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Biomedical DNA hydrogels

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Abstract

Due to considerable progress in DNA nanotechnology, DNA is gaining significant attention as a programmable building block for the next generation of soft biomaterials. DNA has been used as either a single component to form all-DNA hydrogels or a crosslinker or functional entity to form hybrid DNA hydrogels through physical interactions or chemical reactions. The formed hydrogels exhibit adequate biocompatibility, convenient programmability, tunable multifunctionality and the capability of precise molecular recognition, making them an irreplaceable polymeric platform for interfacing with biology. Responsive DNA hydrogels that are prepared through the hybridization of DNA sticky ends, the formation of i-motifs, enzymatic ligation and enzymatic polymerization are commonly reported nowadays and can undergo disassembly induced by various triggers, including alterations in ionic strength, pH, temperature and biomolecules. These hydrogels are envisioned for applications in drug delivery and biosensing. This perspective assesses the most recent and important developments in this emerging class of biomedically useful DNA hydrogels.

Keywords: DNA polymers, DNA hydrogels, drug delivery, biosensing

INTRODUCTION

DNA is made of nucleotide monomers that are covalently linked to each other by phosphodiester bonds. DNA displays excellent mechanical rigidity and can thus precisely position the tethered nanoparticles[1] and proteins[2] along the rigid rod spacer. Furthermore, its complex assemblies even allow for the spatial arrangement of nanoparticles[3] and proteins[4]. DNA can also exhibit dynamic and adaptable properties after specifically interacting with other molecules and can therefore exhibit a wide scope of external

biological signals[5] and manipulate target cells[6] in a dynamic and reversible fashion. Moreover, DNA can be processed precisely by highly specific enzymes, such as ligases, polymerases, endonucleases and exonucleases[7-9]. While the DNA double helix in DNA materials shows a distinct thermally triggered dissociation behavior, its thermal stability can be improved through intercalating agents[10] or covalent crosslinking[11]. Modern DNA synthesis techniques, such as automated solid-phase synthesis, polymerase chain reaction and production in microorganisms, enable rapid preparation of any desired DNA sequence in a large quantity[12,13]. This has further prompted a materials revolution by implementing DNA as a structural or functional entity in biomaterials design. The specific and predictive interactions relying on the Watson-Crick base pairing mechanism provide excellent modeling capabilities and design flexibility, thereby facilitating convenient programming and spontaneous self-assembly of diverse two- and three-dimensional objects with high complexity[14].

Accordingly, DNA has stimulated new directions in soft materials and science[15,16]. In particular, Seeman[17] proposed in 1982 to use DNA as a construction material for assembling geometrically defined objects with nanoscale features, which sets the foundation of an emerging research field, nowadays termed as "structural DNA nanotechnology"[18]. However, since the production of finite DNA nanostructures via structural DNA nanotechnology using DNA tiles remains complicated[19], the development of the "scaffolded DNA origami" technique by Rothemund must be seen as an important milestone. This technique works through predictably folding a circular, single-stranded DNA template into finite, programmable and addressable nanostructures with short, single-stranded DNA staples[20]. Furthermore, DNA is an excellent candidate for the construction of three-dimensional crosslinked networks containing a high amount of water, i.e., supramolecular hydrogels[21]. Unlike many other covalently crosslinked hydrogels derived from synthetic polymers or noncovalently crosslinked hydrogels derived from natural sources, like alginate or gelatin, DNA hydrogels are endowed with desirable features of programmability, stimuli-responsiveness and good biocompatibility by DNA[22]. Therefore, DNA hydrogels are highly promising "smart" platforms in biomedical applications[23].

This perspective focuses on the design principles and different methods used to construct all-DNA and hybrid DNA hydrogels and then highlights their applications in different biomedical applications, in particular, drug delivery and biosensing. This perspective will help to promote the further development of DNA hydrogels and more in-depth studies toward expanding their applications in soft science.

DESIGN AND PREPARATION ASPECTS OF DNA HYDROGELS

Several different design principles have so far been proposed to prepare DNA hydrogels[24-26]. The selected design and preparation methods provide access to customizable DNA hydrogels with unique physiochemical and biological features. In this section, all-DNA hydrogels that consist entirely of DNA sequences and hybrid DNA hydrogels that consist of both DNA sequences and synthetic polymers are introduced.

All-DNA hydrogels

The seminal work on all-DNA hydrogels was carried out by Um *et al.*[27] using branched DNA building blocks, which were pre-designed to associate with other complementary strands. The gelation of DNA building blocks can be achieved through the hybridization of DNA sticky ends [Figure 1A][28], formation of i-motifs [Figure 1B][29] or enzymatic ligation [Figure 1C][27]. All-DNA hydrogels can also be generated during in situ formation of the building blocks by enzymatic polymerization. For instance, hydrogels can be prepared by a polymerase chain reaction via extending and connecting the forward and reverse, Y-shaped primers that are thermally stabilized by psoralen[30]. Another intriguing example has been demonstrated by

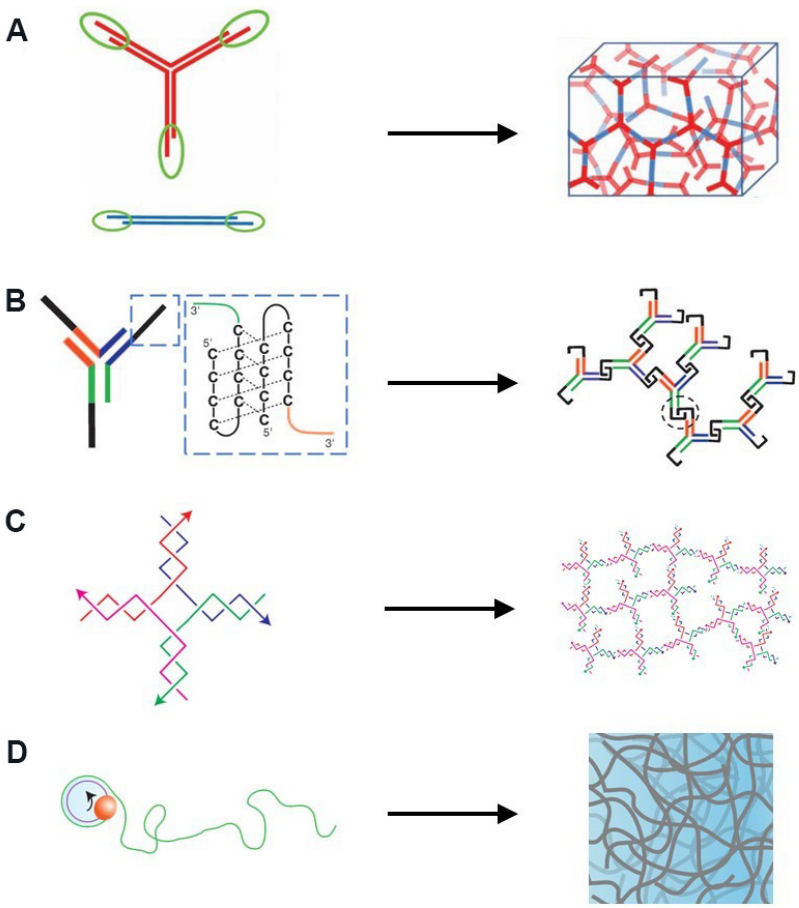

Figure 1. Self-assembly of all-DNA hydrogels through (A) hybridization of DNA sticky ends[28], (B) formation of i-motifs[29], (C) enzymatic ligation[27] and (D) physical entanglement[31]. (A, B) Reprinted with permission from Refs.[28,29]. Copyright 2009, 2011 Wiley-VCH. (C, D) Reprinted with permission from Refs.[27,31]. Copyright 2006, 2012 Springer Nature.

using rolling circle amplification to produce extremely long DNA sequences that eventually form gels through physical entanglement [Figure 1D][31].

The building blocks strongly influence the characteristics of resulting all-DNA hydrogels. For instance, physically crosslinked hydrogels made by the hybridization of sequences with complementary sticky ends can undergo revisable sol-gel transitions upon heating[28] or pH alteration[29]. In contrast, covalently crosslinked hydrogels made by enzymatic ligation do not undergo reversible sol-gel transitions[27]. In addition, enzymatic polymerization techniques result in hydrogels with metamaterial properties exhibiting liquid-like properties when taken out of water and solid-like properties when immersed in water[31]. Furthermore, hydrogels with defined geometries in the shape of the letters D, N and A completely deformed after water removal, but returned to their original shapes upon water reintroduction[31].

Hybrid DNA hydrogels

DNA-polymer hybrid hydrogels utilize both the programmable and smart features of DNA components and the chemical stability, flexibility and accessibility of polymers. In 1996, Nagahara reported the first DNA-polymer hybrid hydrogels based on short DNA sequences grafted to a poly(acrylamide) polymer chain[32]. Since then, various DNA-polymer hybrid hydrogels have been prepared with controlled sol-gel transitions. Branched DNA as a structural component enables simultaneous gelation and functionalization

of hydrogels. While these DNA linkages typically exhibit multi-responsiveness and thixotropic behavior under heat or in the presence of enzyme, their conjugates, like azobenzene-functionalized linkages, can display light-responsiveness upon alternating irradiation with visible and ultraviolet light, inducing the macroscopic volume changes of the hydrogels [Figure 2A][33]. Logically, semiconducting polymers might be practically explored as a functional unit or scaffold to prepare photosensitizing DNA hydrogels due to the π-electron delocalized backbones they possess[34,35]. Furthermore, multi-responsive hydrogels can be constructed based on DNA linkages by additionally implementing i-motifs [Figure 2B][36], G-quadruplex units[37] or aptamers[38].

In contrast, DNA segments have also been explored as functional, bioactive elements to decorate hydrogels for various biomedical applications[39]. The presence of DNA as a bioactive group in these hydrogels typically imparts specific interactions with biomolecules [Figure 2C][40,41] or cells [Figure 2D][42], but does not significantly alter the mechanical properties of the hydrogels. The functionalization of all-DNA hydrogels is straightforward, only requiring the introduction of short DNA tags comprising complementary DNA strands. Alternatively, the functionalization of hydrogels made of synthetic polymers requires the formation of covalent bonds. This is facilitated by phosphoramidite derivatives that provide versatile routes to synthesize chemical group-functionalized oligonucleotides for covalently coupling with polymer chains during or after the gel formation[43-45]. However, a potential drawback of the post-functionalization of hydrogels using DNA is the steric or electrostatic hinderance during infiltration, which is particularly true for larger DNA structures.

BIOMEDICAL APPLICATIONS OF DNA HYDROGELS

The recognition of analytes triggers changes, such as in crosslinking density or mechanical, optical or other properties, in the physicochemical nature of a DNA hydrogel matrix, which can further lead to cargo release for drug delivery or can be transduced into a detectable signal for biosensing[23]. In the following sections, the applications of DNA hydrogels in drug release and biosensing are discussed.

Drug delivery

Conventional chemotherapy based on the systemic injection of small molecule drugs suffers from a lack of specificity toward cancerous cells versus healthy ones, which results in serious side effects. Hydrogel formulations are of particular interest for local and controlled drug delivery to improve drug efficacy and reduce off-target side effects[46]. DNA strands have been extensively explored for enrichment of the anthracycline drug doxorubicin via intercalation into GC/CG-rich sequences. By further incorporating gold nanoparticles, DNA hydrogels allowed for the disassembly of the whole construct and subsequent drug release through a photothermal effect[47]. The anticancer efficacy of this system was found to be improved through the synergy between photothermal therapy and chemotherapy with a reduced dosage of either laser power or drug dosage.

In addition to physical triggers, chemical triggers are attractive for drug release depending on the tumor microenvironment. For instance, adenosine triphosphate (ATP) is overexpressed in cancer cells, making it an interesting trigger for site-selective release systems. An ATP-responsive DNA hydrogel was constructed by incorporating ligand-specific aptamer sequences into the gel scaffold. This hydrogel was able to release the cargo in the presence of ATP due to the dissociation of the gel matrix induced by interactions between the ATP and aptamer [Figure 3A][48]. Furthermore, with delicate design, the pH-sensitive bridges in hydrogels can dissociate via the formation of i-motif structures under tumor acidic conditions, which results in cargo release by increasing the fluidity of gel matrix[48].

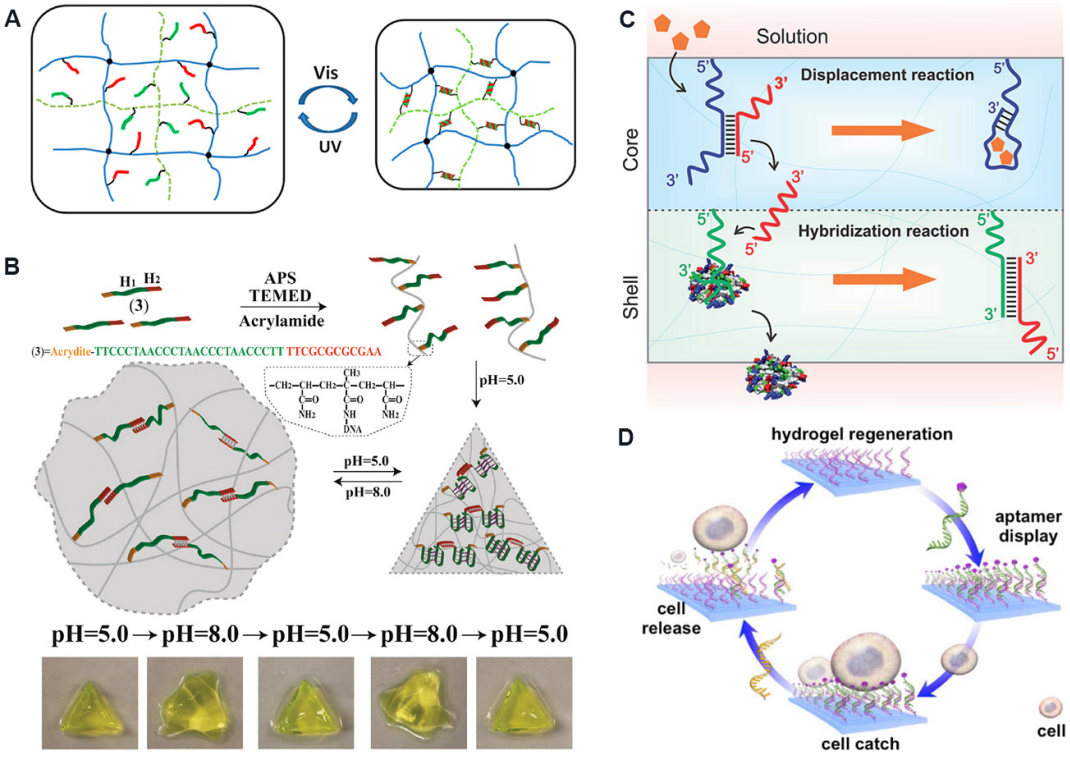

Figure 2. (A) Light-responsive hybrid DNA hydrogels based on azobenzene isomerization. Reprinted with permission from Ref.[33]. Copyright 2012, American Chemical Society. (B) pH-responsive hybrid DNA hydrogels based on cyclic switching of i-motifs. Reprinted with permission from Ref.[36]. Copyright 2015 Wiley-VCH. DNA hybrid hydrogels for (C) biomimetic protein release and signal transduction or (D) cell catch and release. (C) Reprinted with permission from Ref.[41]. Copyright 2017, Royal Society of Chemistry. (D) Reprinted with permission from Ref.[42]. Copyright 2012, American Chemical Society.

The aptamer-containing hydrogels are particularly useful for the delivery and sustained release of bioactive molecules to specific cells or tissues. The stored cargos in hydrogels can be released either periodically[41] or sustainably[49] through external[50] and mechanical triggers[51] by introducing aptamers that specifically bind to the corresponding ingredients. Based on these, the principle of sequential protein release from DNA hydrogels was further expanded by spatially controlling the immobilization of proteins through a combination of photo-patterning [Figure 3B][52]. It has been demonstrated that VEGF and PDGF-ββ proteins bind to the corresponding aptamers that are incorporated into the patterned hydrogels, giving rise to both spatial and temporal control over the release of two separate proteins using the displacement strand strategy. Most strikingly, the aptamer technology can be employed for simultaneous cancer cell recognition and stimuli-responsive drug release. This has been achieved by the incorporation of aptamers that bind receptors, like nucleolin, overexpressed in tumor cells in biological environments[53].

Furthermore, drug-integrated DNA can be considered as an efficient prodrug to overcome the limitations and severe side effects of systemic drug injection. Cytotoxic nucleoside analogs, such as fluoroxidine, have been covalently integrated into DNA oligonucleotides via solid-phase synthesis and then subsequently assembled into DNA hydrogels. These hydrogels acted as novel Trojan Horses, enabling rapid cellular uptake, effective drug release in the presence of DNases and eventually an enhanced anticancer effect[54].

Biosensing

The detection of various analytes in high sensitivity is vital for many biomedical fields, including point-of-care testing, clinical diagnosis and personalized healthcare[55-57]. The typical design strategies of hydrogel

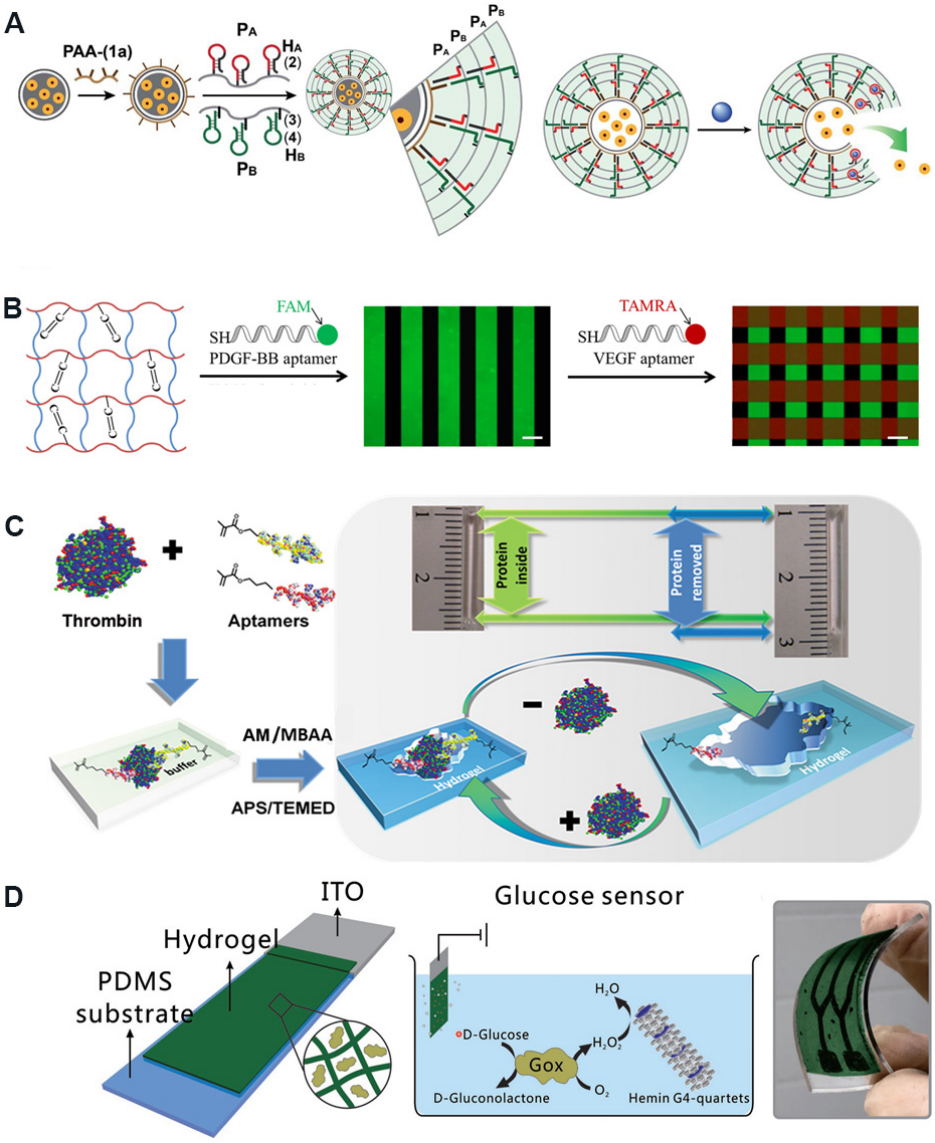

Figure 3. Drug delivery applications of (A) DNA hydrogels and (B) patterned hydrogel films. (A) Reprinted with permission from Ref.[48]. Copyright 2017, Royal Society of Chemistry. (B) Reprinted with permission from Ref.[52]. Copyright 2018, American Chemical Society. Biosensing applications of (C) bioimprinted aptamer hydrogels and (D) flexible electrochemical sensors. (C) Reprinted with permission from Ref.[61]. Copyright 2013, American Chemical Society. (D) Reprinted with permission from Ref.[67]. Copyright 2018, Wiley-VCH.

biosensors employ an analyte-binding DNA as the sensor. The hydrogels display changes in volume, mass, color or mechanical properties when the functional DNA unit dissociates only after recognition of the respective targets[58,59]. Different DNA hydrogels have been designed to detect ions[60], small molecules[38], proteins[61] or viruses[62].

DNA hydrogels even enable visualization of the readout via the naked eye in certain cases and therefore do not need a sophisticated equipment[63,64]. While colorimetry is the commonly used detection method of DNA hydrogel biosensors, it often provides semiquantitative results and relatively low sensitivity[65]. A molecular imprinting approach can overcome these mentioned limitations through macroscopic volumetric shrinkage in the presence of targets. For example, DNA hydrogels were formed by the polymerization of

bifunctional aptamer-protein complexes, so that proteins, like thrombin or PDGF-ββ, were imprinted into the hydrogels. The resulting hydrogels showed remarkable sensitivity down to femtomolar concentrations of proteins [Figure 3C][61]. Recently, surface-immobilized DNA hydrogels were developed as printable sensors for applications in the fields of clinical diagnosis and personalized medicine[65,66]. Such DNA hydrogels can be generally synthesized on a solid surface via a surficial primer-induced strategy. After loading horseradish peroxidase and bilirubin oxidase enzymes, DNA hydrogels have been explored as stable catalytic systems, allowing for the colorimetric or electrochemical detection of hydrogen peroxide and bilirubin, respectively, with high sensitivity and in a recyclable manner[66].

The immense potential of catalytic DNA hydrogels for next-generation biosensors and bioelectronics has been highlighted by the in situ fabrication of a flexible glucose biosensor [Figure 3D][67]. This biosensor was fabricated by loading the glucose oxidase into a DNA hydrogel, followed by printing into a flexible electrochemical electrode. This detection system revealed excellent electrochemical properties and long-term cycling stability. The integration of DNA hydrogels into surface biosensing devices could thereby broaden hydrogel applications. However, the development of biosensing devices that have the ability to accurately detect and quantify trace amounts of analytes in complex body fluids still represents a significant challenge. Furthermore, DNA hydrogel biosensors are quite costly, thereby hampering their real-world applications. Therefore, either the production costs have to be substantially lowered or the reusability of these sensors needs to be significantly improved. It is anticipated that if the abovementioned challenges can be addressed, DNA hydrogel biosensors will offer great potential as implantable sensors for *in vivo* diagnostics or even be used as a powerful toolbox for future personalized medicine.

CONCLUSION AND OUTLOOK

DNA is gaining significant attention as a programmable building block, which provides unique characteristics that have propelled the development of various DNA-based hydrogels accessible for exciting biomedical applications, in particular, drug delivery and biosensing. These examples only signify the beginning of a much larger biomedical field in the future. For example, DNA hydrogels have been recently explored for new immunomodulatory treatment and cell-based approaches. For the former case, DNA hydrogels that programmed with rich CpG sequences and incorporated with certain antigens have been explored as an injectable DNA hydrogel vaccine for cancer immunotherapy by causing strong immune responses[68]. For the latter case, DNA hydrogel-based cell envelop and separation strategies have been reported through crosslinking of cell-anchored, ultralong DNA chains produced via RCA, allowing for fishing stem cells or T lymphocytes from tens of thousands of nontarget cells[69,70]. Moreover, hybrid DNA hydrogels can now be also referred to inorganic nanoparticle-incorporated DNA hydrogels that have been synthesized to tune the mechanical, conductive and optical properties of hydrogels, as well as to instruct multiple cell behaviors[71-77].

Even though DNA hydrogels have seen tremendous progress, several challenges need to be addressed before real-world applications. First, the nuclease resistance of DNA hydrogels under physicochemical and biological conditions needs to be improved, since it will be critical to maintain the designed structures and mechanical properties for i*n vivo* applications. Second, the cost for scaling up DNA hydrogels needs to be reduced regarding the clinical translation. We can foresee that DNA hydrogels would improve human health once those remaining challenges are addressed by combining possible scalable and cost-efficient methods of biotechnological "mass production"[13], liquid-phase oligonucleotide synthesis[78] and DNAzyme-catalyzed production[79].

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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