

# DNA as Nanostructuring Element for Design of Functional Devices

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**Abstract** This chapter gives an overview of the recent developments in the use of natural and synthetic DNA for design of functional devices such as biosensors or optoelectronic platforms. In addition, different strategies for preparation of DNA–protein and DNA–nanoparticle conjugates and their use for DNA origami decoration are discussed. Finally, a summary of DNA-based hybrid materials such as DNA hydrogels are presented with particular emphasis on the current and possible future applications.

## 1 Introduction

Discovery of the double-helix structure has not only brought the revolution to the field of molecular biology and genetics, but opened up a route toward the use of its molecular architecture to design novel devices, enable structuring of different species or design new programmable materials. DNA's structural properties such as specific base pairing, stability of the double helix as well as the powerful combination of stiffness, and flexibility have attracted the interest of the scientists working in different scientific fields ranging from physics and plasmonics to biochemistry and engineering. Their efforts led to the development of DNA nanotechnology field where DNA, rather than being genetic code carrier, is used as a versatile building block. The structuring potential of DNA was hinted in a theoretical paper written by Ned Seeman in 1982, which then led to the

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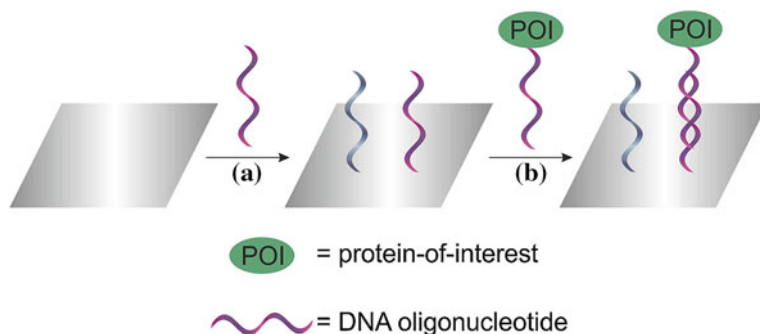
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establishment of the simple rules employed to build different structures out of DNA strands [1, 2]. The field was further advanced by the development of DNA-directed immobilization (DDI) and conjugation of single-stranded DNA to various molecular species [3] and a DNA-folding technique called DNA origami [4]. Of course, this advances would not be possible if it were not for the development of the chemical synthesis of short DNA strands [5–7], resulting in design of automated synthesizer, which enabled production of short DNA strands of desired sequences at affordable costs. In this paper, we wanted to give an overview of the use of DNA in nanotechnology with special emphasis on the design of functional nanodevices such as biosensors, catalytic platforms, or novel biohybrid materials. It should be noted that two types of DNAs are used today for design of such devices—short chemically synthesized DNA and DNA from natural sources such as viral or salmon sperm DNA. This chapter will give a summary of the devices made of both DNA types.

## 2 DNA-Directed Immobilization: Use of Chemically Synthesized Short DNA

Short DNA strands (up to 80 bases) can today be synthesized in a relatively straightforward manner using phosphoramidite chemistry and commercially available DNA synthesizers. Such synthetic oligonucleotides are one of the most powerful tools in biotechnology and nanotechnology. The successful phosphoramidite solid-phase synthesis of DNA used today is a product of the extensive research over the past 50 years and is the combination of effective solid-phase chemistry and phosphoramidite methodology first time used by Beaucage and Caruthers [6]. They have described the reaction of two modified nucleosides, which resulted in a 3'-5' linkage, present in the natural DNA, in high yield. The chemical strategy, which formed the basis of the chemical synthesis of DNA, was also a result of the discovery that P(III) was considerably more reactive than corresponding P(V) acylating agents [8] as well as the work by Sinha et al. [9] with 2-cyanoethyl phosphoramidites used in solid-phase oligonucleotide synthesis. Using phosphoramidite chemistry, numerous modifications can be introduced to the oligonucleotides on both (5' and 3') ends or internally, which additionally opened up a range of applications (design of DNA-based biosensing devices such as molecular beacons). Such ability also led to the development of the DNA microarrays and resulted in a range of chemical methodologies, which can be employed to attach DNA to various surfaces or different molecular species. Once immobilized, single-stranded DNA can be hybridized with complementary strand bearing different molecules, and it can act as an immobilization tool within a process called DDI (DNA Directed Immobilization, Fig. 1). Developed in mid-1990s [3], it has been used in various applications such as the preparation of biosensing platforms, but also for precise positioning of biomolecules to enable study of their function.

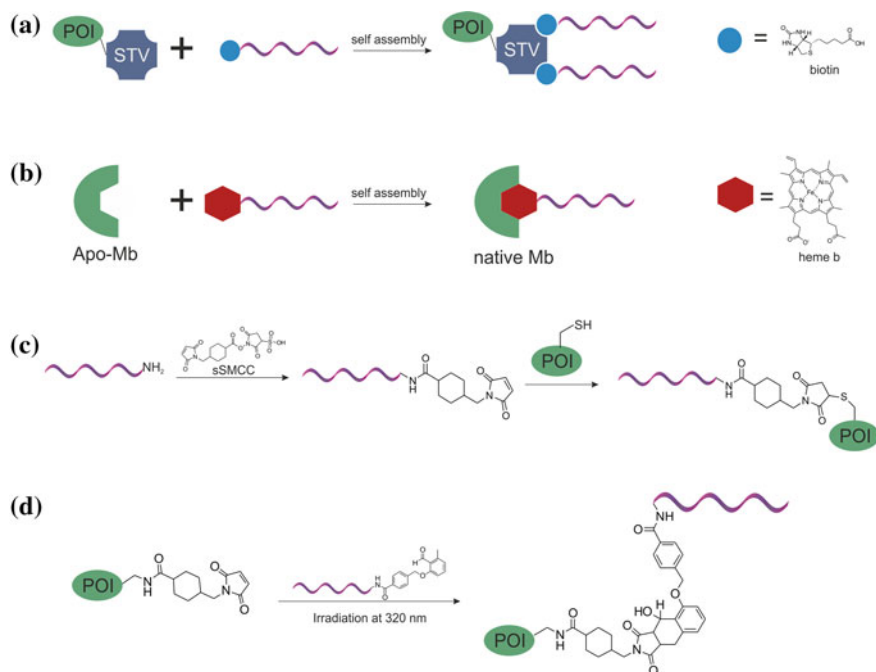


**Fig. 1** Schematic illustration of DNA-directed immobilization (DDI). Shown is the formation of a protein microarray in 3 steps. After immobilization of DNA oligonucleotides on a suitable surface (a), a DNA-modified protein-of-interest (POI) containing complementary sequence can be hybridized (b). Complementary sequences are shown in the same color

## 2.1 DNA as an Immobilization Tool

To enable the use of DNA as immobilization tool, on the one side, capture DNA needs to be anchored to the desired surface (i.e., magnetic bead, nanoparticle (NP), or planar surface). On the other side, suitable techniques need to be developed for the conjugation of oligonucleotides to the species, which need to be immobilized (biomolecules and NP) [10, 11]. As the biosensing devices are functional devices of huge importance for the investigation of basic biological principles of molecular interaction within the cell but also for diagnostics, the capture and immobilization of important biomolecules such as various proteins are of tremendous significance. The first step, however, is finding appropriate chemical methodology (non-covalent or covalent) to prepare DNA–biomolecule conjugates and vast efforts have gone into developing strategies that enable tight binding and preservation of both DNA and biomolecular functions.

Most common non-covalent coupling methodologies are based on streptavidin (STV)–biotin interaction [12] or use of protein tags such as His tag [13], through which DNA can be attached specifically onto a pre-defined position (Fig. 2a). Another approach applicable to a class of cofactor-containing proteins involves the replacement of the natural cofactor with DNA-modified cofactor, during the process known as cofactor reconstitution [14, 15] (Fig. 2b). Site-specific and stoichiometric heme protein–DNA conjugates were prepared by reconstitution of heme into apoenzymes [15] and successfully used to design electrochemical biosensors [16] and artificial, protein-based photocatalysts [17]. Along the similar line, Simon et al. [18] used flavin-modified DNA to reconstitute apoflavin reductase and designed the system where enzymatic activity can be controlled by DNA hybridization. However, non-covalent approaches often result in the protein–DNA complexes sensitive to the environmental conditions and prone to dissociation, which renders them unsuitable for studies under cellular matrix conditions.



**Fig. 2** Overview of different coupling methods for the synthesis of protein–DNA conjugates. **a** Use of STV–biotin interactions to combine protein-of-interest–STV conjugates with biotinylated DNA. **b** Reconstitution of apomyoglobin with DNA-modified cofactor heme. **c** Covalent coupling method with the help of the bifunctional linker sSMCC by modifying a Cys residue inside the protein-of-interest. **d** Light-triggered reaction of maleimide-modified protein-of-interest and photoreactive caged DNA [22]

More robust covalent linkage provides chemical stability and the most widely used methodology for preparation of DNA–protein conjugates involves the use of bifunctional linkers to enable cross-linking of thiol- or amine-modified single-strand DNAs with appropriate amino acid residues on the protein surface (Fig. 2c) [19]. One of the most widely used coupling reagents is heterobifunctional cross-linker sulfosuccinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate (sSMCC) (Fig. 2c) containing a maleimide moiety (thiol-reactive group) and NHS active ester (amine reactive), which then react with naturally occurring or genetically introduced lysines (Lys) and cysteines (Cys) and thiol- or amino-modified DNA [20, 21].

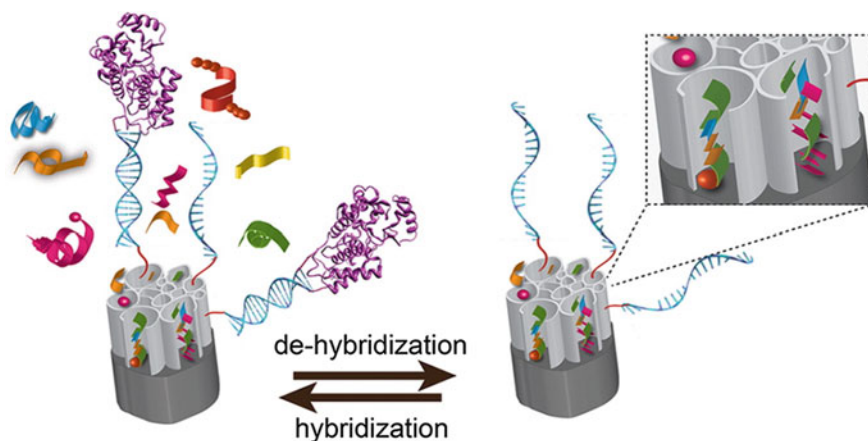
Maleimide-reactive group introduced to the protein using sSMCC can not only be used for modification of Lys with thiolated DNA, but also used for other mild conjugation strategies. In a recent example, Lys groups of horse heart myoglobin (Mb) were converted to maleimide groups to which DNA could be attached via a mild photochemical approach representing a first example of DNA–protein conjugation under light-triggered bioorthogonal conditions [23]. This was achieved by

using an oligonucleotide containing a photoreactive caged diene, which can be activated by irradiation and coupled to the maleimide-modified Mb to afford Mb–DNA conjugate (Fig. 2d).

Recently, bioorthogonal approaches have been developed, which allow DNA coupling independently of specific amino acid functional moieties present in a native protein. Using bioorthogonal expressed protein ligation, in which a recombinant protein containing thioester can react with Cys-modified nucleic acids, different DNA–protein conjugates were prepared [24]. Other approaches are based on Huisgen 1,3 dipolar cycloaddition of azide and alkyne [25], Staudinger ligation [26], keton–aminoxoy [27], or enzymatically aided reactions [28, 29]. However, these methods usually include additional modifications of the protein either by addition of bioorthogonal functional groups through Lys and Cys residues or by introduction of artificial amino acids [30]. However, for certain classes of proteins, the introduction of common affinity protein tags or artificial amino acids is often a complicated process from a molecular biology side, which results in low yields of desired protein and often in the loss of activity. On the other side, modification through Cys might not be feasible due to the highly conserved Cys regions making thiol unavailable for further modifications and there might be simply too many Lys on the surface, the modification of which effects the distribution of the surface charges and might influence the inherent protein–protein interactions. Therefore, there is often a need to employ other amino acids for attachment of DNA. Along this line, Bauer et al. [22] designed specific tyrosine-binding bifunctional linkers, which were used to modify STV and Mb proteins using mild click chemistry procedures.

In general, DDI methodology can be used to immobilize different species onto a range of surfaces and it is in particular interesting for design of biosensing devices. In one such example, Bano et al. [31] designed a protein nanoarray for detection of proteins using atomic force microscopy (AFM) nanografting by employing DDI of protein–DNA conjugates and using topographic AFM height measurements to characterize the interactions within the nanoarray. Recently, a protease-sensing device was developed employing DDI immobilization of protease trypsin onto nanoporous silica substrate [32]. Silica platform was tuned in such a way to contain nanopores of a particular size, and the DNA–protease conjugate was immobilized onto the surface, while pores remain empty. When protein mixture is exposed to such device, degradation of proteins occurs in the presence of trypsin and small peptide proteolytic products can be captured within the pores. In the case of this sensor, the use of DNA for immobilization enables the mild removal of proteases after digestion and the successive analysis of the fragments captured within pores by mass spectrometry (Fig. 3)

The combination of DDI with mass spectrometry can also be used to determine protein–protein interaction of the Ypt family of small GTPases, which are modified by native chemical ligation to yield protein–DNA conjugates [33]. The successful immobilization of these conjugates could be visualized by exchanging the cofactor GDP with a fluorescently labeled GTP analogue. To test for nucleotide-dependent activity of immobilized Ypts, fluorescence experiments were conducted



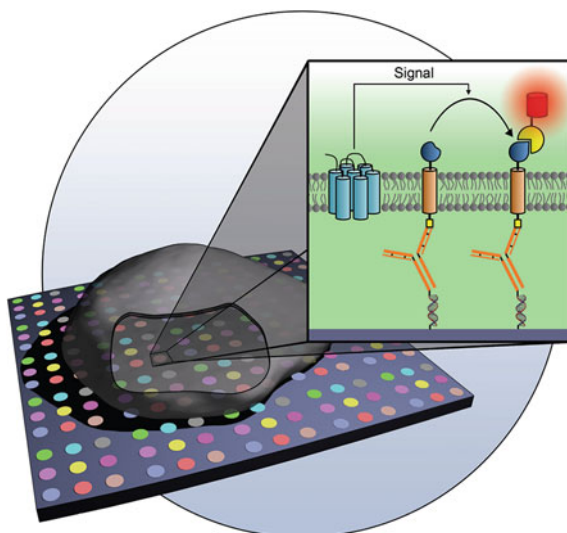
**Fig. 3** Use of trypsin–DNA conjugates for the development of a biosensor for detection of the products of protein digestion by mass spectrometry. Reprinted with permission from [32]. Copyright 2013 American Chemical Society

with the labeled guanine nucleotide exchange factor DSS4, which binds to a specific Ypt causing the release of its cofactor GDP. Binding of DSS4 to immobilized Ypt1–DNA conjugates could also be detected after coating the microarray with matrix by conduction MALDI-MS measurements on the slide.

Besides the fabrication of chips for mass spectrometry, immobilization of protein–DNA conjugates was also used to build up electrochemical biosensors for detection of DNA hybridization. Capture DNA probes were bound to nanoelectrode ensembles followed by hybridization with glucose oxidase-labeled target DNA and the success of the immobilization determined by detection of an electrocatalytic current after addition of the glucose substrate and a redox mediator [34].

In addition to the immobilization of proteins, several applications were published using DDI to capture cells on functionalized surfaces. Niemeyer et al. [35] compared the labeling efficacy, specificity, and effects on cell viability of different methods and found that there is a strong influence of the employed cell line. Besides previously published methods based on direct coupling of *N*-hydroxy-succinimide or strain-promoted alkyne-azide cycloaddition, they utilized a new method based on the oxime ligation. Cell-surface glycans were modified by periodate cleavage to form aldehyde groups, which reacted with amino-biotin before STV–DNA conjugates were coupled to the cell surfaces leading to the high labeling densities while retaining a high percentage of living cells. Another approach to capture specific cells on a surface was developed by DDI of the antibodies, which selectively bind kidney or lymphoma cells [36]. Using this modular setup of biotinylated antibodies in combination with STV–DNA conjugates, the method could be applied to immobilize modified cells and investigate the protein interactions within (Fig. 4) [37].

**Fig. 4** Measurement of protein interactions inside living cells by immobilization of cells via DNA-modified antibodies on a solid support. Reprinted with permission from Ref. [37]



DNA modification was also applied to prepare glycoconjugates in order to design carbohydrate microarrays for the analysis of their interactions with the galactose-specific lectin PA-IL in search of a suitable inhibitor. PA-IL is suspected to play an important role in the adhesion and biofilm formation of *Pseudomonas aeruginosa* (PA), the bacterium involved in various infections. Use of the DDI, in comparison to other direct immobilization methods for attachment of glycoconjugates, enabled the specific recognition of binding events in a complex mixture [38].

In another application, Homola and coworkers developed a system to detect protein biomarkers relevant to cancer diagnostics in buffer solution as well as in the complex mixture of blood serum, utilizing surface plasmon resonance (SPR) imaging [39]. Antibody–DNA conjugates were immobilized using DDI on the sensing area of an SPR sensor previously spotted with complementary thiol–DNA enabling a high-throughput screening of biomarkers with low limits of detection.

Since the first use of complementary DNA as immobilization tool for proteins two decades ago, the method has been employed for a vast variety of applications including development of biosensors and diagnostic methods. This methodology evolved even further and enabled the immobilization of complex systems such as the whole living cells. Overcoming the limitation of the DNA conjugation to a range of molecular species will open up a whole range of new exciting applications of DDI as immobilization tool.

Besides being used in immobilization of biomolecules onto planar surfaces, DNA can also be employed for functionalization of NPs to design functional devices such as biosensors or plasmonic materials. Next paragraph will present some of the developments in the field of NP–DNA conjugates.

## 2.2 DNA–Nanoparticle Conjugates

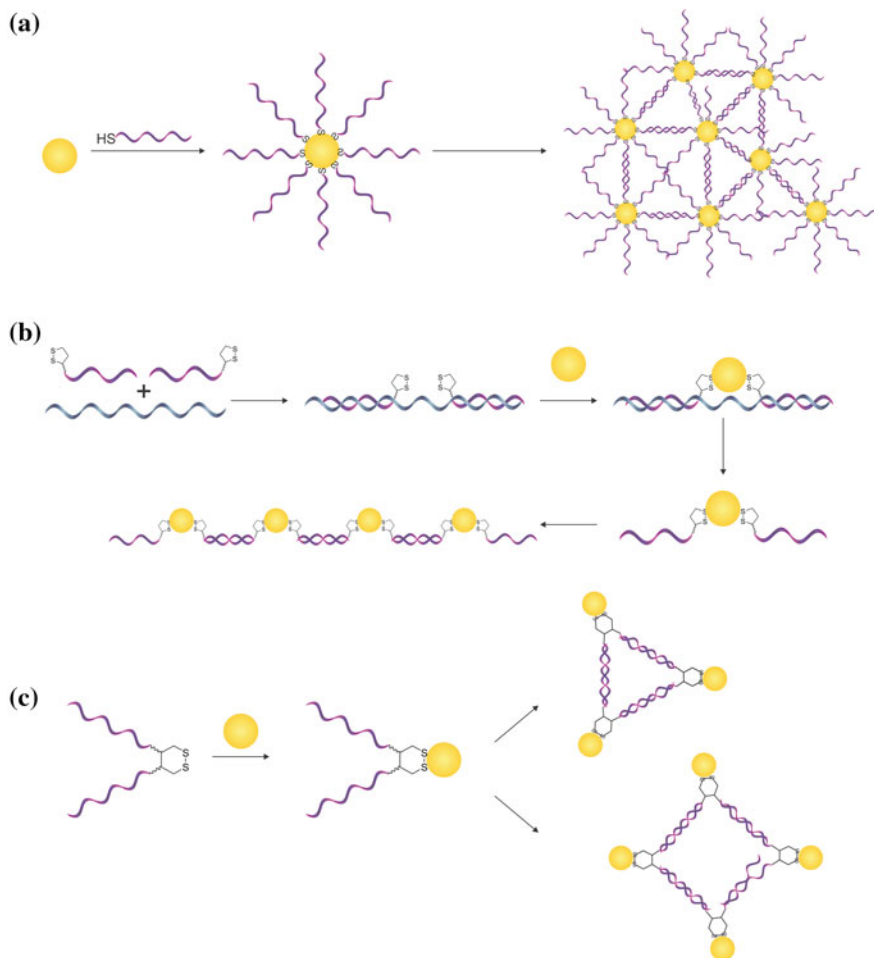
Since the first synthesis of DNA–Nanoparticle (DNA–NP) (AuNPs) conjugates almost 20 years ago [40], the stability of these conjugates was continually improved [41]. The most common method for the synthesis of DNA–AuNP today is the ligand exchange with thiolated oligonucleotides, which are bound through sulfhydryl group to the gold surface, therefore enabling the coupling without additives. Usually, the stability is improved by using salt aging of the conjugates over the course of some days [42], but recently, a faster method has been reported using a pH-dependent attachment of DNA to gold or silver NP to yield quantitative adsorption [43]. Other techniques involve first the functionalization of NPs with a suitable bifunctional linker followed by coupling of an oligonucleotide using mild chemical approaches. For example, silver nanoparticles (AgNP) were modified with DNA using one pot synthesis of NP in the presence of benzotriazole maleimide and subsequent Diels–Alder reaction with furan-modified DNA [44]. The conjugation of NP with DNA enables further hybridization, therefore facilitating arrangement of DNA-modified NP into secondary structures with different geometries using complementary-modified NP in order to develop new materials [41]. For a controlled assembly, several methods were developed to immobilize DNA–NPs at specific position and in fixed angles to each other. An overview over these methods is shown in Fig. 5.

To achieve a linear geometry of several DNA–AuNP, a template-assisted approach can be used, fixing two NP-binding groups in a  $180^\circ$  angle to each other. Following the binding of AuNP to these groups, the template strand is removed enabling the successive hybridization with similarly modified DNA–AuNP conjugates (Fig. 5b) [43]. Because of the limits of single-stranded DNA as template, branched DNA structures can be employed covalently coupling two DNA strands in a fixed angle to one internal cyclic dithiol for binding of AuNP (Fig. 5c) [45]. Depending on the choice of the DNA, trapezoid or triangle geometries could also be obtained. Combining the programmable hybridization of DNA–AuNP with layer-by-layer thin-film fabrication, it is also possible, as shown recently, to synthesize free-standing NP films that are capable of programmable transformation [46].

All of those different forms of DNA–NP conjugates can be used as solid support for the immobilization of several DNA-modified molecules, such as biomarkers or proteins using the DDI approach [47, 48]. The advantage of using DNA is in controllable hybridization and dehybridization, leading to programmable biosensing nanomaterials [49, 50].

The specific recognition between two complementary DNA strands led to the development of colorimetric sensors for the detection of mutations in DNA sequences using DNA-modified AuNPs [51, 52]. This molecular recognition can be analyzed by utilizing the spectrometric properties of AuNPs, which change color upon aggregation caused by hybridization. Simple methods of exploring this phenomenon employ UV–Vis spectroscopy or size monitoring by DLS [53]. A





**Fig. 5** Schematic illustration of the immobilization of DNA onto AuNP using monothiol DNA (a) [40], template-assisted immobilization (b) [43], and branched DNA structures for flexible assembly of different geometries (c) [45]

more sensitive method was developed by combining DNA-modified NPs with surface-enhanced Raman scattering (SERS). Using SERS-sensitive dye and two differently modified NP containing complementary oligonucleotide strands, SERS can be exploited in identification of target oligonucleotides [54].

To identify single-base mismatches with high specificity, a method was developed using hairpin oligonucleotide-modified AuNP [55]. The hairpin oligonucleotide was designed in a way that only the hybridization of two single-base mismatches triggers the conformation change, which enables recognition of an immobilized oligonucleotide with the stem region of the hairpin. By using this double-target binding approach, it was possible to accumulate AuNPs in a testing

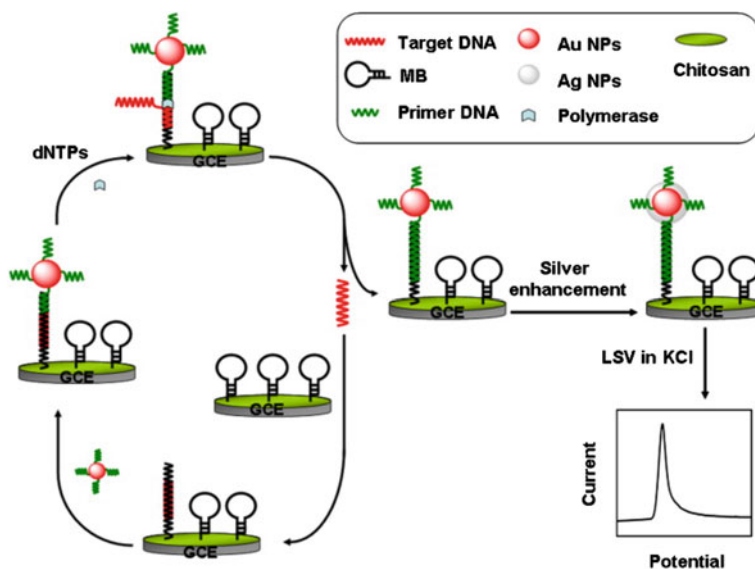
zone of a lateral flow strip, therefore enabling a visual detection of red AuNP bands. Compared to perfectly matched DNA, the single-base mismatches yielded a 28 times higher signal. To demonstrate its possible application as nucleic acid-based biosensor, the method was applied to the detection of two different mutation sites involved in the skin disorder autosomal-recessive congenital ichthyosis (ARCI) [55]. Apart from single-base mismatches in genes, DNA-modified AuNPs were also used for miRNA profiling of prostate cancer markers in fM concentrations [56]. A scanometric assay was developed utilizing a universal DNA sequences for the modification of AuNP. The complementary sequence was used as universal cloning linker, which was ligated to synthetic miRNA by T4 ligase. Following this modification, miRNA was captured by a low-density DNA array, leaving the universal cloning linker free for hybridization with complementary DNA–AuNP. Upon immobilization of AuNP onto the array, where binding of miRNA occurred, binding could be detected by gold enhancement. Therefore, this method enables the read out of hybridization events of AuNP on the surface with a light scanner [56].

Gao et al. combined the electrochemical enhancement with immobilized hairpin oligonucleotides for efficient detection of target DNA. Addition of target DNA causes a structural change in the hairpin, which enables binding of the reporter DNA–AuNP. So-called circular strand-replacement polymerization (CSR) causes the release of target DNA by elongation of the reporter strand through addition of polymerase. This target DNA can be bound again by another hairpin oligonucleotide, therefore increasing the sensitivity of this assay. Bound AuNP catalyzed the deposition of silver, which was analyzed by electrochemical stripping, allowing the differentiation of single-base mismatched DNA (Fig. 6) [57].

These examples and those covered in a range of excellent reviews [47, 58–64] show that DNA–NP offer a broad range of possible applications due to their unique optical and electrochemical properties, which enable immobilization of molecules of interest in a programmable manner as well as DNA mismatch detection and design of protein biosensing platforms. The next step is to use both biomolecule–DNA and NP–DNA conjugates on a solid support to design sensing chips, new plasmonic materials, or even programmable catalytic platforms. Recent introduction of DNA origami, a folding methodology to enable structuring of DNA in an easily programmable way, opened new avenues to the use of different conjugates.

### **3 DNA Origami: Combination of Natural and Chemically Synthesized DNA**

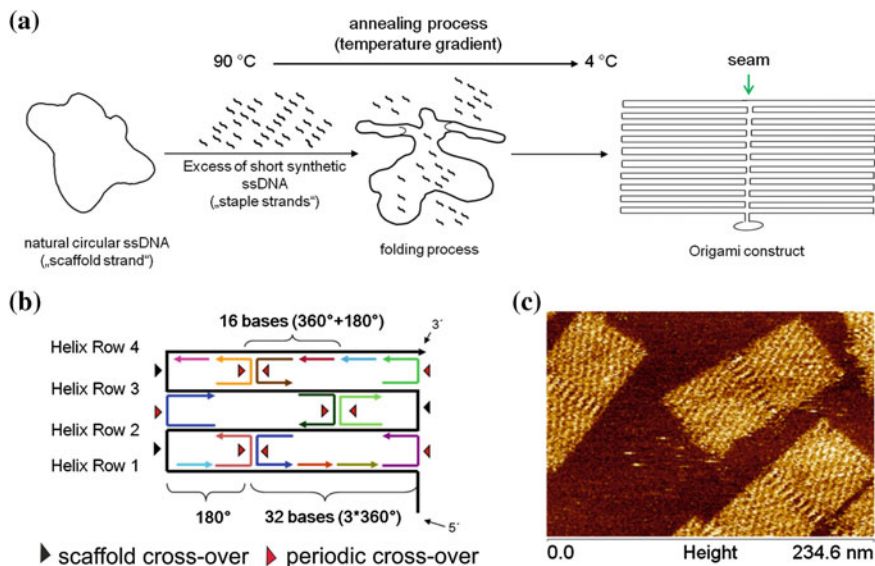
DNA origami technique is one of the fastest-growing fields in structural DNA nanotechnology, and nanostructures prepared in this way are characterized by higher yields and higher mechanical flexibility of 2D and 3D structure assemblies.



**Fig. 6** Schematic illustration of dual-signal amplification strategy for DNA detection by electrochemical enhancement and circular strand-replacement polymerization. Reprinted with permission from [57]

This method of DNA folding, named after Japanese traditional technique of origami (From *ori*: folding and *kami*: paper), was first reported by Rothemund, who used a long viral circular ssDNA strand from bacteriophage (7.25 kilobases) to prepare customized shapes [4]. This can be achieved using short synthetic DNA strands, called the staple strands (mostly between 20 and 50 bases), which can fold long viral DNA by a simple thermal annealing process (Fig. 7a). While the first publication was limited to 2D structures such as rectangles, triangles, and stars, more complex planar geometrical forms as well as 3D structures such as tetrahedral shapes [65], DNA boxes with a controllable lid [66] or honeycomb [67] structures followed quickly few years after, indicating the applicability of presented approach.

The scaffold assembling strategy involves special staple strand design, whereby the customized folding process of the natural scaffold is controlled by base pairing with the staple strands following geometrical rules of helical structure formation and crossover design (Fig. 7b for 2-dimensional design). In the case of 2D objects, the helix row formation is stabilized by a regular progression of crossovers, which are replicated every 1,5 helical turns (16 bases in natural B-DNA) between two neighboring helices (Fig. 7b), which means that the alternated crossovers take place every  $180^\circ$  resulting in a folding process of the helices in a planar shape. By changing the crossover angles between two helices inside of the structure, folding process of 3D structures can be achieved. A thorough explanation on crossover



**Fig. 7** **a** Scheme for the folding process of 2D origami construct in a shape of a *rectangle*. The scaffold strand is heated with an excess of hundreds of staple strands and cooled down for the folding process to proceed. **b** Scheme of the scaffold strand pathway (*black arrow*) and staple strand pathways (*colored arrows*) in design of 2D. The triangles represent the distances for periodic crossovers of the staple strands (*red triangles*) and the crossovers of the scaffold strand (*black arrows*). **c** Characterization of a rectangle-shaped DNA origami by atomic force microscopy (AFM) (authors unpublished work)

patterns of 2D and 3D origami shapes is given in a mini-review by Sacca et al. [68].

It is important to note that DNA itself is limited in terms of chemical, optical, or electronic properties and that the functionalization of DNA origami for future applications has been, and it will continue to be one of the research challenges. To enable further modification of DNA origami, short staple strands containing various functional groups can be employed as already described previously in the case of DNA conjugate preparation. In origami, there are more than 200 unique staple strands, which can individually be modified at defined positions up to a resolution of 6 nm [69]. Nowadays, the automated synthesis of oligonucleotides in combination with different orthogonal chemical reactions has led to development of diverse strategies to functionalize DNA nanostructures. One of the first strategies employed was STV–biotin interaction, with origami surface being decorated with biotinylated staple strands at nanometer-defined positions. For example, Kuzuya et al. [70] described a planar punched DNA origami structure with periodic wells in nanometer scale ( $6.8 \times 12 \times 2.0$  nm). These wells were functionalized with biotinylated triethylene glycol (TEG) staple strands, which act as capture points for single STV protein. In a subsequent study, it was also shown that a small

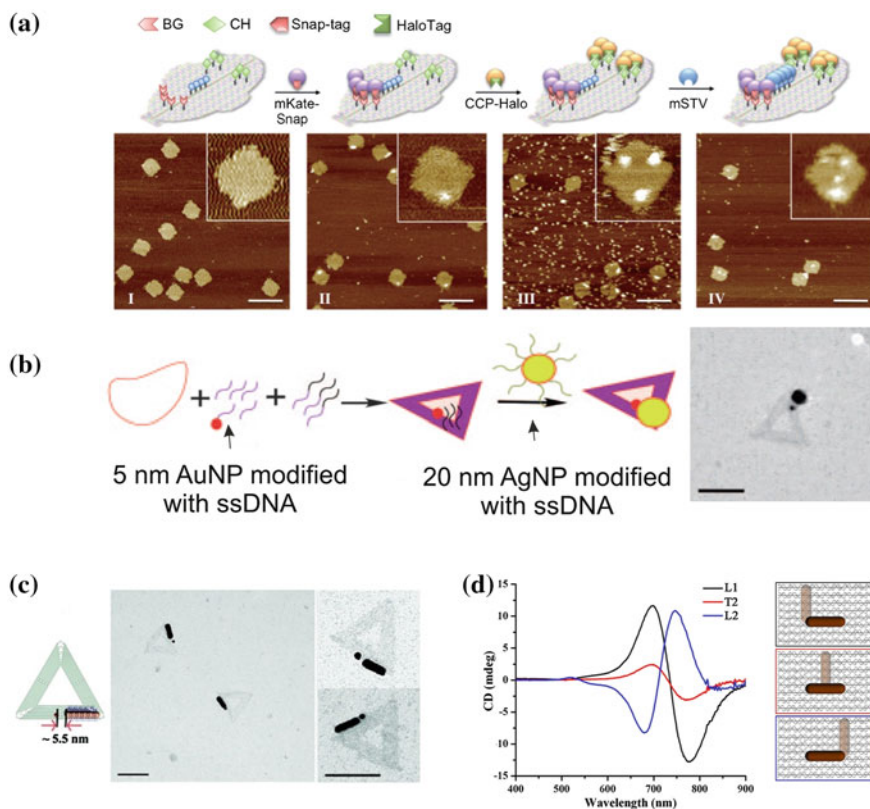
modification of the staple strands with toehold anchor extensions inside the wells could be used to produce a stepwise and reversible nanoplatform for the selective binding and removal of STV by single-strand displacement, which can be followed by AFM imaging [71].

To illustrate how the staple strand modifications can be used as a versatile method for the imaging of orthogonal chemical reactions at single-molecular level, one could use a recent example by Voigt et al. [72]. In this work, staple strands on customized positions were modified with biotin groups containing selectively cleavable linkers such as disulfide bridges, which can be reduced by DDT, or an electron-rich 1,2-bis(alkylthio)ethene moiety, for the cleavage by singlet oxygen generated with light in the presence of a singlet oxygen photosensitizer (PS). The orthogonal addressing of different functional biotin groups on the origami platform surface was achieved by the introduction of alkyne- and azide-groups for click chemistry or primary amines for active ester amidation, whereby the orthogonal cleavage process was easily characterized by STV binding and AFM imaging. Orthogonal decoration of origami with proteins can be also achieved using protein tag strategies such as SnapTag and HaloTag as recently demonstrated by Niemeyer and coworkers (Fig. 8a) [73].

On the other side, direct immobilization of DNA-tagged molecules can be employed to introduce NPs or proteins directly to the staple strands. For example, origami can be decorated with complementary protruding staple strands, which act as a capture oligonucleotides. In this way, different origami platforms were designed, which organized DNA-tagged molecules in predefined 2D or 3D structures [75, 77–81].

As described previously, DNA modification of metallic NP is now a well-established strategy. However, designing devices that make use of plasmon-distance effects of different NPs for new applications in nanophotonics and nanoelectronics still poses a challenge [77, 82–85], and DNA origami might be just the right solution. The immobilization of NPs of different sizes was recently described by Ding et al. [85] who used a triangle-shaped DNA origami structure for the immobilization of AuNPs with different sizes to form a linear structure with well-controlled orientation and <10-nm spacing. This spacing and orientation could be used to generate an extremely high field enhancement for the construction of nanolenses.

The DNA origami nanostructures could also be used for the preparation of new hybrid materials with different metallic NPs as in the case of rectangle-shaped origami decorated with AuNP (5 nm)–AgNP (20 nm) heterodimer structures [74] (Fig. 8b). Besides NPs, DNA-modified nanorods (NRs) were also successfully immobilized onto origami structures. Yan and coworkers [75] used the origami platform for the bottom-up construction of well-ordered AuNR–AuNR and AuNR–AuNP hybrid nanoarchitectures with precise inter-rod angles and distances (Fig. 8c). These new hybrid materials showed unique plasmonic properties, which enhanced the possibility to characterize the effect of interparticle distances and geometrically dependent photonic interactions leading to a new class of plasmonic materials.



**Fig. 8** **a** Orthogonal decoration of DNA origami with proteins by using protein tags and biotin-STV binding strategies [73]. **b** Schematic representation of a 5-nm AuNP and 20-nm AgNP dimer on a triangle-shaped origami structure and characterization with TEM [74]. **c** Scheme diagram and TEM images of an end-on AuNR-AuNP heterodimer structure on an origami triangle platform [75]. **d** Scheme and CD spectra of discrete 3D plasmonic AuNR dimer structures on a rectangle-shaped origami nanostructure [76]. All scale bars are 100 nm. All figures are adopted from named publications with kind permission

One interesting model system, to use plasmonic effects for the design of new materials with useful biosensing properties, was described by Fan and Govorov [86]. In this model system, the authors described that neighboring NPs can create a circular dichroism (CD) effect when they are organized in asymmetrical geometries such as pyramids, tetramers, or helices with the strongest signal being obtained from the helical structures. The effect is produced by a collective chiral plasmon resonance, which is released by Coulomb and electromagnetic interactions [87]. Moreover, the response of CD activity could be controlled by the metal compositions and different particle sizes [78, 80]. Also NRs showed tailored optical chirality in well-defined spatial configuration, which was described the first time by Lan et al. [76] (Fig. 8d). These systems demonstrate that shifting the

location of single AuNR on an origami platform at the nanometer scale has a strong influence of the plasmonic CD effect and could be used for new material design named by authors the “chiral plasmonic ruler.” Recently, the metallization of DNA was utilized to grow arbitrarily shaped AuNPs on the origami structure [88]. Au clusters with a size of 1.4 nm were coated with positively charged amines and were used to bind to negatively charged origami templates with different shapes, in which they act as seeding sites for the cluster growth. The pre-seeded origami shapes were metallized by electroless deposition of gold ions from solution and could grow in predefined formations such as gold nanocuboids, polymerized nanorods, or nanodonuts. In this case, it was shown that DNA origami could be used as an addressable platform for the controlled metallization of seeding sites in customized shapes with the nanometer precision, which could find new applications in optical and electrical devices.

All of above examples used original viral DNA scaffold strand. However, the customized changes of the scaffold strands could lead to new designs and new modification capabilities. For this purpose, several different techniques were developed for the scaffold strand production, keeping in mind that the scaffold extraction from natural sources or the use of natural DNA as templates for the production seemed to be the most promising route. Several methods have already been described for the scaffold production. The one introduced by Pound et al. [89] involves the use of a polymerase chain reaction (PCR)-based techniques and two different viral DNA sources as templates, the  $\lambda$ -DNA (48.5 kb) and the commonly used M13mp18 DNA (7.25 kb). Resulting dsDNA PCR products with a length of 765–4,808 bp are flanked with 3' biotinylated primer, whereby one of the complementary strands could be bound to streptavidin-coated magnetic beads and used for purification. Nevertheless, the production of the scaffold using this method is limited by time-consuming purification steps, which decrease the amount of obtained DNA that can be further used. The viral  $\lambda$ -DNA was also used by Zhang et al. [90] as a template to produce a 26-kb-long dsDNA strand, which can then selectively be digested into ssDNA by using enzyme  $\lambda$ -exonuclease. This enzyme catalyzes the digestion of dsDNA into mononucleotides from 5' to 3' direction in a highly progressive manner and if a primer is designed in such a way that one strand of dsDNA is protected, this strand can be used further, while the other is digested by the enzyme. In another variation of PCR methodology, Said et al. [91] used the M13mp18 DNA as a template for the production of a 1.4-kb-long origami scaffold with the help of restriction and ligation processes for the cyclization of the ssDNA scaffold product. Recently, a new methodology was employed based on an isothermal nucleic acid amplification technique called rolling circle amplification (RCA) [92]. In this technique, a long ssDNA is directly produced in the presence of a specific  $\Gamma$ 29-Polymerase by using deoxynucleotide triphosphates (dNTPs) and short DNA primer strands [93]. A significant advance in origami design was made by enabling direct folding of dsDNA by using a derivative of M13 and plasmids [94] or digested fragments of  $\lambda$ -DNA [95]. Use of dsDNA as a scaffold could have a huge potential as there is an abundant supply of natural dsDNA and that would also remove the need of ssDNA production prior to folding. However, the staple

strand design for such scaffolds is more complex as it needs to take into account the proper folding paths from both ssDNA strands and it will take time to optimize.

Alternative scaffolds can also be obtained by generating circular ssDNA from plasmid sources. In such a way, Douglas et al. [96] established a convenient methodology, which employs the ability of Nb.BsrDI enzyme, a nicking endonuclease, to site specifically cleave the phosphodiester bond of one strand of dsDNA plasmids. The nicked strand could be selectively digested by treatment with T7- and  $\lambda$ -exonuclease and the constructed ssDNA scaffolds then used to fold 2- and 3-dimensional origami structures. This technique was recently further extended by Erkelenz et al. [97], who explored a highly efficient method for a large-scale production to prepare scaffold strands with customized length and sequences from plasmids. To achieve this, molecular cloning techniques of site-directed mutagenesis [98] and SLIC cloning [99] were combined to produce tailored plasmids, which also contain genetic regulatory elements and tailored nicking endonuclease restriction site for the production of circular scaffold strands in high amounts. Besides viral ssDNA, bacterial ssDNA and dsDNA, eukaryotic ssDNA could also be used as a scaffold for future origami design. The application of the origami technology could further be extended by the customized scaffold strand production from natural sources, to which genetic modification is introduced to enable additional modification or preparation of custom length DNA.

In such a way, the combination of a nanoscale control over design and tailored genetic information could be used for design and decoration of origami with signal molecules to control different biological process or enable controlled transport of genetic information to the targets within cell. Origami methodology is based on the use of both natural scaffolding DNA strand and numerous short, chemically prepared DNA strand. However, when larger quantities of DNA are desirable, cheap sources of natural DNA are needed. This is the case with DNA-based optoelectronic devices, which move away from nano- to microscale. Next paragraph will give a short overview of recent developments in DNA thin-film design and their uses in preparation of optoelectronic devices.

## **4 DNA in Design of Thin Films and Optoelectronic Devices: Use of DNA from Natural Sources**

Some optoelectronic devices, which will be discussed in this section, have been realized with enhanced efficiency due to the special properties of dsDNA. Namely, DNA molecule has a  $\pi$ - $\pi$  stacking structure basically forming a tunnel ready for electron transfer, it has high affinity for metal ions acting as a good template for metallic NP preparation, DNA films exhibit high optical transparency in a broad spectrum range, and finally, the fluorescence efficiency of numerous fluorescence dyes can be enhanced due to the intercalation or insertion between adjacent base pairs or minor grooves. Such intercalation or groove binding of dyes to DNA helix



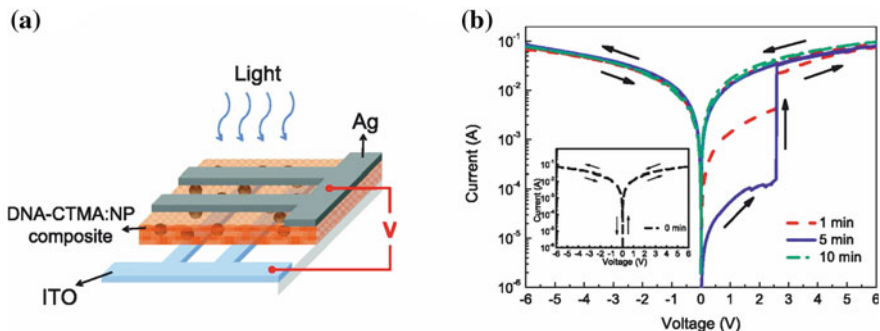
is particularly interesting as it has been shown that in such a way the aggregation of dyes at high concentration is reduced, and therefore, DNA is superior to conventional polymer hosts. However, it should be taken into account that DNA is also more sensitive than polymers to the environmental conditions, such as moisture and temperature, and does not possess sufficient mechanical strength for practical microdevice implementation. Additional processing is therefore required to make natural DNA biopolymer suitable for application in thin-film production. In 2001, Ogata et al. described the large-scale preparation and characterization of a series of natural DNA–cationic surfactant complexes, demonstrating a simple method to prepare optical-quality natural DNA biopolymer film from raw DNA derived from salmon testes [100]. Since then, several research groups worldwide have been devoted to advance the material processing and broaden the device implementation.

Experiments have shown that the use of DNA biopolymers as host materials can dramatically enhance light emission compared to conventional polymer hosts [101]. It is also reported that organic light-emitting diodes (OLEDs) that incorporate DNA thin films as electron-blocking layers show improvements in one to two orders of magnitude in terms of efficiency and brightness [102]. We can recommend several excellent reviews and books that summarize these developments in the past few years [103–109], but in the following paragraphs, we have chosen to focus onto the most recent developments in DNA thin-film preparation and application.

One of the most widely used DNA in optoelectronics is DNA from salmon testes. The marine-derived raw DNA normally has a high molecular weight, which makes it hard to process. Furthermore, such high molecular weight DNA increases the viscosity when dissolved in solvents, which, in turn, affects the film morphology and uniformity. Therefore, it is necessary to reduce the molecular weight by sonification to afford uniform thin films with desired thicknesses [110]. Following the reduction of the molecular weight, formation of DNA–cationic surfactant complexes is performed via an ionic exchange reaction, where sodium ions within natural DNA are substituted by cationic surfactants. The most commonly used surfactants are long alkyl quaternary ammonium compounds, such as cetyl trimethylammonium (CTMA) chloride [100, 107]. The advantage of such protocol is that all of the used materials are commercially available in large amounts. The use of different surfactants for preparation of DNA complexes can extend the range of available solvents, and it has also been reported that they can affect the material performance and optical switching and lasing properties.

The most common techniques to form thin films of DNA–surfactant complexes are by spin-coating or casting. Depending on the coating protocols, nanometers to micrometers of films can be prepared with high optical quality [107, 111]. Detailed characterization of the films, including thermal, optical, and electrical properties, have been carried out, and the results indicate that the films exhibit high transparency within a broad spectrum range from visible to infrared.

Great progress has been made in use of DNA–surfactant complexes for optoelectronic applications. Previously, DNA–surfactant complexes have been utilized



**Fig. 9** **a** An illustration of the memory device based on natural DNA films and **b** a current–voltage ( $I$ – $V$ ) curve of device under different periods of UV exposure time. *Inset*  $I$ – $V$  curve of device without UV irradiation. Reprinted with permission from Ref. [114]

as an effective electron-blocking material in organic light-emitting devices (OLEDs) and as an insulating layer in organic field-effect transistors (OFETs). Due to the high transparency in the communication wavelengths, they were also employed in preparation of electro-optic modulators.

Owing to the high dielectric constant and insulating characteristic, DNA complex films have been incorporated in field-effect transistors (FETs) as gate dielectrics [112, 113]. The device can also be operated as a memory device owing to the hysteresis property of the transfer function [113]. Recently, it was demonstrated that an optical memory device based on photoinduced DNA complex–NP nanocomposite can be prepared [114]. This is achieved by phototriggered growth of AgNP on a DNA film using Ag salt precursor and photoinitiator [107]. Memory device consists of a DNA complex thin film sandwiched between two electrodes, and the electrical bistability is activated by in situ formation of silver NPs embedded in biopolymer upon light irradiation (Fig. 9).

This facile technique takes the advantage of DNA's affinity for metal ions and solution processing and can optically manipulate the properties of DNA nanocomposite thin films and therefore holds a promise for optical storage and plasmonic applications.

Many researchers working in the field of optoelectronics have at first considered DNA to be an exotic material with limited use. However, recent results have shown that not only DNA can be an excellent and versatile device platform but in combination with the new advances in nanotechnology can also lead to new DNA-based materials with enhanced properties useful for engineering of new generation of biohybrid devices. One interesting generation of these materials combines DNA with polymers and will be discussed in our closing paragraph.

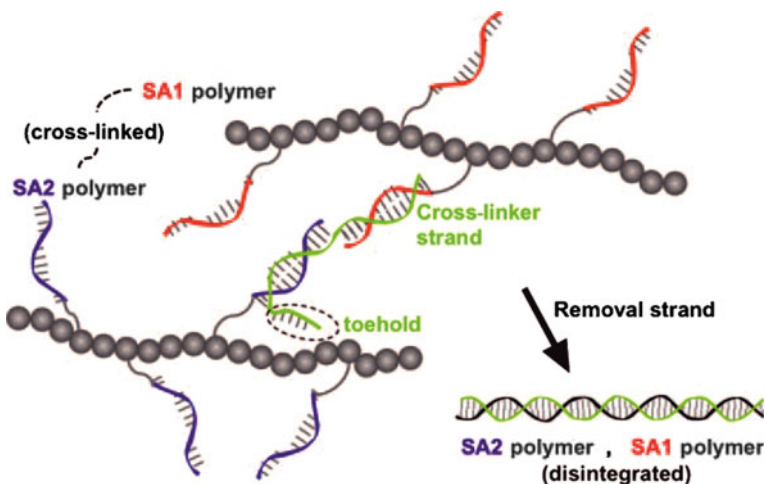
## 5 DNA-Based Materials

### 5.1 DNA-Based Hydrogels

Hydrogels are water-swollen cross-linked polymeric networks with distinct three-dimensional structure [115–117], which can adapt to their environment. This stimulus responsiveness is primarily associated with swelling and de-swelling of the polymeric materials, which is mediated by change in temperature, pH, ionic strength, solvent type, or photon flux. Hydrogels have been made out of pure DNA [117, 118], but they are expensive and do not have good sensitivity. However, sensing gels were prepared by combining polymers and DNA by first attaching DNA to the polymer backbone and using different strategies to transform it into a cross-linked architecture. The first strategy based on gel-to-sol transition was reported by Nagahara and Matsuda [119] in 1996, and it involves the hybridization of two conjugates (two different polymers, each with different DNA sequence attached). In second strategy, hydrogel was built up by chemically cross-linking dsDNA strands [120] using ethylene glycol diglycidyl ether as a cross-linking agent. Recently, Tan and coworkers prepared fast-responding gels by using adenosine-binding DNA aptamer as a cross-linker [121]. Without adenosine, the aptamer acted as a stable cross-linker to hold the gel together. When adenosine is added, it induces aptamer folding, which breaks the cross-link causing the change in materials' properties. In another application, pH-triggered, fast-responding DNA hydrogel was prepared by Liu and coworkers by cross-linking the gel using a pH-sensitive DNA I-motif, which causes the disruption of the gel within a minute by adding appropriate base [122].

Hydrogels do not only have interesting properties, but can be employed as effective sensing platforms. For example, amylase/iodine was entrapped within the hydrogel cross-linked with cocaine aptamer [123]. Such hydrogel changes color from blue to colorless in the presence of cocaine due to conversion of amylase (amylase/iodine is blue) into glucose (colorless). Willner and coworkers designed an ion sensor using a switchable sol–gel transition in the presence of  $K^+$  by using G-quadruplex DNA [124]. Addition of free  $K^+$  to G-rich DNA attached to the polymer chains induced the formation of G-quadruplex, which cross-linked the gel in a reversible way as the sol state could be achieved by removal of  $K^+$  ions by addition of  $K^+$ -binding 18-crown-6-ether. Another interesting approach was recently presented by Yang group, and it involves use of DNAzyme cross-linker, which cleaves DNA substrate in the presence of  $Cu^{2+}$  and allows detection by a color change in gel induced by the presence of pre-trapped AuNPs [125].

Recently, hydrogels were used for sensing of target DNA [126] and, in combination with quartz crystal microbalance (QCM) and appropriate aptamer, for detection of avian influenza virus [127]. Furthermore, DNA hydrogels are also interesting as they can be an excellent platform for preparation of thermoreversible materials [119], drug release from nanosized [128] and macroscopic networks



**Fig. 10** Scheme of reversible DNA cross-linked polyacrylamide hydrogel. The overhang of the cross-linker DNA enables the reversible disintegration of the network by the hybridization of removal strand, which is complementary to the cross-linker strand in full length [136]

[129, 130], and detection of target DNA by use of stem-loop cross-linking structures [131].

DNA hydrogels with convertible mechanical states induced by hybridization have also been prepared by making use of the switching process previously employed for design of DNA-fueled machines, where changes can be induced by addition of short DNA [132, 133]. A further advance to this concept was achieved by use of toehold, overhang DNA, which can be used as a zipper to open up the gels (Fig. 10) [134]. Using this strategy, Simmel et al. [135] presented the controlled trapping and release of quantum dots in DNA hydrogel by employing single-molecule fluorescence microscopy and fluorescence correlation spectroscopy. They employed the DNA cross-linker strands equipped with an additional unhybridized “toehold” section that acts as a “recognition tag” for DNA release strands. When release strands fully complementary to the cross-linker strands are added to the gel, they attach to the toeholds and remove the cross-linker strands via branch migration causing the gel to dissolve into a solution and in such a way liberate the trapped particles.

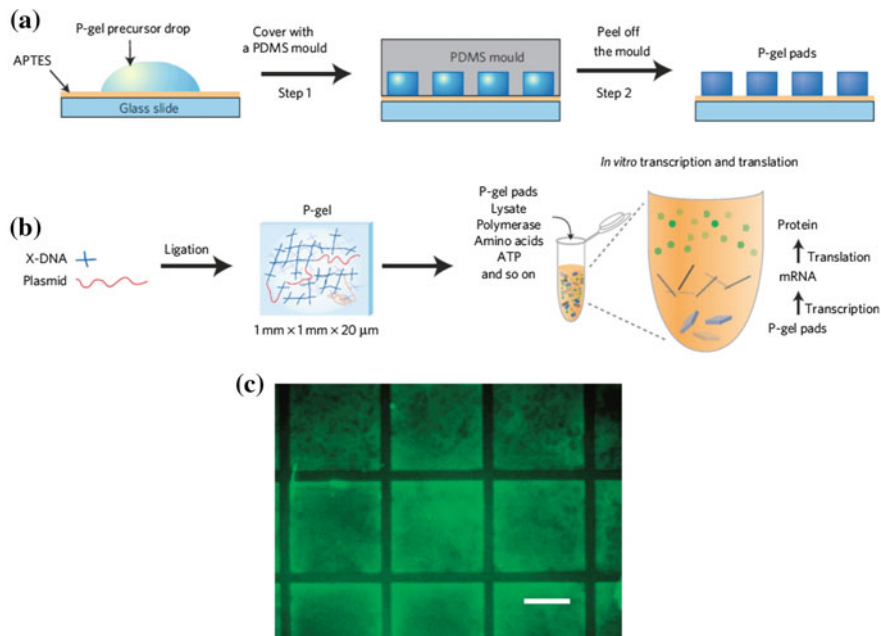
DNA hydrogel networks containing only DNA have also been produced by chemical cross-linking of salmon testes DNA (st-DNA) with ethylene glycol diglycidyl ether [120]. A discontinuous volume transition upon addition of acetone to the aqueous DNA hydrogel was observed with 15-fold shrinking of the material relative to its initial volume. Such cross-linked DNA networks can be generated by PCR where two Y-shaped trisoligonucleotides in combination with a double-stranded template can be transformed into hydrogels with segment lengths between the branching points ranging from 70 to 1062 nucleotides [137]. DNA hydrogels were also prepared by enzyme-catalyzed assembly [117], in vitro

transcription/translation system for functional proteins with DNA hydrogels [138] and responsive DNA-based hydrogels from Y-shaped building blocks [122]. Interesting photoresponsive platform was presented by Kang et al. in which an azo molecule was incorporated into the backbone of the cross-linker DNA sequences. Under visible light, the trans-form of azo molecule allowed cross-linker DNA to hybridize with DNAs on the polymer side chains forming three-dimensional hydrogel networks. When the gel was irradiated with UV light, the azo molecule photoisomerized to the cis-form, which prevented hybridization, thus reverting gel to sol state [139].

The DNA components in gel bare some level of mechanical roles to support the gel–sol transition or volume expansion. One drawback of using DNA as a cross-link to observe gel mechanical property is the high concentration of DNA required, which not only increases the cost but also reduces the sensitivity of the system. To overcome this problem, the gel matrix was used for sensor immobilization (in particular heavy-metal detection) and the DNA, instead of being used as building material, was used to generate optical signals. In one such example,  $\text{Hg}^{2+}$ -binding DNA, rich on thymine, was embedded in the gel [140]. In the presence of  $\text{Hg}^{2+}$ , the aptamer adopts a hairpin configuration that produces strong green fluorescence with SYBR Green I [141], which can further be improved by tuning the gel charge [142]. Similar gel–DNA sensor for lead detection using a guanine-rich DNA, which allowed visual detection of  $\text{Pb}^{2+}$  at the concentration as low as 20 nM, was also designed [143]. Recently, Ag nanoclusters (AgNC) in combination with DNA-based hydrogels have also been employed for detection of  $\text{Hg}^{2+}$  [144]. Namely, DNA of particular sequence can bind  $\text{Ag}^+$  and induce the formation of two types of AgNCs emitting red and green fluorescence, respectively. Interestingly, some of the red emitter can be converted to the green due to the intrinsic properties of AgNC in the presence of  $\text{Hg}^{2+}$  [145–148], leading to development of  $\text{Hg}^{2+}$  ion sensor.

However, one of the most exciting applications of DNA hydrogels is probably their potential use as a biofriendly platform either for cell growth (for example stem cells) or for production of proteins. Latter was already demonstrated by Park et al. who prepared a DNA hydrogel that produces functional proteins without any living cells with efficiency about 300 times higher than current, solution-based systems. This protein-producing gel termed as “the P-gel system” or “P-gel” contains genes as gel scaffolding [138]. The P-gel can be fabricated by ligating X-DNA and linear plasmids within a polydimethylsiloxane (PDMS) micromould. Subsequently, proteins can be expressed simply by incubating the P-gel micropads with cell lysates for a specific time period (Fig. 11).

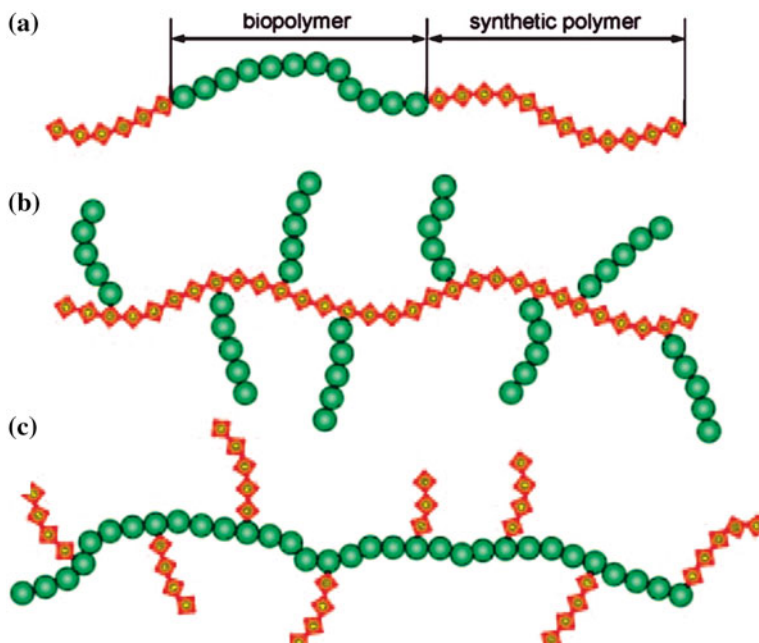
Besides above examples, DNA hydrogels have also been shown to be useful for preparation of high surface area materials [149], DNA hydrogel-based supercapacitors [150], hydrogels for controlled release of plasmid DNA [151–156], and DNA hydrogel bead as selective adsorbent of dioxins [157]. Taking into account vast possibilities for the use of such hybrid material in both materials science and bionanotechnology, it could be expected that more work will be done in controlling their architecture, mechanical properties, and function in the near future.



**Fig. 11** Fabrication of protein-making gel (P-gel) matrix. **a** schematic diagram illustrating the formation of P-gel micropads (*side view*). The P-gel precursor drop, which contains X-DNA, genes, and T4 DNA ligase, was confined within a PDMS mold with precisely defined dimensions. Extra solution was able to flow out owing to the surface modification (*Step 1*). After gelation, the PDMS mold was peeled off from the substrate (*Step 2*), and P-gel micropads were formed. **b** A scheme of the gelation process through enzymatic cross-linking and cell-free expression with P-gel pads. **c** A fluorescent image of the P-gel pads after staining with SYBR I (scale bar: 500  $\mu\text{m}$ ). Reprinted with permission from Ref. [138]

## 5.2 DNA-Polymeric Hybrid Materials

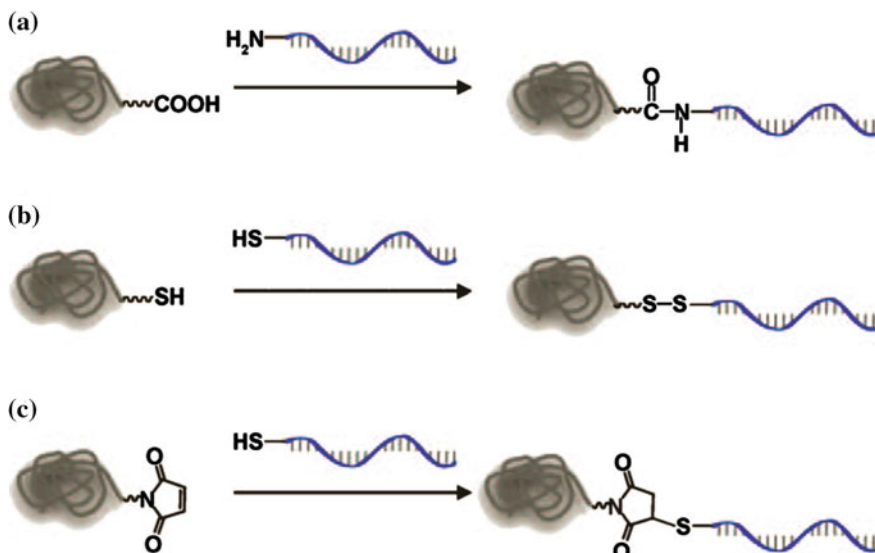
Over the past two decades, one of the most exciting and emerging goals in chemical synthesis was the macromolecule generation with a well-defined monomer sequence, which performs complex functions. The combination of synthetic macromolecules with biopolymers is an interesting and powerful opportunity for merging the distinctive properties of each class of material and at the same time, overcoming specific limitations such as decreased stability of biopolymers and poor structural control of synthetic systems [158, 159]. The combination of proteins and peptides with synthetic macromolecules has been explored in depth. Extensive efforts have been made for the development of covalently bonded hybrid structures consisting of biomacromolecules and organic polymers. Different architectures are observed depending on how the biological moieties are connected to the synthetic macromolecules. For example, the connecting building blocks can be arranged in an alternating fashion leading to linear



**Fig. 12** Illustrations of covalently bonded biopolymers (*green circles*) and synthetic (*yellow diamonds*) polymers. **a** Linear block copolymer composed of biopolymer and synthetic polymer blocks. **b** Biomacromolecules grafted onto a synthetic polymer backbone. **c** Synthetic polymer side chains on a biomacromolecule backbone. Reprinted with permission from Ref. [160]

block copolymers (Fig. 12a) [160] and side-chain polymer structures can be obtained by arranging several peptides or nucleic acid moieties along a polymer backbone (Fig. 12b). The opposite case in which several synthetic polymers are attached to a biomacromolecular backbone is rare (Fig. 12c) [161].

Combination of peptides and the organic polymers was already explored [162, 163], but much less attention went to an important class of bioorganic hybrids consisting of nucleic acids and synthetic polymers [164]. The very first reports of DNA–polymer conjugates were presented in 1980s where antisense oligonucleotides were grafted onto a poly(L-lysine) (PLL) backbone. These conjugates were employed to inhibit the synthesis of vesicular stomatitis virus proteins, therefore basically acting as antiviral agents [165–167]. There are numerous applications of these materials, besides the gene or oligonucleotide delivery, which range from the purification of biomaterials to the detection of DNA. Recently, hydrophobic polymers instead of hydrophilic polymers such as PLL and poly(ethylene glycol) (PEG) have been connected to oligonucleotides to generate macromolecular amphiphiles, which tend to self-assemble into micellar systems with nanometer dimensions. Such materials have promising potential for applications in the fields of bionanotechnology and nanomedicine, i.e., as drug delivery systems.

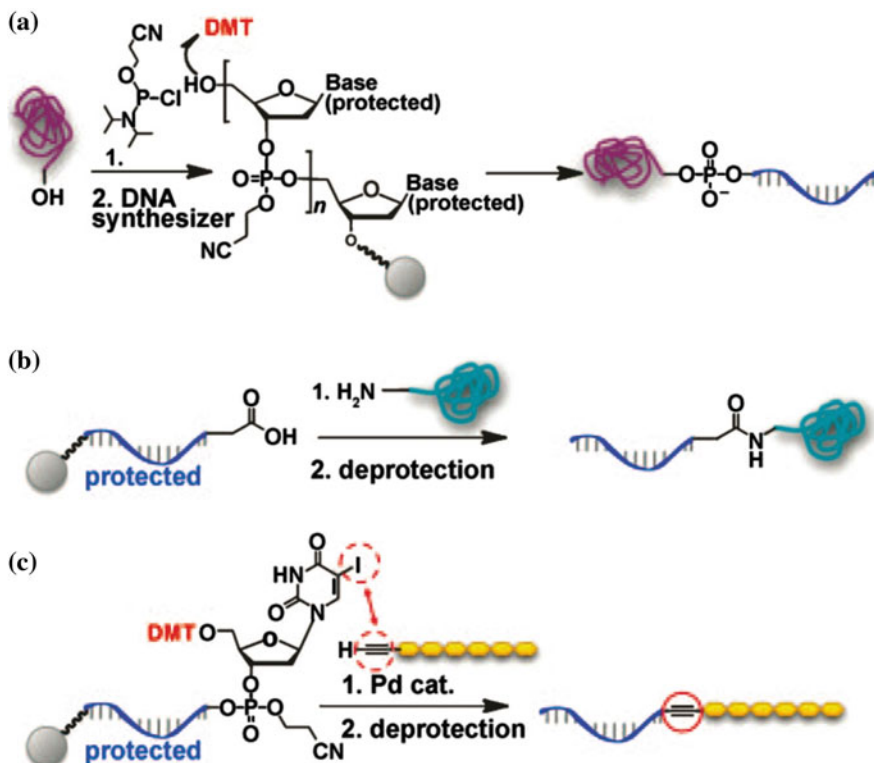


**Fig. 13** Coupling methods for the synthesis of DNA block copolymers in solution. **a** Carboxylic acid-terminated polymer coupled with an amino-DNA. **b** Disulfide bond formation between polymer and thiolated DNA thiols. **c** Michael addition of a polymer containing a terminal maleimide and thiolated DNA. Reprinted with permission from Ref. [160]

The coupling of the nucleic acid blocks and the organic polymers can be done in solution or on solid support. For example, amino-functionalized short DNA can be reacted with water-soluble polymer having terminal carboxylic acid group such as PEG [168, 169], poly(*N*-isopropylacrylamide) (PNIPAM) [170, 171], poly(*D,L*-lactic-*co*-glycolic acid) [172], and poly(*p*-phenyleneethynyl-ene) [173] to form an amide bond (Fig. 13a). In another approach, disulfide bonds are formed between thiolated DNA and PEG-containing 2-pyridyl disulfide (Fig. 13b) or maleimide (Fig. 13c) group. Besides purely chemical strategies, Marx and coworkers used DNA polymerases to catalyze the reaction for the synthesis of DNA polymers that can be grafted with short polymer blocks leading to entities of high molecular weight, modification density, and defined structure [174]. Herrmann and coworkers used PCR successfully to prepare DNA-polymer hybrids with ultrahigh molecular weight and high structural accuracy [175].

When hybrid materials such as amphiphilic DNA coblock polymers are desired, it is difficult to prepare them in solution due to different solubility properties of each component. In that case, the strategy involves grafting polymers on DNA on a solid support using phosphoramidite strategy (Fig. 14a). After deprotection with ammonia from the solid support, ssDNA diblock copolymers could be obtained, for example, DNA-*b*-polystyrene (PS) [176] and DNA-*b*-poly(propylene oxide) (PPO) [177], and triblock architectures of the type DNA-*b*-PEG-*b*-DNA can be made [178] when both termini of the organic polymer were activated as

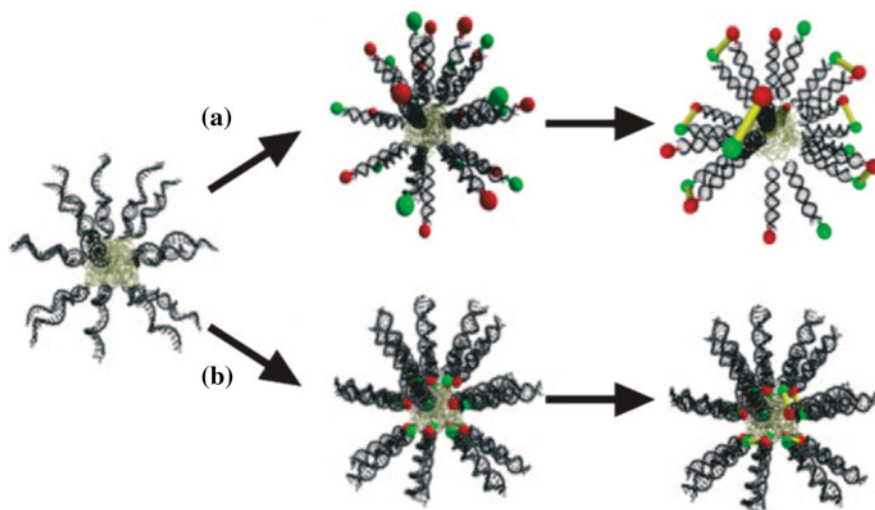




**Fig. 14** Coupling reactions that can be used to prepare DNA block copolymers on a solid support. **a** A hydroxylated polymer was converted into the phosphoramidite and coupled with 5'-OH group of DNA in the last step of the DNA synthesis. DMT = dimethoxytrityl. **b** An amino-modified polymer was added to a carboxylic acid-modified DNA on a solid support. **c** Pd-catalyzed Sonogashira-Hagihara coupling of an acetylene-terminated p-conjugated polymer and a 5-iodouracil nucleobase on the solid phase. Reprinted with permission from Ref. [136]

phosphoramidites. Besides using phosphoramidite strategy, terminal amino group could be grafted onto immobilized carboxyl-modified DNA through amide bond formation (Fig. 14b) [179] or DNA coupled by Sonogashira-Hagihara coupling (Fig. 14c) [180].

The advantages of DNA are specific recognition and self-assembly of the oligonucleotides of appropriate sequences, which can be employed in design of programmable nanoreactors based on DNA block copolymers (DBC) [177, 181]. The ssDBC aggregates were hybridized with reactant DNA-bearing functional groups, and due to the close proximity of these groups within the micellar confinement, several organic reactions such as the Michael addition and amide bond formation could be carried out sequence-specifically within the programmable nanoreactors. It is even possible to spatially define the transformations to take



**Fig. 15** DNA-templated synthesis on the surface of a PPO-b-DNA micelle (a) and in the core of the micelle (b). Red and green spheres correspond to reacting functional groups, and yellow sticks represent the resulting covalent bonds. Reprinted with permission from Ref. [177]

place either at the surface of the micelles (Fig. 15a) or within the interior of the bioorganic particles shielded from the environment (Fig. 15b).

DBC micelles can be used as a scaffold for the enzymatic conversions [182] or to generate higher-ordered organic/inorganic particle networks through sequence specific hybridization with other DNA-modified nanoparticles [176]. Exciting application is also a design of microcapsules, which can be obtained through alternating layers of DBCs assembled on silicon templates and then used for the delivery of small interfering RNA (siRNA) and anticancer drugs [183]. Recent examples have also shown that such materials could be used in therapeutic purposes by being effective drug delivery systems [169, 184, 185].

### 5.3 DNA Side-Chain Polymers

The side-chain polymer structures can be obtained by arranging several peptides or nucleic acid moieties along a polymer backbone or less frequently by attaching several synthetic polymers to a biomacromolecular backbone [161, 186]. In one of the first examples, polyacrylamide or PNIPAM was attached to bacteriophage T4 (166 kbp) or  $\lambda$ -phage DNA (48.5 kbp) [187, 188]. In addition to direct attachment, intercalators such as phenzinium or psoralen can be used to combine polymer and DNA in a non-covalent fashion [189–191]. Such DNA polymers have found and will continue to find application in DNA detection assays [192–194] and in design of novel drug delivery systems.

After the potential of DNA was recognized in particular for design of programmable platforms and hybrids, search for new DNA-based materials continues. One recent example is preparation of spherical nucleic acids (SNA), densely packed highly oriented nucleic acids in a spherical geometry—termed SNA [40, 60]. This kind of unique arrangement and orientation of one-dimensional linear nucleic acids within this three-dimensional framework offers new chemical, biological, and physical properties. For example, such SNA can be used for intracellular gene regulation [195–198], *in vitro* biodetection [51, 199–203], intracellular assays [204–207] and as a potent-cell transfection tool [195, 208–210]. Initially, SNA consisted of 3'-SH-terminated oligonucleotides covalently attached to the surface of spherical AuNPs by salt aging in order to obtain dense nucleic acid loading [40]. These nanostructures exhibit properties (physical and chemical) that are distinct from those of both the NPs and DNA from which they derive. Although different core materials such as inorganic nanoparticles [211–213] and semiconductor materials [214] were used to provide physical and chemical stability as well as to act as a scaffold, many of the properties of these nanostructures were shown to be core independent but rather originated from the dense layer of oriented nucleic acids. This idea was further exploited by Mirkin and coworkers to prepare polyvalent nucleic acids (PNANs) [215] from alkyne-modified 3'-thiolated DNA which comprised of only cross-linked and oriented nucleic acids, which were capable of effecting high cellular uptake and gene regulation without the need of a cationic polymer cocarrier. These examples show that there is more to short DNA than it meets the eye—new combinations of different nanoelements and DNA might lead to powerful tools, which can be used in drug delivery or *in vivo* biosensing.

## 6 Conclusion

Being a natural polymer with highly programmable sequence, DNA emerged as an exciting material for both molecular structuring and design of novel hybrids with applications ranging from molecular biology to catalysis and optoelectronic device design. Advances in chemical modification of short synthetic oligonucleotides and the folding or film casting of the natural DNA showed that the field of DNA research is far from exhausted. Future will probably focus on merging DNA and nanomaterials to produce new therapeutic (clever drug delivery) systems or robust but biodegradable materials for applications in energy material design and electronic devices. DNA has indeed shown that it is more than a genetic carrier and it will continue to be one of the pillars of interdisciplinary research crossing the fields of molecular biology, chemistry, physics, and engineering.

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