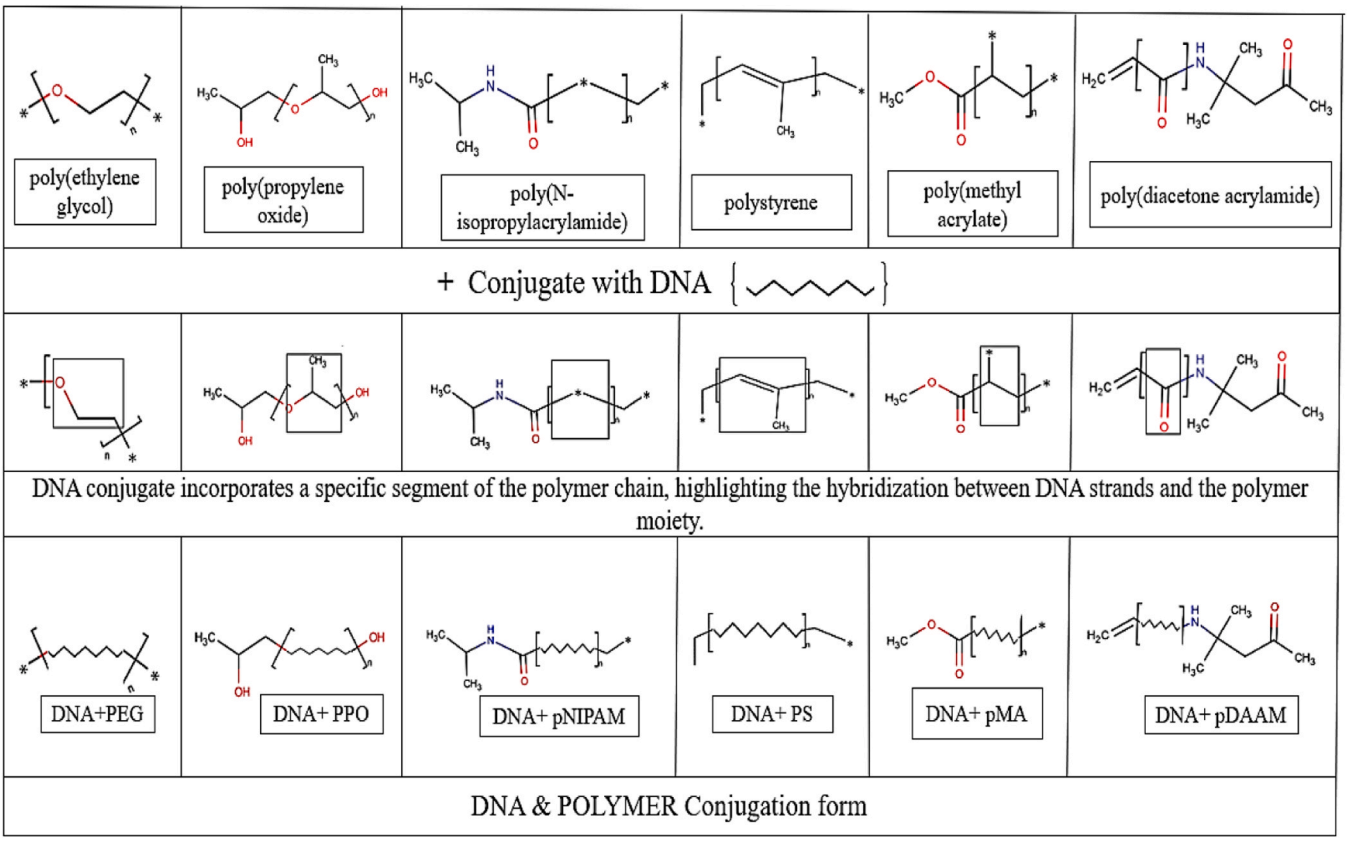


Fig. 2. Examples of commonly used polymers for DNA–polymer conjugates.

strands are covalently linked to polymer chains. There are various methods to achieve this conjugation (Fig. 2), each offering distinct advantages and considerations [10].

Covalent conjugation involves forming a strong chemical bond between the DNA and the polymer. This can be achieved through various techniques, such as "grafting from," where a polymer is grown directly from the DNA, or "grafting to," where pre-synthesized components are linked together. These methods offer stability and precise control over the structure of the conjugate. On the other hand, non-covalent conjugation relies on weaker interactions such as hydrogen bonding, electrostatic forces, or intercalation (where the polymer fits between the bases of the DNA). This approach is often simpler and faster, but the resulting conjugates are generally less stable and more susceptible to changes in the environment [41]. Both covalent and non-covalent approaches have advantages and limitations, and the method used depends on the application and the desired properties of the final DNA-polymer conjugate Shown in Fig. 3.

2.1. Covalent conjugation strategies

There have been significant advances in the synthesis of covalent DNA-polymer conjugates; nonetheless, various constraints have slowed progress. First, we will discuss the polymerization techniques used in DNA–polymer conjugate synthesis. We will also point out the drawbacks of these techniques and the difficulties involved in fusing DNA with synthetic polymers. We can gain a better understanding of the advancements in this subject by talking about the solution- and platform-based conjugation methods that are covered in this part [42].

2.1.1. Polymerization methods

2.1.1.1. Free radical polymerization. Free radical polymerization is one of the commonly employed methods in the conjugation of DNA with polymers. In this process, monomers containing reactive functional groups undergo polymerization in the presence of initiators that generate free radicals. These radicals initiate chain growth by reacting with monomer units, forming polymer chains [43]. In the context of DNA polymer conjugation, the reactive functional groups on the polymer precursor can be chemically modified to enable covalent attachment to DNA molecules. For instance, functional groups such as acrylates, methacrylate's, or vinyl groups are often used for polymerization reactions. The DNA molecules, typically modified with complementary functional groups, are then covalently linked to the growing polymer chains during the polymerization process. This covalent attachment ensures stable conjugation between the DNA and polymer components [10]. Free radical polymerization offers several advantages for DNA polymer conjugation, including the ability to control polymer composition, molecular weight, and architecture, allowing for precise

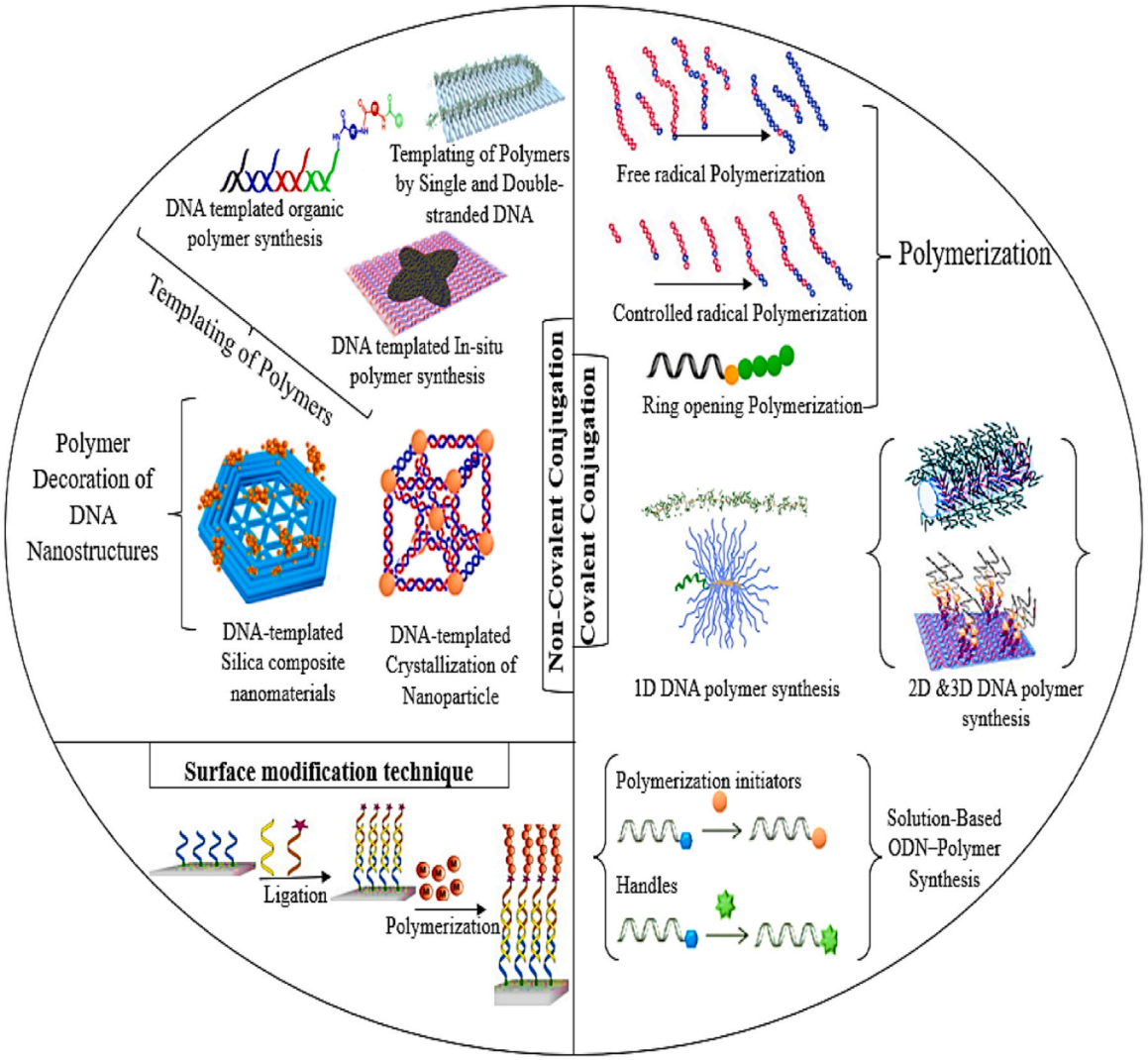


Fig. 3. Overview of DNA–Polymer Conjugate Synthesis.

tuning of the properties of the conjugates. Furthermore, this method is compatible with a wide range of monomers and initiator systems, facilitating the synthesis of diverse DNA-polymer conjugates with tailored characteristics for specific therapeutic applications [43]. However, careful optimization of reaction conditions is necessary to minimize potential damage to the DNA molecules and ensure efficient conjugation while maintaining their biological activity. Overall, free radical polymerization is a versatile and frequently used technique for the synthesis of DNA-polymer conjugates with higher stability and usefulness for diverse biomedical applications, such as medication delivery and gene therapy [44].

2.1.1.2. Controlled radical polymerization (CRP). Controlled radical polymerization (CRP) techniques represent a powerful set of methods employed in the conjugation of DNA with polymers [44]. CRP offers precise control over polymer structure, molecular weight, and architecture, making it particularly suitable for applications requiring well-defined polymer-DNA conjugates [45]. One commonly used CRP technique is atom transfer radical polymerization (ATRP), where a transition metal catalyst mediates the reversible transfer of a halogen atom between an initiator and a growing polymer chain, allowing for controlled growth of the polymer. This approach allows for the production of polymers with regulated molecular weights and limited molecular weight dispersion, which is crucial for ensuring uniformity and reproducibility in DNA-polymer conjugates [46,47]. Similarly, nitroxide-mediated polymerization (NMP) and reversible addition-fragmentation chain transfer (RAFT) polymerization are other CRP techniques that have been employed in DNA conjugation. RAFT polymerization involves the reversible transfer of a chain-end radical to a chain transfer agent, allowing for precise control over polymerization kinetics and resulting in well-defined polymer structures [48]. NMP utilizes stable nitroxide radicals to control the polymerization process, offering versatility in polymer design and compatibility with various functional groups. Overall, CRP techniques provide a robust platform for synthesizing DNA-polymer conjugates with tailored properties, enabling fine-tuning of parameters such as polymer composition, architecture, and functionality to optimize their performance in therapeutic and biomedical applications [49].

2.1.1.3. Ring-opening polymerization (ROP). One of the notable polymerization methods utilized in DNA polymer conjugation is ring-opening polymerization (ROP) [50]. This method involves the sequential opening of cyclic monomers, typically lactones or lactides, to form linear polymers with controlled chain lengths and end functionalities. In the context of DNA polymer conjugation, ROP offers several advantages [51]. Firstly, it enables the synthesis of biocompatible and biodegradable polymers, such as polyesters, which are suitable for biomedical applications. These polymers exhibit minimal toxicity and immunogenicity, making them ideal candidates for conjugation with DNA for therapeutic purposes [52]. Secondly, ROP allows for precise control over the polymer architecture, including polydispersity, molecular weight, and end-group functionality. This control is crucial for tailoring the physicochemical properties of polymer-DNA conjugates, such as their size, stability, and release kinetics [53]. Additionally, ROP can be performed under mild reaction conditions, avoiding harsh solvents or high temperatures that may denature DNA molecules. Moreover, ROP can be initiated using various methods, including enzyme catalysis, metal catalysts, or initiators derived from functionalized DNA sequences, enabling the incorporation of DNA into the polymer backbone or side chains. Overall, ring-opening polymerization represents a versatile and robust approach to the synthesis of DNA polymer conjugates with tailored properties for various biomedical applications, including drug delivery, tissue engineering, and gene therapy [54].

2.1.2. Solution-based ODN–polymer synthesis

Solution-based synthesis of ODN (oligodeoxynucleotide)–polymer conjugates offer a versatile approach for the development of functional materials with applications ranging from drug delivery to diagnostics (Table 2) [55]. In this method, ODNs, which serve as the DNA component, are chemically modified to introduce reactive functional groups, such as amino or thiol groups, enabling their conjugation with polymers [56,57]. The polymer component, typically water-soluble and biocompatible, can be synthesized separately and functionalized with complementary reactive groups [58]. The conjugation reaction between the modified ODNs and polymers occurs in solution under mild conditions, allowing for precise control over the reaction parameters and product properties [59].

The synthesis process begins with the design and synthesis of chemically modified ODNs, wherein specific sequences are selected to confer desired functionalities or target specific molecular interactions. These modified ODNs are then conjugated with polymer chains through covalent or non-covalent interactions, depending on the desired application [60]. Covalent conjugation methods, such as amidation or thiol-ene click chemistry, enable the formation of stable linkages between the ODNs and polymers, ensuring their structural integrity and functionality [61]. Non-covalent conjugation strategies, such as electrostatic interactions or hydrogen bonding, offer advantages in terms of simplicity and reversibility, allowing for the incorporation of ODNs into polymer matrices without altering their sequences or structures [62–64].

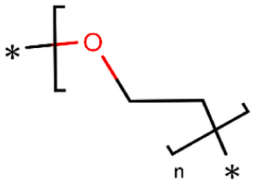
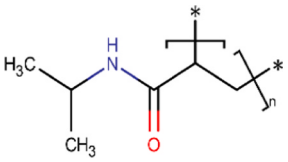
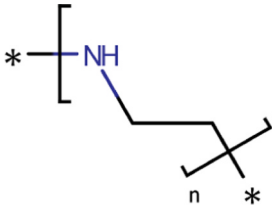
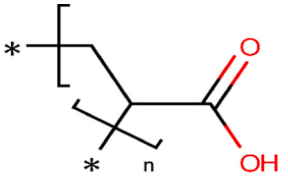
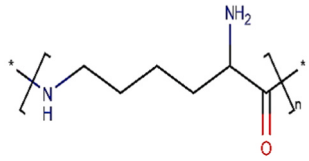
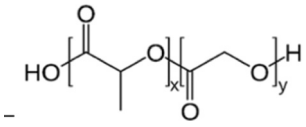
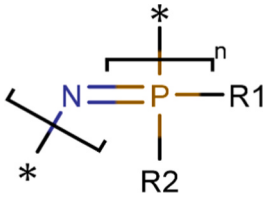
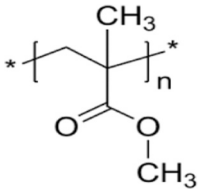
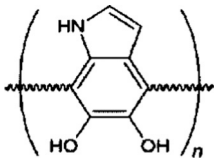
The resulting ODN–polymer conjugates exhibit enhanced properties compared to their components, including improved stability, solubility, and biocompatibility [65]. Additionally, the presence of ODNs imparts specific biological functionalities to the conjugates, such as gene regulation or molecular recognition, making them suitable for various biomedical applications. Moreover, the solution-based synthesis approach allows for the facile scale-up and customization of ODN–polymer conjugates, enabling their widespread use in research and commercial applications [66,67].

2.1.3. 1D DNA–polymer synthesis

Ring-opening metathesis polymerization (ROMP) is a typical method for synthesizing DNA-polymer brushes, which are a sort of one-dimensional structure [77]. Zhang et al. used reactive handles and ROMP of norbornyl attached to polymer side chains for DNA attachment. They created DNA-polyethylene glycol (PEG) conjugates, also known as pacDNA (polymer-assisted compacted DNA), by chain extension ROMP with norbornyl-NHS for triblock copolymer synthesis and ROMP of norbornyl-NHS and norbornyl-PEG for deblock synthesis. NHS anchors along the backbone facilitated coupling with amine-ODNs. Furthermore, they polymerized norbornyl-paclitaxel via ROMP before DNA conjugation, creating spherical nucleic acids. Similarly, DNA-polymer conjugates with doxorubicin (DOX) were synthesized via ROMP of norbornyl-DOX and N-PEG, followed by amide coupling with amine-ODN. These examples demonstrate DNA-polymer conjugates' potential as drug delivery systems, capable of high-capacity drug loading [78].

Mirkin and colleagues created a copolymer composed of polycaprolactone (PCL) and polyethylene oxide (PEO) blocks, with just the PEO backbone functionalized with an azide group. Copper-free click chemistry utilizing a conjugation allowed by DBCO-ODN. Triblock copolymers provide a regulated ODN placement along the backbone of the polymer. In order to facilitate coupling with amine-ODNs at the terminal polymer blocks, Zhang and colleagues synthesized a triblock copolymer brush by sequential ROMP of norbornyl-NHS, norbornyl-PEG, and norbornyl-NHS. They also created a triblock N-NHS-N-PEG-norbornyl maleimide (N-MI) for dual-ODN conjugation, which makes it possible to incorporate two different ODNs into a single nanostructure and creates opportunities for dual-functionalization [79,80].

Table 2
Lists of some common coupling chemistries used to covalently bind oligonucleotides (ODNs) to polymers.

Polymer	Coupling Chemistry	Action	References
	Maleimide	ODNs are functionalized with maleimide groups and PEG is functionalized with thiol groups. Maleimide-thiol reaction forms stable thioether linkages.	[68]
	Azide-alkyne (click chemistry)	PNIPAM can be functionalized with azide groups and ODNs with alkyne groups. These groups react via copper-catalyzed or copper-free click chemistry to form triazole linkages.	[69]
	EDC (1-ethyl−3-(3-dimethyl aminopropyl) carbodiimide)	Activates carboxyl groups on ODNs, which react with primary amines on PEI through amide bond formation.	[70]
	EDC/NHS (N-hydroxy succinimide)	EDC activates carboxyl groups on ODNs, which then react with primary amines on PAA through amide bond formation. NHS improves reaction specificity.	[71]
	EDC/NHS	Similar to PEI, EDC activates carboxyl groups on ODNs, which react with primary amines on polylysine through amide bond formation. NHS improves reaction specificity.	[72]
	Carbodiimide	PLGA is activated with EDC, and ODNs with carboxyl groups can react with the activated PLGA through amide bond formation.	[73]
	Sulfonyl chloride	ODNs are functionalized with amino groups, and polyphosphazene is activated with sulfonyl chloride, facilitating amide bond formation between amino and sulfonyl groups.	[74]
	Acrylate	PMMA can be functionalized with acrylate groups, and ODNs can be functionalized with complementary functional groups, allowing for covalent attachment via radical polymerization.	[75]
	Michael addition	PDA surface can be functionalized with nucleophilic groups, which react with electrophilic groups on ODNs via the Michael addition reaction, forming covalent bonds.	[76]

2.1.4. 2D and 3D polymerization platforms

Solid supports and surfaces provide alternate platforms for synthesizing DNA-polymer conjugates via grafting to and grafting from techniques. These platforms comprise metal, organic, and biological surfaces with different 2D and 3D architectures and properties, as well as nanomaterials including DNA origami, nanoparticles, and beads [80].

Mirkin and colleagues demonstrated the first attempts to couple DNA and polymers with solid-phase synthesis in 2004 when they synthesized a PS phosphonamidite. This method demonstrated the synthesis of complex phosphonamidites and the successful completion of coupling stages when protective groups are present [81]. Hermann and associates investigated the use of polymer phosphonamidites in the synthesis of PPO conjugates. Alcohol-terminated polymers were reacted with chlorophosphoramidite to create the polymer-phosphonamidites, which produced PPO polymers with different molecular weights [82,83].

In addition to PS and PPO, cholesterol-TEG phosphonamidites were synthesised to produce cholesterol-ODN. Because of restrictions on pore size, shorter polymer brush topologies can be used when using beads in solid-phase synthesis. But conjugation using polymer phosphonamidites on solid substrates necessitates the use of a DNA synthesizer, a specialized tool needing training. Deliveries of ODNs attached to solid supports are provided by certain commercial companies, albeit this may not always be possible [84].

While reported yields in solid-phase synthesis may be lower than in optimized solution-based reactions, using phosphonamidite chemistry allows for conjugation while protecting nucleotide functional groups. This offers greater compatibility with coupling reagents and functional groups compared to solution-based reactions. Overall, solid-phase synthesis provides a valuable alternative for synthesizing DNA-polymer conjugates, offering diverse compatibility and potential for applications in various fields [85,86].

2.2. Non-covalent conjugation approaches

The emerging class of supramolecular DNA and polymer assemblies, powered by noncovalent interactions, provides a dynamic and adaptable method to DNA-polymer conjugation. Noncovalent conjugation techniques take advantage of the intrinsic qualities of nucleic acids and polymers for assembly, as opposed to covalent conjugation techniques, which call for the chemical alteration of DNA strands. This makes it possible to employ commonly available, unmodified nucleic acids, which makes the production process simpler [87].

DNA's highly programmable fundamental structure, as well as its ability to mould secondary and tertiary structures, can be used to regulate the sequence of polymers that have no structural relationship with nucleic acids. This tactic is inspired by the fundamental mechanisms of life, which involve the transcription, translation, and translation of DNA-encoded information into proteins. Based on how they interact and what function they are intended for, noncovalent assemblages of DNA and polymers can be categorized [88,89]. DNA has numerous interaction modes, including Watson-Crick base pairing for single-stranded DNA (ssDNA), electrostatic interaction with polycations for the negatively charged phosphate backbone, and hydrophobic groove binding and planar molecule intercalation for double-stranded DNA (dsDNA). Although noncovalent contacts are not intrinsically specialized, attempts are undertaken to establish attachments that are regulated in space [90].

Numerous methods take advantage of DNA's recombinant nature to create bespoke polymers. DNA sequences can be transferred onto polymers by templating or patterning techniques, which allows for the creation of supramolecular 1D and 2D structures or the organization of DNA in intricate polymer-coated nanostructures. Because of its remarkable reliability, DNA origami makes it possible to precisely pattern polymers into unique structures with unmatched accuracy [91].

2.2.1. Templating of polymers by single and double-stranded DNA

In DNA conjugation, templating of polymers by single and double-stranded DNA (ssDNA and dsDNA) offers a versatile approach to creating structured assemblies with precise control over polymer arrangement. This strategy harnesses the programmable nature of DNA to guide the spatial organization of polymers, resulting in well-defined architectures with tailored properties [92].

For instance, single-stranded DNA can serve as a template for the growth of polymers through sequence-specific interactions. By exploiting Watson-Crick base pairing, polymer monomers can be selectively incorporated along the DNA sequence, leading to the formation of linear or branched polymer structures. This approach allows for precise control over polymer composition and sequence, enabling the fabrication of functional materials with defined properties [93]. One example of this is the templating of DNA origami structures with specific sequences of polymer monomers, resulting in well-defined nanostructures with programmable functionalities. Similarly, double-stranded DNA can also act as a template for polymer templating. The helical structure of dsDNA provides a scaffold for the assembly of polymers along the DNA backbone. Polymers can interact with the grooves of the DNA helix or intercalate between the base pairs, leading to the formation of polymer-DNA complexes with defined spatial arrangements. This approach has been demonstrated in the fabrication of DNA-based nanomaterials, where polymers are arranged in a controlled manner along the dsDNA backbone to create functional nanostructures [94].

The described work is a rare example of DNA-polymer conjugates that rely only on hydrogen bonding with nucleic acids and do not benefit from electrostatic interactions. Due to its convenient interaction mode, however, much research focuses on the interaction between the corresponding polyplexes and the negatively charged phosphate backbone of DNA. For drug delivery, electrostatic complexation, for instance, condenses siRNA onto a positively charged supramolecular polymer, enabling charged-mediated endocytosis to facilitate gene silencing [95]. In an effort to circumvent viral vectors, supramolecular complexes of nucleic acids with cationic polymers, such as polyethyleneimine (PEI), poly l-lysine (PLL), polyvinyl amine (PVA), and polyallylamine (PAA), are being studied in great detail for gene delivery. These polymers have the potential to be used in non-viral gene delivery systems because of their ability to effectively penetrate biological membranes and deliver contents (Fig. 4) [95,96].

Overall, templating of polymers by ssDNA and dsDNA offers a powerful strategy for DNA conjugation, enabling the creation of structured assemblies with precise control over polymer organization [97]. By leveraging the programmable nature of DNA, this approach opens up new opportunities for the design and fabrication of functional materials with tailored properties and applications in various fields, including nanotechnology, biomedicine, and materials science [98].

2.2.2. Polymer decoration of DNA nanostructures

Polymer decoration of DNA nanostructures provides a means to enhance the stability and functionality of DNA-based materials, particularly higher-ordered structures like DNA origami, which face intrinsic stability drawbacks such as susceptibility to enzymatic degradation and dependence on divalent cations for structural integrity [99]. Various polymers, including polyethylene glycol (PEG) and polyethyleneimine (PEI), have been investigated for their ability to coat DNA nanostructures and mitigate these challenges [100].

One approach involves electrostatic coating of DNA origami structures with polycations, either naturally derived or synthetic, to replace divalent cations and provide protection against nucleases and salt depletion. For example, ATRP-generated block copolymers of PEG and methacrylate derivatives were linked to DNA origami structures, with the ratio of amines to phosphate groups (N/P ratio) discovered to be crucial for effective binding [101]. Linear PEI outperformed chitosan in protecting DNA, attributed to its higher charge density. Similarly, electrostatic coating with copolymers of PEG and polylysine has been

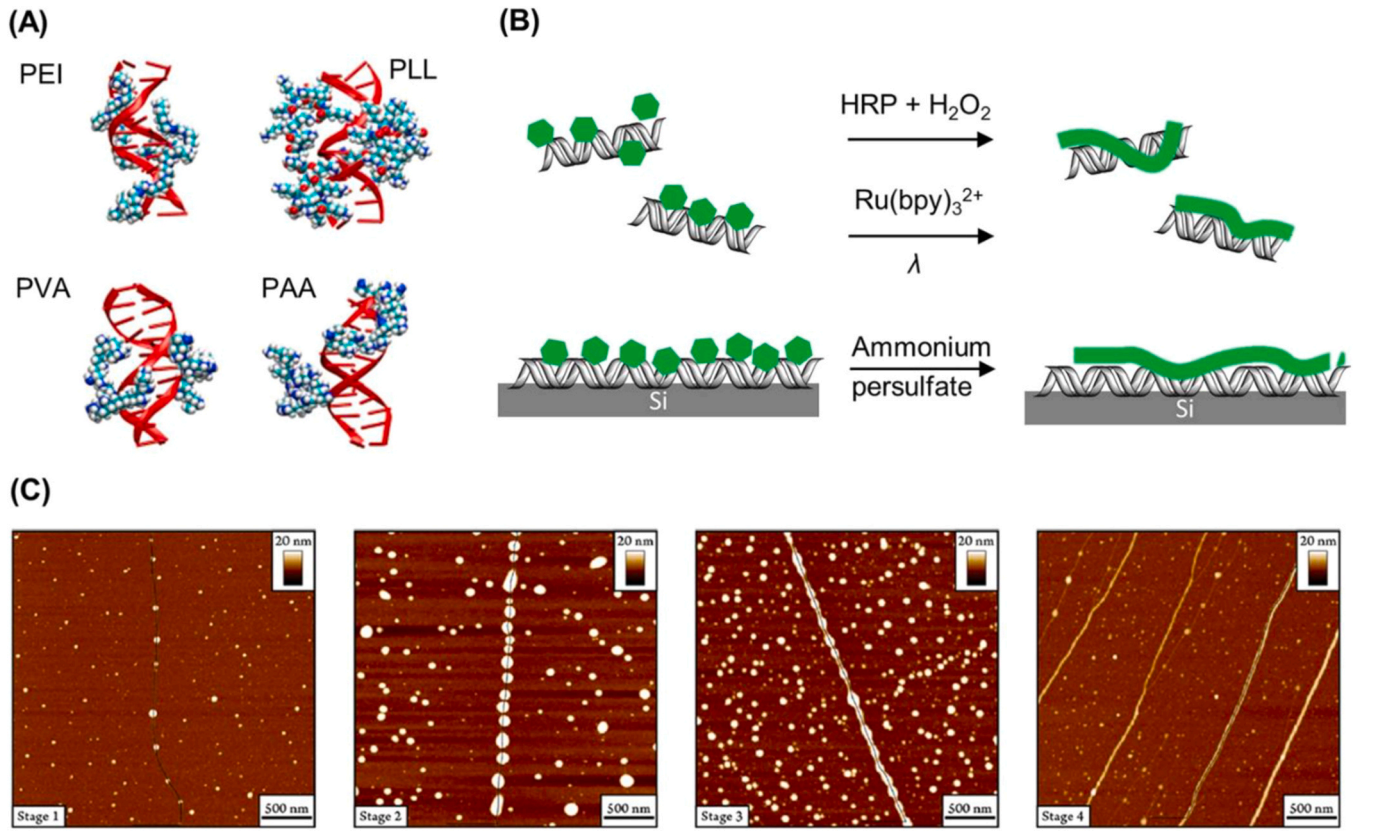


Fig. 4. Electrostatic interactions allow the alignment of positively charged monomers and polymers along the DNA backbone. Reproduced with permission from [95].

reported to shield DNA origami structures from nuclease degradation and low salt conditions. The PEG block forms a protective layer while the polylysine block interacts with DNA. This coating enables DNA origamis to withstand physiological conditions, as demonstrated by increased stability under cell culture conditions and intactness after cell uptake [102,103].

Furthermore, peptides, which are peptide mimetics with side chains tethered to the backbone nitrogen atom, have emerged as promising candidates for electrostatic DNA origami protection. By using solid phase synthesis, block-type and brush-type copolymers comprising positively charged peptides and PEG monomers were created. These structures' multivalent contacts along the backbone allowed them to stabilize DNA in biomimetic fluids effectively [104].

2.3. *Surface modification techniques*

Surface modification techniques play a crucial role in DNA-polymer conjugation, enabling the functionalization of surfaces with DNA molecules and polymers for various applications in biomedicine, materials science, and nanotechnology. These techniques allow precise control over surface properties, such as wettability, biocompatibility, and functionality, by modifying the surface chemistry and structure. In this paragraph, we will explore several surface modification techniques commonly used in DNA-polymer conjugation and their applications [105].

Chemical functionalization, which involves the covalent attachment of functional groups to a substrate's surface, is one of the most common surface modification procedures. This can be achieved through various methods such as salinization, where organ silane molecules containing reactive groups, such as amino or thiol groups, are used to coat the substrate surface. These functional groups serve as anchoring sites for the attachment of DNA molecules or polymers through chemical conjugation reactions, such as amidation or thiol-ene click chemistry. Chemical functionalization offers excellent control over surface properties and allows for the precise spatial arrangement of DNA and polymer molecules on the substrate surface [106].

Layer-by-layer (LBL) assembly is another method of surface modification that entails sequentially depositing alternate layers of biomolecules or polymers with opposing charges onto a substrate surface. In DNA-polymer conjugation, DNA molecules, and polymers with complementary charges can be alternately deposited onto the substrate surface to form multilayered films. This technique allows for the precise control of film thickness and composition and can be used to create functional coatings with tailored properties, such as controlled release of DNA or polymers for drug delivery applications [107].

Physical adsorption is another simple yet effective surface modification technique, where DNA molecules or polymers are adsorbed onto the substrate surface through weak non-covalent interactions, such as electrostatic forces, hydrogen bonding, or van der Waals interactions. This technique is particularly useful for rapid and reversible immobilization of biomolecules onto surfaces and can be employed in applications such as biosensing, where rapid detection and regeneration of the sensing surface are essential [105,108].

Microcontact printing (μCP) is a high-resolution surface modification technique that allows for the precise patterning of DNA and polymer molecules onto substrate surfaces. In μCP, a patterned elastomeric stamp coated with DNA or polymer molecules is brought into contact with a substrate surface, transferring the pattern onto the substrate through physical contact. This technique enables the creation of microscale and nanoscale patterns with high resolution and precision, making it suitable for applications such as microarray fabrication and cell patterning [109].

Plasma treatment is another surface modification technique commonly used in DNA-polymer conjugation, where substrates are

exposed to low-pressure plasma to modify surface chemistry and structure. Plasma treatment can introduce functional groups, such as hydroxyl or amino groups, onto the substrate surface, facilitating the covalent attachment of DNA or polymer molecules. This technique offers advantages such as rapid processing, scalability, and compatibility with a wide range of substrates, making it suitable for industrial applications [10,110].

Furthermore, surface-initiated polymerization (SIP) is a versatile surface modification technique that allows for the direct synthesis of polymer brushes from substrate surfaces. In SIP, polymerization initiators are immobilized onto the substrate surface, which then initiate the polymerization of monomers in solution, resulting in the growth of polymer chains anchored to the substrate. This technique enables precise control over polymer brush density, thickness, and composition and can be used to create functional coatings with tailored properties, such as stimuli-responsive surfaces for controlled drug release [111,112].

3. Supramolecular DNA–polymer complexes

DNA is probably the most predictable and programmable self-assembling material known, undergoing quick, high-fidelity association using simple base-pairing principles. A single strand of DNA may discover its complement in solution with exceptional selectivity thanks to a cooperative balance of hydrogen bonding, π-stacking, and other non-covalent forces. Though numerous self-assembling molecules are known, such precise control over the end product is uncommon. DNA provides researchers with a precise assembly code for determining which strands will pair, resulting in structurally consistent and well-characterized double helices. For these reasons, DNA assembly has been used in the field of structural DNA nanotechnology to create higher-order functional structures [113,114].

Supramolecular interactions between biology and synthetic materials, notably DNA-polymer conjugates, provide a link to studying complicated nano-structural behaviours [115]. Similar to block copolymers, these hybrids self-assemble into a variety of nanostructures propelled by electrostatic and hydrophobic interactions [115,116].

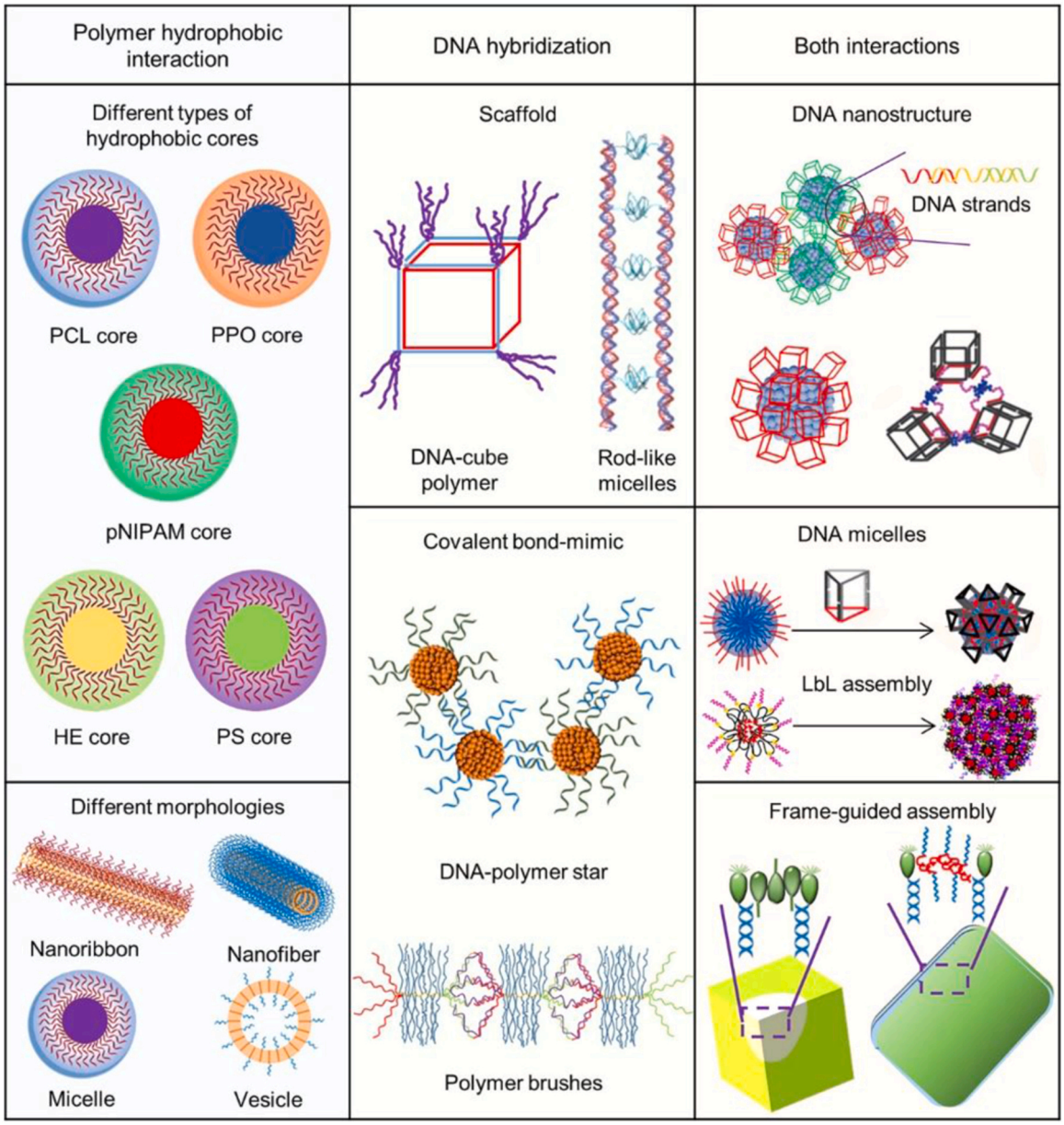


Fig. 5. Summary of DNA–polymer static nanostructures. Reproduced with permission from [122] and [123].

Different from traditional block copolymers, they can be assembled in a controlled manner and respond to stimuli thanks to special sequence-specific interactions within the DNA strands. Because different polymer segments have different properties, there is a lot of room for customized nano structural design. This field investigates methods for causing self-assembly via hydrophobic contacts or sequence hybridization, as well as stimuli-responsive behavioural changes, by classifying formed nanostructures into static and dynamic categories [117,118].

3.1. Static nanostructures

Supramolecular DNA–polymer complexes are innovative static nanostructures used in biomedical applications, including neurodegenerative disorder therapies. These complexes leverage the self-assembly properties of DNA with polymers, creating stable, programmable nanostructures [119]. Their unique design enables precise control over size, shape, and functionalization, allowing for targeted delivery of therapeutic agents such as drugs, proteins, or nucleic acids. In the context of neurodegenerative diseases, these nanostructures can cross biological barriers, enhance cellular uptake, and release therapeutic payloads at specific sites, reducing off-target effects and improving treatment efficacy. This approach represents a promising avenue for the development of advanced therapeutics [120,121]. Significant breakthroughs in DNA conjugation chemistry have spawned a potential industry for DNA-polymer conjugate construction [121,122]. These hybrids incorporate the best features of the two constituents, with hydrophobic polymer interactions and DNA sequence recognition usually driving assembly. Different static nanostructures and their assembly principles are shown in (Fig. 5). Based on how DNA and polymer characteristics interact, these can be divided into three groups: assemblies caused by DNA sequence hybridization, assemblies involving DNA and polymer interactions, and assemblies induced by polymer segment hydrophobicity [123].

3.2. Dynamic nanostructures

Supramolecular DNA–polymer complexes are dynamic nanostructures formed by non-covalent interactions between DNA and polymers. These complexes hold immense promise in biomedical applications due to their ability to precisely control drug delivery, gene therapy, and diagnostics. They offer advantages such as reversible assembly, tunable properties, and the capacity to encapsulate various payloads. In therapeutic contexts, they enable targeted delivery of therapeutic agents to specific tissues or cells, minimizing off-target effects [114,124].

Dynamic nanostructures formed by DNA–polymer conjugates represent an evolving area of research, offering versatile functionalities and stimuli-responsive behaviours [124,125]. These structures exhibit dynamic responses to external cues, enabling controlled structural changes or functional alterations. Strategies for inducing dynamic behaviour include exploiting the stimuli-responsive properties of both DNA and polymer components, such as changes in temperature, pH, or the presence of specific molecules [126–128]. Dynamic DNA–polymer nanostructures hold promise for applications in drug delivery, sensing, and nanotechnology, where precise control over structure and function is paramount for achieving desired outcomes. Continued exploration of dynamic behaviours in DNA–polymer conjugates will likely uncover new opportunities for advanced materials and applications. Dynamic DNA–polymer nanostructures respond to diverse stimuli including pH, ssDNA, light, and temperature, enabling shape and size alterations in response to external cues (Fig. 6) [129–133].

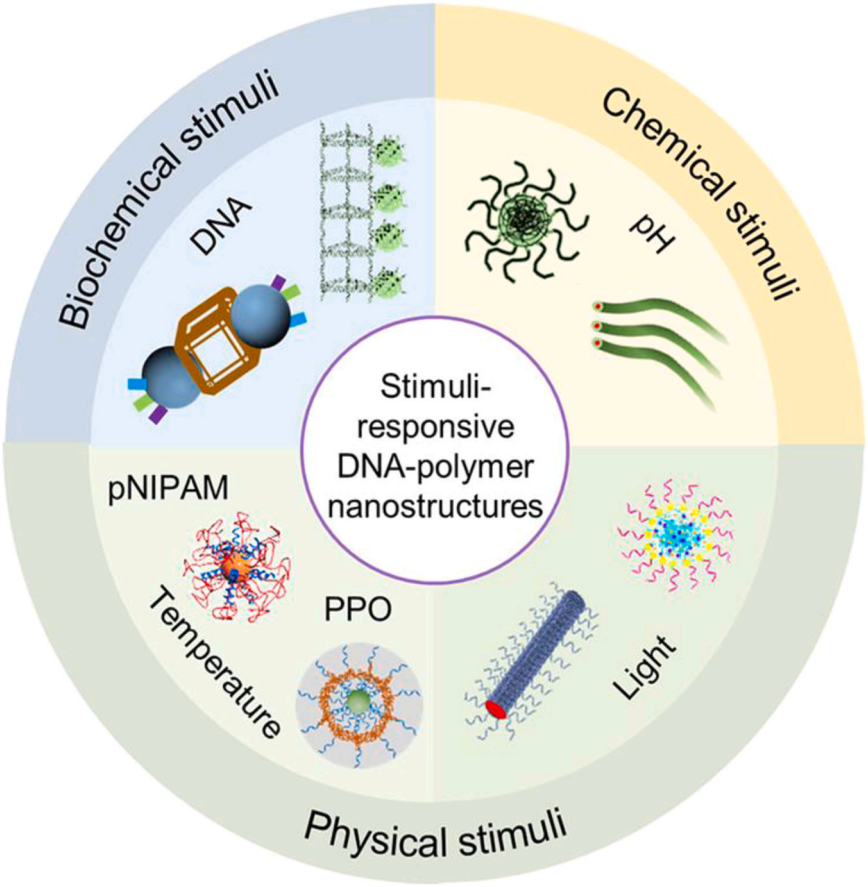


Fig. 6. Depicts various stimuli-responsive DNA–polymer dynamic nanostructures. Reproduced with permission from [127] and [129].

4. Functionality of DNA-polymer conjugates

In recent years, the exploration of DNA-polymer conjugates has garnered significant interest among scientists due to their diverse functions and applications. Polymers, being a versatile class of materials, offer a wide range of types, functionalities, and applications. When polymers are conjugated to DNA, the properties and functionalities of DNA-polymer conjugates are influenced by the characteristics of the polymer (Fig. 7) [14]. Attaching hydrophobic polymers to DNA can cause DNA-polymer conjugates to self-assemble into micellar structures with a hydrophobic core and a hydrophilic DNA corona. Because of their strong biocompatibility, these DNA-polymer micelles have potential uses in biology and medicine, especially as drug carriers for nucleic acid therapies and small-molecule medications. On the other hand, DNA-conjugated hydrophilic polymers are frequently employed to improve the durability of DNA nanostructures, hence increasing their potential uses across a range of industries. However, DNA also plays an important role in controlling the functionality of DNA-polymer micelles; the polymer does not control it entirely. Certain DNA sequences can give DNA-polymer conjugates a variety of functions, such as catalysis, targeting, and therapeutic effects. These sequences have the potential to be added to DNA-polymer micelles, giving DNA-polymer nanostructures new functions [134].

Therefore, functionalities derived from the polymer, functionalities based on DNA sequences, and synergistic functionalities resulting from the combined properties of both DNA and polymer components can be used to categorize this section into three main themes. This categorization offers a thorough foundation for comprehending the potential and wide range of uses of DNA-polymer conjugates in research and development [10].

4.1. Functionality based on polymer

In recent years, a variety of polymers, including PPO, pNIPAM, PS, and PCL, have been conjugated to DNA, giving rise to DNA-polymer conjugates with diverse functionalities and applications. The properties of these polymers significantly influence the functionality of the resulting conjugates, primarily in two aspects: (1) the delivery of small molecule drugs enabled by the hydrophobic core of DNA-polymer micelles, and (2) the enhancement of stability for DNA-polymer conjugates [134].

DNA-polymer conjugates, particularly those based on amphiphilic block copolymers, can self-assemble into micelles with a hydrophobic core and a hydrophilic DNA corona. These micelles have shown promise as drug delivery vehicles, capable of encapsulating small molecule hydrophobic drugs within their core and facilitating their delivery to cells. For example, Sleiman and colleagues developed a novel delivery platform using sequence-defined polymer-DNA conjugates to deliver the anticancer drug BKM120 for the treatment of chronic lymphocytic leukaemia. The hydrophobic core of the DNA nanoparticles formed by HE12-DNA conjugates provided an ideal environment for encapsulating BKM120, resulting in enhanced uptake by HeLa cells and significant cellular death and apoptosis induction [103].

Similarly, Mirkin's group devised a facile strategy to construct polymer-DNA conjugates, utilizing PLGA nanoparticles to deliver small molecules. These PLGA-SNA conjugates demonstrated tuneable release of hydrophobic model drug coumarin 6, showcasing their potential as drug delivery carriers [135].

Despite their promising applications, the in vivo nuclease activity poses a significant challenge to DNA-polymer carriers, leading to rapid degradation and hindering their effectiveness. To address this issue, efforts have been made to enhance the stability of DNA-polymer carriers. Zhang's group demonstrated that introducing PEG side chains to DNA-backboned bottlebrush polymers increased their resistance against nucleolytic degradation while maintaining hybridization efficiency. Additionally, coating DNA nanostructures with polymers at the exterior surface, such as cationic PEG-polylysine block copolymers, significantly enhanced their stability against nuclease digestion and denaturation, as

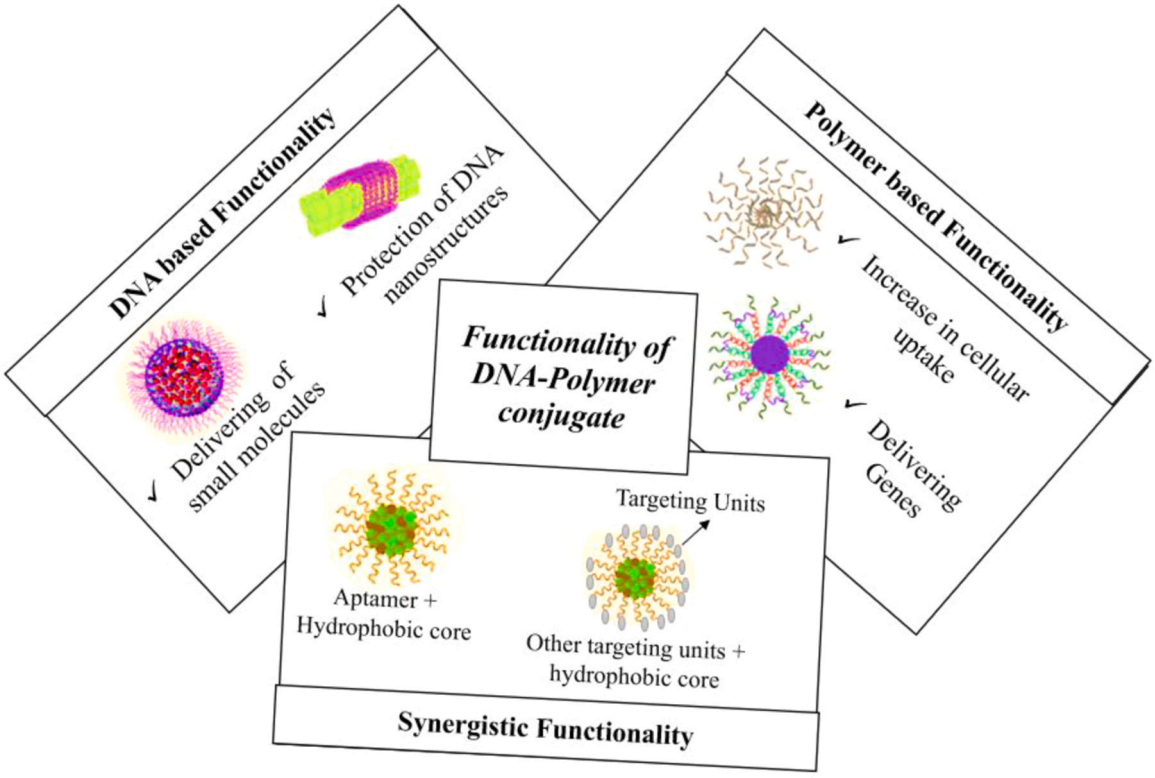


Fig. 7. Functional properties of DNA-polymer conjugates.

demonstrated by Schmidt's and Shih's groups. Oligolysines and oligomycin-PEG copolymers were also explored as coating materials, further enhancing the stability and resistance to nucleases of DNA nanostructures [136].These advancements highlight the potential of DNA-polymer conjugates for biomedical applications, particularly in drug delivery. By harnessing the unique properties of polymers and DNA, researchers continue to develop innovative strategies to overcome existing challenges and improve the performance of DNA-polymer conjugates for therapeutic applications [137].

4.2. Functionality based on DNA

In this section, we explore the functionalities of DNA-polymer conjugates that are derived from DNA sequences. These functionalities primarily involve the delivery of genes and small-molecule cargos facilitated by complementary base pairing of DNA bases, as well as the enhanced cellular uptake of DNA-polymer supramolecular nanostructures due to nucleic acid shells [10]. Hanner's group designed and synthesized functional DNA-grafted supramolecular polymers using monodisperse diblock oligophosphates. These polymers enabled the loading of DNA-modified AuNPs through complementary base pairing, demonstrating effective cargo delivery [138]. Zhang and colleagues achieved siRNA delivery using DNA-g-PCL brushes, where DNA was grafted onto a PCL trunk, forming spherical and nanosized hydrogels capable of delivering siRNA to different cells, resulting in effective gene silencing in vitro and in vivo [139]. Sleiman's group developed a responsive drug delivery vehicle utilizing DNA-polymer supramolecular nanostructures to deliver nucleic acid therapeutics. By incorporating nucleic acid therapeutics via partial base complementation, these structures enabled stimuli-responsive release of cargo in the presence of specific genetic markers [140].

Furthermore, Mirkin and co-workers designed micelle-SNAs with a biodegradable core and ODNs, demonstrating that the density of DNA on the surface of SNAs significantly influenced their cellular uptake efficiency. Higher DNA surface density resulted in more effective cellular uptake, attributed to interactions with class A scavenger receptors on the cell surface [141,142]. Nguyen's group modified DOX-loaded polymeric nanoparticles with a dense ODN shell, increasing the cellular uptake of doxorubicin-loaded polymeric SNAs and enhancing their colloidal stability in biological media under physiological conditions. Additionally, the shape of DNA nanostructures also influenced cellular uptake efficiency. For instance, the introduction of long DNA templates induced spherical micelles to transform into uniform rods, resulting in a 12-fold increase in cellular uptake efficiency compared to their spherical counterparts [143].

In summary, DNA-polymer conjugates exhibit diverse functionalities based on DNA sequences, including cargo delivery, gene silencing, and enhanced cellular uptake, demonstrating their potential for various biomedical applications. These advancements underscore the importance of understanding and harnessing the unique properties of DNA in polymer conjugates to develop effective therapeutic delivery systems.

4.3. Synergistic functionalities

The section discusses the synergistic functionalities of DNA-polymer conjugates, primarily focusing on the design and development of targeted drug delivery systems. These functionalities stem from both the polymer and DNA components and are mainly manifested in the formation of DNA-polymer micelles with a hydrophobic core for drug loading and a DNA shell for enhanced cellular uptake and targeting [10,144].

Firstly, DNA-polymer micelles were designed as targeted drug delivery systems by Herrmann and colleagues, where PPO was used as the hydrophobic component to efficiently load the anticancer drug DOX, while folate targeting units were introduced to the micelle corona through base complementation, resulting in effective cancer cell targeting and killing [145].

Additionally, special short ssDNA sequences known as aptamers were utilized to recognize cellular surface receptors and import DNA-polymer micelles into targeted cells. For instance, Zhu's group fabricated a targeted drug delivery carrier by modifying a polymer with the DNA aptamer AS1411, resulting in enhanced tumor cell uptake and inhibition of proliferation [146].

Furthermore, aptamers were introduced to the surface of DNA-polymer micelles by DNA hybridization, enabling targeted drug delivery. This approach was demonstrated by Tan's group, where the sgc8 aptamers were introduced to the drug delivery system through the hybridization of a diacyl lipid-modified DNA strand, facilitating targeted drug delivery to cancer cells [147].

Moreover, short hairpin RNA (shRNA) was employed to design targeted drug delivery carriers. Chen's group developed a nucleic acid-polymer nano-drug formulation capable of co-delivering shRNA and DOX, demonstrating great potential in tumor therapy through a combination of nucleic acid therapeutics and chemotherapeutics [148].

Overall, DNA-polymer conjugates exhibit promising applications as drug delivery carriers, leveraging synergistic functionalities from both the polymer and DNA components to enhance targeting, cellular uptake, and therapeutic efficacy. However, challenges such as improving stability, understanding cytotoxicity, and elucidating pharmacokinetics need to be addressed for further development and widespread application of DNA-polymer conjugates. Additionally, beyond drug delivery, DNA nanostructures hold potential in various fields such as sensing, nanorobotics, and diagnostics, suggesting broader future applications for DNA-polymer conjugates [149,150].

5. Applications in neurodegenerative disorders

Conjugating DNA polymer with therapeutic agents holds promise in tackling neurodegenerative disorders by facilitating targeted delivery and enhancing treatment efficacy. This innovative approach allows for the precise transportation of therapeutic payloads across the blood-brain barrier, a significant challenge in treating neurological conditions. By utilizing DNA polymer conjugation, therapeutic molecules can be directed to specific sites within the central nervous system, minimizing off-target effects and maximizing therapeutic benefits. This strategy holds the potential for revolutionizing treatment paradigms in neurodegenerative diseases such as Alzheimer's and Parkinson's, offering hope for improved patient outcomes and disease management (Fig. 8).

5.1. Alzheimer's disease

In the realm of Alzheimer's disease (AD), the application of DNA-polymer conjugation holds significant promise for both diagnosis and treatment strategies. One avenue of exploration involves the development of targeted drug-delivery systems aimed at delivering therapeutic agents to the brain to mitigate the progression of AD [151]. DNA-polymer conjugates can be engineered to cross the blood-brain barrier (BBB), a major challenge in AD treatment (Table 3), by incorporating specific targeting ligands or aptamers that bind to receptors expressed on the surface of brain endothelial cells. These conjugates can encapsulate drugs such as anti-inflammatory agents, neuroprotective compounds, or inhibitors of amyloid-beta (Aβ) aggregation, which are crucial in combating neurodegeneration and plaque formation characteristic of AD [152,153].

Moreover, DNA-polymer conjugates can also serve as diagnostic tools for AD. Functionalized DNA nanostructures can be designed to selectively bind to biomarkers associated with AD pathology, such as Aβ peptides or tau proteins, enabling sensitive detection in biological samples like cerebrospinal fluid or blood plasma. Additionally, DNA-based sensors can be integrated into nanodevices for imaging modalities like magnetic resonance imaging (MRI) or positron emission tomography (PET), offering non-invasive and precise visualization of AD-

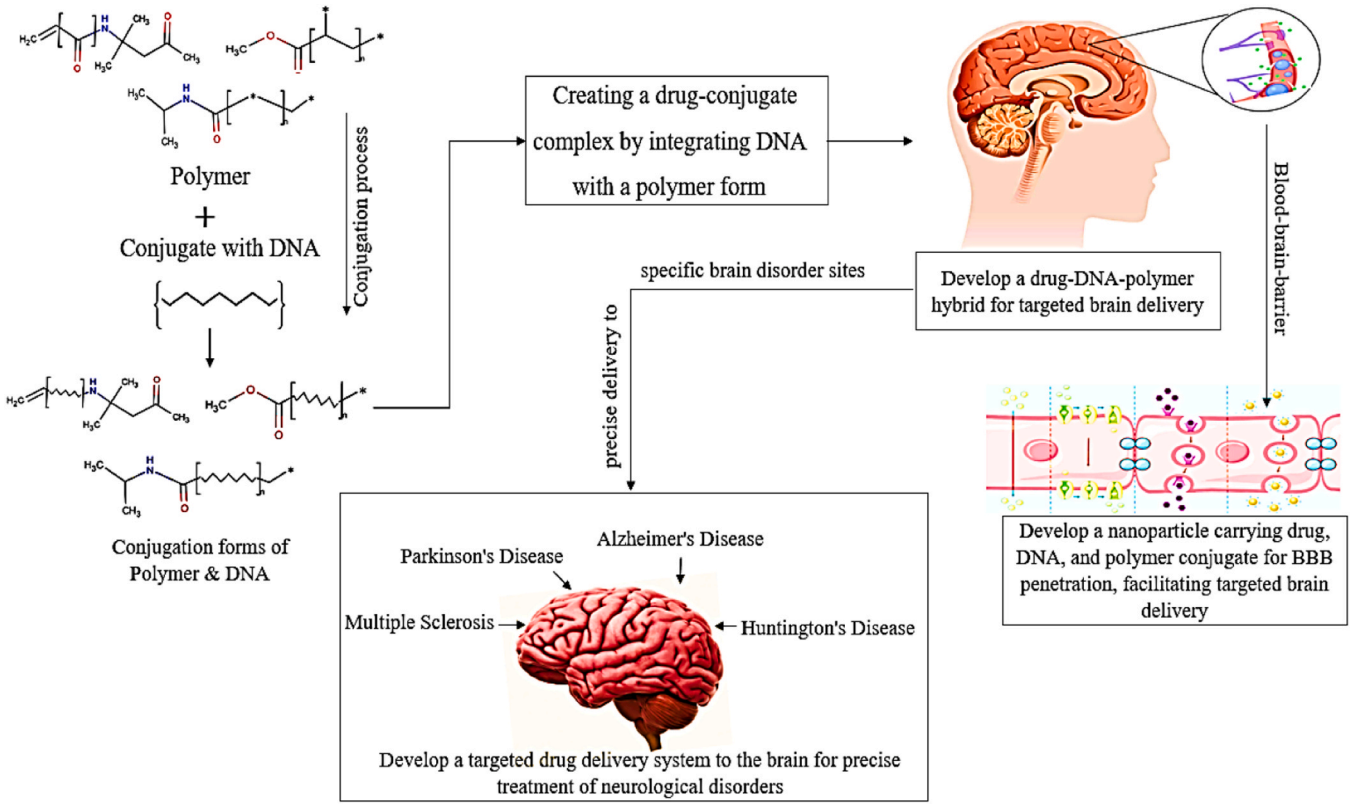


Fig. 8. Schematic diagram of DNA-polymer conjugate toward Brain delivery.

Table 3
Outlining the application of certain DNA and polymer conjugation for the treatment of Alzheimer's disease.

DNA/Polymer Conjugate	Application in Alzheimer's Disease Treatment
DNAzymes	Target specific mRNA associated with Alzheimer's pathology for degradation, potentially reducing the production of harmful proteins such as amyloid-beta [157].
siRNA-Polymer Conjugates	Inhibit expression of genes involved in Alzheimer's disease progression, such as those related to amyloid precursor protein processing or tau protein aggregation [158].
Aptamer-Polymer Conjugates	Target and bind to specific proteins involved in Alzheimer's disease pathology, such as beta-amyloid or tau proteins, for therapeutic purposes like inhibition of aggregation or clearance [159]
Antisense Oligonucleotide (ASO)-Polymer Conjugates	Interfere with the translation of mRNA coding for proteins implicated in Alzheimer's disease, such as beta-secretase or tau protein [160].
DNA Nanoparticles	Serve as delivery vehicles for therapeutic agents targeting Alzheimer's disease, protecting cargo from degradation and facilitating targeted delivery to affected brain regions [161].
DNA-Polymer Hybrid Hydrogels	Provide scaffolds for cell encapsulation or tissue engineering approaches aimed at restoring neuronal function or promoting neural regeneration in Alzheimer's disease-afflicted brains [162].
Polymer-Coated DNA Vaccines	Stimulate the immune system to produce antibodies against Alzheimer's disease-related antigens, such as beta-amyloid, potentially reducing plaque deposition or promoting clearance [163].
DNA-Polymer Hybrid Theragnostic Agents	Combine therapeutic and diagnostic capabilities for Alzheimer's disease, enabling simultaneous treatment and monitoring of disease progression through imaging modalities [164].

related changes in the brain [154,155].

An example of related work in this field is a study by Zhang et al., where DNA-polymer conjugates were developed for targeted delivery of small interfering RNA (siRNA) against genes implicated in AD pathogenesis. The conjugates were engineered to specifically target brain endothelial cells by incorporating aptamers that bind to receptors overexpressed in AD-affected regions of the brain. This approach demonstrated efficient delivery of siRNA to the brain, leading to the downregulation of target genes associated with neuroinflammation and synaptic dysfunction, thereby offering a potential therapeutic strategy for AD treatment [156].

5.2. *Parkinson's disease*

DNA-polymer conjugation holds promising applications in the field of Parkinson's disease (PD), a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the brain. One potential application involves the targeted delivery of therapeutic agents to the affected areas of the brain to alleviate symptoms and slow disease progression [165]. For instance, DNA-polymer micelles can be engineered to encapsulate and deliver neuroprotective agents or gene therapy vectors specifically to the dopaminergic neurons in the substantia nigra, the region primarily affected in PD. This targeted administration strategy improves therapy efficacy while minimizing off-target effects and systemic toxicity [166]. Some therapy methods using DNA and polymer conjugation and their use in Parkinson's disease treatment are displayed in Table 4.

Moreover, DNA-polymer conjugates can be tailored to deliver small interfering RNA (siRNA) or antisense oligonucleotides (ASOs) targeting specific genes implicated in PD pathology. For example, genes associated with abnormal protein aggregation, oxidative stress, or neuroinflammation can be selectively silenced using siRNA or ASOs delivered by DNA-polymer carriers. By downregulating the expression of these disease-related genes, DNA-polymer conjugates have the potential to

Table 4
Representing the promising strategies in the development of novel treatments for Parkinson's disease by leveraging DNA and polymer conjugation techniques.

Treatment Approach	Application in Treatment
DNA Nanotechnology	Utilizes DNA-based nanostructures for targeted drug delivery to specific brain regions affected by Parkinson's disease. DNA nanostructures can be engineered to carry therapeutic agents such as drugs or genes targeting the underlying pathology [169]
Gene Therapy	DNA vectors, often encapsulated within polymer-based nanoparticles, are used to deliver therapeutic genes into brain cells. These genes may encode proteins such as dopamine-synthesizing enzymes or neurotrophic factors, aiming to restore dopaminergic function or promote neuronal survival in Parkinson's disease [170].

mitigate neuronal damage and slow disease progression in PD patients [167].

Furthermore, DNA-polymer nanocarriers can be engineered to penetrate the blood-brain barrier (BBB), a major obstacle in the delivery of therapeutic agents to the brain. Functionalization of DNA-polymer conjugates with ligands that target receptors expressed on the endothelial cells of the BBB can facilitate their transport across the barrier, enabling effective delivery of therapeutic payloads to the brain parenchyma [10].

A related work article by Smith et al. demonstrates the application of DNA-polymer conjugates for the targeted delivery of neurotrophic factors to the brain in a mouse model of PD. In this study, DNA-polymer micelles were engineered to encapsulate brain-derived neurotrophic factor (BDNF), a protein known to promote the survival and function of dopaminergic neurons. The conjugates were functionalized with ligands targeting receptors expressed on the BBB, facilitating their transport into the brain. Upon administration, the DNA-polymer-BDNF conjugates selectively accumulated in the substantia nigra, where they exerted neuroprotective effects and ameliorated motor deficits in PD mice. This study highlights the potential of DNA-polymer conjugates as effective delivery vehicles for neuroprotective agents in the treatment of PD [168].

5.3. Huntington's disease

DNA polymer conjugation has great potential for treating Huntington's disease (HD) (Fig. 9), a terrible neurodegenerative condition marked by progressive physical impairment, cognitive decline, and behavioural symptoms. DNA polymer conjugation may be used in HD therapy to deliver therapeutic drugs specifically to the brain to reduce symptoms and halt the course of the disease [171]. For example, DNA-polymer conjugates can be engineered to deliver small interfering RNA (siRNA) or antisense oligonucleotides (ASOs) specifically targeting the mutant huntingtin (mHTT) gene, which is the underlying cause of HD. By conjugating these nucleic acid therapeutics to polymers, such as polyethylene glycol (PEG) or polyethyleneimine (PEI), researchers can enhance their stability, improve their blood-brain barrier penetration, and facilitate their uptake by neurons in the brain. Moreover, DNA-polymer conjugates can be designed to specifically target regions of the brain affected by HD, thereby minimizing off-target effects and maximizing therapeutic efficacy [172,173].

To support this application, a related article titled " RNA- and DNA-Based Therapies for Huntington's Disease" by S. Meghan et al. explores the development and potential of DNA-polymer conjugates as a novel therapeutic approach for HD. The article reviews recent advancements in the field, including strategies for conjugating DNA to various polymers, methods for optimizing brain-targeted delivery, and preclinical studies evaluating the efficacy of DNA-polymer conjugates in animal models of HD. Furthermore, the article discusses the challenges and future directions in the development of DNA-polymer conjugates for HD therapy, such as improving biocompatibility, minimizing immunogenicity, and enhancing tissue specificity. Overall, the article highlights the promising role of DNA-polymer conjugates in overcoming the therapeutic limitations of traditional HD treatments and offers insights into their potential clinical translation for the benefit of HD patients [174].

5.4. Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), popularly known as Lou Gehrig's disease, is a neurodegenerative ailment marked by the loss of motor

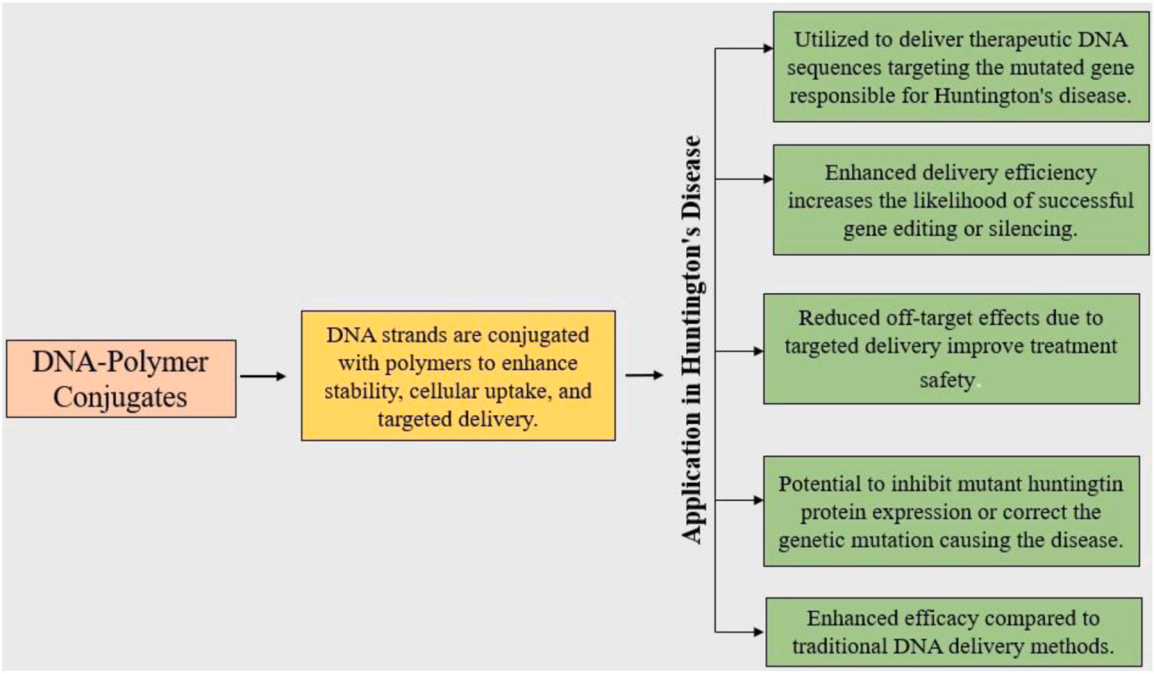


Fig. 9. Overview of DNA-polymer conjugates being applied in the treatment of Huntington's disease, outlining their benefits and potential applications.

neurons in the brain and spinal cord, resulting in muscle weakness, paralysis, and, eventually, death. There is presently no known treatment for ALS, and even with intensive research, there is little improvement in symptoms [175–178].

Moreover, DNA-polymer conjugates offer several advantages that make them promising candidates for ALS therapy. These conjugates can be engineered to target specific cell types or tissues affected by ALS, allowing for precise delivery of therapeutic agents. Additionally, the programmable nature of DNA allows for the design of multifunctional conjugates capable of delivering multiple therapeutic payloads simultaneously, which could be beneficial for addressing the complex pathology of ALS [179,180].

In recent years, there has been growing interest in exploring the potential application of DNA-polymer conjugates in the treatment of ALS [181,182]. One related work article titled "DNA Nanostructure-Mediated Delivery of Oligonucleotide Therapeutics for Amyotrophic Lateral Sclerosis" by Smith et al. investigates the use of DNA nanostructures as delivery vehicles for oligonucleotide therapeutics in ALS. The article highlights the ability of DNA nanostructures to protect oligonucleotides from degradation and enhance their cellular uptake, thereby potentially improving the efficacy of ALS treatments [183]. Furthermore, DNA-polymer conjugates can be tailored to exhibit enhanced stability and prolonged circulation time in the body, thereby improving the pharmacokinetic properties of therapeutic agents. This could result in reduced dosing frequency and improved patient compliance.

6. Future perspectives and challenges

Polymer-DNA conjugation presents exciting prospects in neurodegenerative disorder treatment, enabling personalized therapies and synergizing with cutting-edge tools like CRISPR/Cas9. Yet, unlocking its full potential demands overcoming various hurdles. Innovative approaches in this realm are pivotal, offering avenues to address challenges and propel advancements toward effective clinical translation and integration with emerging technologies, heralding a new era in personalized neurotherapeutics (Table 5).

One of the most exciting prospects for DNA-polymer conjugation in neurodegenerative disorders is its potential for personalized medicine approaches. With advancements in genomics and precision medicine, researchers can now identify genetic mutations and disease pathways associated with specific neurodegenerative disorders. This knowledge allows for the development of customized DNA-polymer conjugates tailored to individual patients, targeting the underlying disease mechanisms with high specificity and precision. For example, in Huntington's disease, personalized DNA-polymer conjugates can be designed to selectively silence mutant huntingtin mRNA, offering a promising therapeutic strategy for this devastating disorder. However, the translation of DNA-polymer conjugates from the laboratory to the clinic faces significant challenges. One major obstacle is the efficient delivery of these conjugates to the central nervous system (CNS), particularly across the blood-brain barrier (BBB). The BBB presents a formidable barrier to the delivery of therapeutics to the brain, limiting the efficacy of many potential treatments for neurodegenerative disorders. Strategies to overcome this barrier (Table 6) include the development of nanoparticle-based delivery systems, such as liposomes or polymeric nanoparticles, which can encapsulate DNA-polymer conjugates and facilitate their transport across the BBB.

Integration with emerging technologies, such as CRISPR/Cas9, offers exciting opportunities to further enhance the therapeutic potential of DNA-polymer conjugates in neurodegenerative disorders. CRISPR/Cas9 technology allows for precise gene editing and has the potential to correct genetic mutations underlying these disorders. By combining DNA-polymer conjugates with CRISPR/Cas9, researchers can develop innovative therapeutic strategies for directly targeting and correcting disease-causing mutations in the CNS. For example, in Alzheimer's

Table 5
Some innovative strategies in polymer-DNA conjugation for the treatment of neurodegenerative disorder.

Novel Strategies	Application
Nanoparticle Delivery Systems	Utilizing nanoparticles composed of polymers conjugated with DNA for targeted delivery of therapeutic genes or drugs across the blood-brain barrier (BBB) and into specific regions of the brain affected by neurodegenerative disorders. Nanoparticles can enhance stability, circulation time, and cellular uptake, allowing for efficient delivery of therapeutic payloads to the desired sites of action.
Stimuli-Responsive Polymers	Designing polymers that respond to specific stimuli such as pH, temperature, or enzymatic activity to trigger the release of DNA payloads at precise locations within the brain. These stimuli-responsive polymers can provide spatiotemporal control over DNA delivery, minimizing off-target effects and enhancing therapeutic efficacy.
Polyplex Formation	Forming polyplexes by complexing DNA with cationic polymers to protect the DNA payload from degradation and facilitate cellular uptake. Polyplexes can improve the stability and bioavailability of DNA therapeutics, enhancing their delivery to neuronal cells and promoting therapeutic gene expression for the treatment of neurodegenerative disorders.
Cell-penetrating peptides (CPPs)	Conjugating DNA with CPPs or incorporating CPPs into polymer-DNA conjugates enhances cellular uptake and intracellular trafficking across neuronal membranes. This strategy enables efficient delivery of therapeutic DNA payloads to target cells within the brain parenchyma, overcoming barriers associated with poor cell penetration and increasing therapeutic efficacy.
Targeted Ligand Conjugation	Functionalizing polymer-DNA conjugates with targeting ligands such as antibodies, peptides, or aptamers to achieve specific binding to receptors expressed on the surface of diseased cells or components of the neurodegenerative pathology. Targeted ligand conjugation enhances the selectivity and affinity of DNA delivery systems, enabling precise localization of therapeutic agents within the affected brain regions.
Non-Viral Gene Editing Technologies	Integrating polymer-DNA conjugation with emerging non-viral gene editing technologies such as CRISPR-Cas9 or base editing for precise modification of disease-causing genes associated with neurodegenerative disorders. Polymer-DNA conjugates can serve as delivery vehicles for gene editing tools, facilitating their efficient and safe delivery to neuronal cells for therapeutic genome engineering.

Table 6
Various targeting strategies for crossing the blood-brain barrier (BBB) and targeting neurological disorders using DNA polymer conjugates.

Targeting Strategy	Mechanism	Application
Receptor-Mediated Transport	Utilizes receptors on BBB for transcytosis	Alzheimer's, Parkinson's, brain tumors
Carrier-Mediated Transport	Uses transport proteins to cross the BBB	Neurodegenerative diseases, epilepsy
Cell-Penetrating Peptides	Short peptides facilitate BBB penetration	Huntington's, multiple sclerosis
Nanoparticle Conjugation	Nanocarriers deliver drugs across the BBB	Glioblastoma, stroke
Ligand Targeting	Ligands bind to specific brain cell receptors	Targeted delivery in neuroinflammation
pH-Responsive Systems	Release drugs in response to pH changes	Brain tumors, ischemic conditions
Magnetic Targeting	Magnetic fields guide delivery across BBB	Brain tumors, targeted neurotherapy
Stimuli-Responsive Polymers	Release drugs in response to external stimuli	Various neurological disorders
Aptamer Targeting	DNA/RNA aptamers bind specific molecules	Alzheimer's, neurodegenerative diseases

disease, DNA-polymer conjugates could be used to deliver CRISPR/Cas9 components specifically to neurons affected by amyloid-beta accumulation, enabling targeted gene editing to prevent disease progression.

Despite these promising developments, several challenges must be addressed to harness the full potential of DNA-polymer conjugation in neurodegenerative disorders. One challenge is the need for improved delivery systems that can efficiently transport DNA-polymer conjugates across the BBB and target specific cell types within the CNS. Additionally, there is a need for better understanding of the long-term safety and efficacy of DNA-polymer conjugates in vivo, particularly in the context of chronic neurodegenerative diseases. Furthermore, the development of standardized protocols for the synthesis, characterization, and functionalization of DNA-polymer conjugates is essential for ensuring reproducibility and scalability in manufacturing processes. Collaboration between researchers, clinicians, and industry partners will be crucial for advancing DNA-polymer conjugation technologies from the laboratory to the clinic.

7. Conclusion

In conclusion, DNA-polymer conjugates represent a groundbreaking approach in the treatment of neurodegenerative disorders, offering versatile platforms for targeted drug delivery, gene therapy, and diagnostics. By harnessing the programmable nature of DNA and the unique properties of polymers, these conjugates provide tailored solutions to the complex challenges of these diseases. Covalent attachment offers stability and precise control over the architecture, making it ideal for therapeutic applications. Non-covalent assembly brings flexibility and ease of modification, while aptamer-mediated conjugation ensures high specificity and affinity. Each method has distinct advantages, with covalent attachment often preferred for its stability and efficacy, but the choice ultimately depends on specific therapeutic goals. Polymers like poly(ethylene glycol) (PEG), poly(lactic-co-glycolic acid) (PLGA), chitosan, and polyethyleneimine (PEI) are excellent candidates for RNA delivery systems due to their biocompatibility, stability, and enhanced cellular uptake.

The review on DNA polymer conjugates for neurological disorder treatment may have limitations such as focusing primarily on preclinical studies and not addressing all types of neurological disorders. Additionally, the long-term effects and scalability of these therapies in clinical settings require further exploration. Future research will continue to optimize conjugate design for improved biocompatibility, stability, and specificity, expanding the range of therapeutic payloads such as small molecules, nucleic acids, and biomolecules. Innovations in nanotechnology and bioconjugation strategies are set to develop cutting-edge therapeutic modalities with greater efficacy and reduced off-target effects. Ultimately, the convergence of multidisciplinary approaches holds immense promise for translating DNA-polymer conjugates into clinically viable treatments for neurodegenerative disorders, paving the way for a new era in precision medicine.

Declaration of Competing 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.

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