DNA-Guided Assembly of Molecules, Materials, and Cells
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DNA is the genetic blueprint for most known living organisms on Earth, but it is not merely the secret of life. Because of its programmability derived from Watson–Crick base-pairing, DNA exhibits unparalleled versatility in constructing designer molecular structures by self-assembly—a field called DNA nanotechnology. After decades of active pursuit, DNA has demonstrated unprecedented capability in designing highly prescribed and sophisticated artificial nanostructures, which could be either static, with well-controlled physicochemical properties, or dynamic, with the ability to change in response to external stimuli. Researchers have devoted considerable efforts to exploring the utility of DNA nanotechnology in a variety of fields, with the majority related to harvesting their assembling power, since they are highly capable of guiding the assembly of other entities—molecules, materials, living cells, and so on—to fabricate artificial assemblies with emergent properties and functions. Herein, a brief introduction is given to self-assembly methods in DNA nanotechnology, including DNA tiles, modular DNA bricks, and DNA origami. Four sections are then dedicated to covering the utilization of DNA nanotechnology for guided assembly of organic materials, inorganic materials, biological materials, and living cells. Lastly, DNA-enabled molecular intelligent systems that are able to compute and execute algorithms are discussed.

1. Introduction

Through 4 billion years of evolution, nature has designed numerous versatile strategies to enrich life forms and to advance intelligence. Molecular self-assembly is among the most abundant strategies that biology has adapted on every level. Biological entities, including proteins, nucleic acids, cellular machineries, cells, tissues, organs, and living organisms including human beings, are all complex systems self-assembled from one or millions of diverse molecular components. Deoxyribonucleic acid (DNA) is the genetic information carriers for all known living organisms and some viruses on Earth, which determines the identity of every single one of these life forms. DNA is a biomacromolecule composed of nucleotides encoded by adenine (A), thymine (T), cytosine (C), or guanine (G), whose specific interactions are governed by Watson–Crick base-pairing where A pairs with T, and C pairs with G. By programming the sequences, one can make DNA molecules interact and bind in a highly specific and prescribed manner. Such programmability makes DNA a perfect building block for molecular assembly and leads to the foundation of the field named DNA nanotechnology, where DNA molecules are designed to self-assemble to form nanoscale to macroscale designer structures, to guide the assembly of guest entities, or to realize molecular intelligent systems that capable of executing algorithms. For each category, a few representative, up-to-date examples were selected to demonstrate the assembly and computing power of DNA nanotechnology.

2. Self-Assembly of DNA Structures

The field of DNA nanotechnology was founded by Nadrian Seeman in the early 1980s, who was by then a crystallographer proposing to use DNA crystals to aid the crystallization of proteins for crystallography studies. Although no protein structures have been solved by DNA crystals yet after 40 years of development, DNA nanotechnology has significantly outgrown Seeman’s initial scope, by becoming one of the...
most versatile technologies toward nanostructure fabrication. Numerous self-assembly strategies have been developed to harvest the programmability of DNA molecules. The size, complexity, and robustness of assembled DNA structures have drastically evolved over decades. Generally, one can design and assemble DNA structures of arbitrary geometries with sizes ranging from several nanometers to hundreds of nanometers in all three dimensions.\(^2\)

Single-stranded DNAs (ssDNAs) represent the most basic and widely used building blocks in DNA nanotechnology, by simply utilizing sequence complementarity-induced DNA hybridization (Figure 1a).\(^3\) Aaptamers are a special type of ssDNAs that exhibit certain secondary structures, thus capable to recognize specific cargos, including small molecules, proteins, and cells.\(^4\) With rational design, a number of ssDNAs may interact and assemble into a prescribed structure, e.g., an octahedron (Figure 1b). In addition, DNAs may first assemble into a building module, often called a motif or a tile, which can further grow into higher order structures in one, two, or three dimensions in hierarchical fashion (Figure 1c,f,g,h).\(^5\)

Single-stranded tile (SST, or DNA brick) can be considered as a special version of DNA tiles, where each single DNA is a tile with unique sequence (Figure 1d).\(^6\) A master set of SSTs could serve as a modular canvas for constructing arbitrary 2D (Figure 1i)\(^7\) and 3D objects (Figure 1j)\(^8\) via sculpting a number of tiles at designated positions, which can be designed in silico. DNA origami is a technique that uses excessive amount of a pool of short ssDNAs to fold a long, ssDNA (e.g., M13 DNA) into predesigned structures (Figure 1e).\(^9\) A large diversity of structures with precisely controlled geometry has been designed and assembled using DNA origami, including 2D objects (Figure 1k),\(^9\) 3D cages (Figure 1l),\(^10\) and 3D wireframe object (Figure 1m).\(^11\) Higher order structures may be realized by programming the hierarchical assembly of DNA origami tiles (Figure 1n,o).\(^12\)

3. DNA-Guided Assembly of Molecules, Materials, and Cells

Given the programmability of DNA molecules and DNA structures, one of the most popular applications is to guide the precise assembly of guest entities, including molecules, materials, and even living organisms (e.g., cells), with controlled configurations across multiple dimensions. These assemblies may exhibit emerging properties and functions that can be applied to a broad array of research fields.

3.1. DNA-Guided Assembly of Organic Molecules, Polymers, and Hydrogels

DNA molecules are active for chemical modifications to form hybrid materials with organic molecules and materials. Yan and co-workers constructed an artificial light-harvesting antenna by placing three fluorophores (Py, Cy3, and Cy5) at designated positions in a sequential order on a DNA bundle template. Organic fluorophores are molecules that can accept or donate photons upon excitation. Energy transfer between fluorophore pairs may happen if they are positioned in close proximity. These fluorophores were first chemically conjugated onto ssDNAs, which served as linkers to anchor fluorophores onto designated docking sites with protruding capture strands of complementary sequences. This antenna was able to realize unidirectional energy transfer between fluorophores (Figure 2a).\(^13\) Rothemund and co-workers precisely anchored designated number of fluorophores onto a DNA origami template. Then DNA-fluorophore hybrid structures were placed into photonic crystal cavities at selected positions to digitally tune the light emission intensities, with which they have generated an image mimicking Van Gogh’s The Starry Night (Figure 2b).\(^14\) Zhang and co-workers grafted an anticancer small molecule drug (paclitaxel) onto ssDNAs, which formed a micellar structure with hydrophobic paclitaxel residing inside the core and hydrophilic DNA protruding outward serving as the shell (Figure 2c).\(^15\) The molecular recognition capability of DNA shell remained available to load functional moieties such as targeting ligands. This system demonstrated potent suppression efficiency on the growth of xenograft tumors in mice. In addition to organic molecules, DNA structures may also aid the arrangement of...
polymeric materials. For instance, distinct number of conductive polymers like (2,5-dialkoxy)paraphenylene vinylene (APPV) were mounted onto DNA origami template by Gothelf and co-workers (Figure 2d). The routing path of APPV was precisely controlled by varying the positions of capturing handle strands on the template. Such system holds great promise on fabricating organic electric devices like circuits or transistors. Compact arrangement of organic molecules or polymers will lead to the formation of polymeric membranes. For instance, Liu and co-workers tethered DNA-block copolymer onto DNA origami objects, which served as seeds or nucleation sites to attract more block copolymers to stay along via hydrophobic interactions to form 2D polymeric sheets (Figure 2e). The size and shape of nanosheet were precisely determined by the underneath DNA origami templates. 3D polymeric vesicles or polysomes may be assembled using 3D DNA templates. Yang et al. designed a series of ring-like DNA origami templates with varied diameters decorated with a number of lipid molecules within the interior perimeter (Figure 2f). Similar to the aforementioned report, these lipids served as seeds to initiate lipid molecule compacting in three dimensions to form liposomes. Due to spatial constraint by the ring template, the diameters of as-assembled liposomes were accurately defined. By using a DNA cuboid template, Liu and co-workers showed that cuboid-shaped polymeric vesicles could be successfully assembled. One potent advantage of DNA molecule is its molecular recognition and responsive capability to induce dynamic changes upon external stimulations, which may be physical, chemical, or biological. For example, Tan and co-workers integrated azobenzene-modified DNA molecules into polymeric hydrogels to enable light-responsive volume change (Figure 2g). Azobenzene molecules were chemically grafted onto DNA, whose conformations (trans vs cis) are responsive to light stimulation. The conformational change of azobenzene could control the hybridization and

dehybridization of DNA molecules, therefore the cross-linking density and eventually the apparent volume of polymeric hydrogels. Collins and co-workers designed a nuclease-responsive (Cas12a) polymeric hydrogel to realize controlled release of cargos (e.g., small molecule, protein, nanoparticles [NPs], cells) from the gel (Figure 2h).

Cargoes were tethered to ssDNAs or physically encapsulated within the gel. Introduction of dsDNA trigger of specific sequence led to Cas12a-mediated degradation of ssDNAs and thus release of cargoes to the environment. The authors also attached a DNA-based hydrogel to an electrode surface that acts like a fuse to switch off conductivity upon exposure to the trigger. The versatility of the system was further
demonstrated by coupling the gel response with multilayered
dpaper microfluidic chips to engineer a point-of-care diagnostic
tool for the rapid and sensitive detection of viruses.\textsuperscript{[22]}
Sophisticated configuration of liposomes were realized by Lin
and co-workers via dynamically programming the DNA tem-
plates (Figure 2i).\textsuperscript{[23]} A string of liposomes were fused to lon-
titudinal lipid tubes by bringing DNA templates into close
proximity using DNA molecular triggers. Furthermore, lipid
tubes could be bent into curved structures by reconfiguring
the DNA template surrounding and supporting the lipid tube.

3.2. DNA-Guided Assembly and Synthesis of Inorganic
Materials

It has been widely reported that assembly and synthesis of inor-
ganic materials under precise control can produce metamaterials
with emergent artificial properties that may be used in numerous
fields, including chemistry, physics, medicine, biology, and
potentially artificial intelligence. DNA-guided assembly may be
one of the most versatile techniques, if not the most, to construct
such metamaterials.\textsuperscript{[24]} Metallic NPs are among popularly used
materials to integrate with DNA self-assembly forming hybrid
metamaterials. The relative spatial positions of NPs determine
how the assemblies respond to environmental electromagnetic
fields, also known as plasmonic interactions. Generally, ssDNAs
need to be tethered onto the surface of NPs for stabilizing the
NPs and for serving as linkers to react with DNA molecules
via hybridization. Liu and co-workers arranged 24 gold nanopar-
ticles (AuNP) onto a DNA origami ring exhibiting left-handed or
right-handed helical configurations with programmable chirality
(Figure 3a).\textsuperscript{[25]} By assembling silver nanoparticles (AgNPs) into
cyclic ring geometry, magnetic resonance and propagation at
visible frequencies were experimentally realized by Wang et al.
(Figure 3b).\textsuperscript{[26]} Such property is a prerequisite for making invis-
ible materials. A chiral gold nanorod (AuNR) nanodevice was fab-
ricated by assembling two AuNRs onto a DNA origami template

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\caption{DNA-guided assembly and synthesis of inorganic materials. a) A chiral AuNP metamolecule assembled on a DNA origami ring structure. Reproduced with permission.\textsuperscript{[25]} Copyright 2016, American Chemical Society. b) An AgNP cluster assembled on DNA origami hexagon. Reproduced with permission.\textsuperscript{[24]} Copyright 2019, John Wiley & Sons Inc. c) An AuNR dimer with reconfigurable chirality as programmed by DNA and controlled by light. Reproduced with permission.\textsuperscript{[27]} Copyright 2016, Springer Nature. d) QDs were positioned on a DNA rod with precise control over number and distance. Reproduced with permission.\textsuperscript{[28]} Copyright 2010, American Chemical Society. e) Magnetic Fe$_3$O$_4$ NPs were assembled into 3D superlattice structure by DNA. Reproduced with permission.\textsuperscript{[29]} Copyright 2013, Springer Nature. f) Fluorescent nanodiamonds were positioned on DNA origami templates. Reproduced with permission.\textsuperscript{[30]} Copyright 2015, American Chemical Society. g) AuNPs were tethered onto a UCNP core by DNA. Reproduced with permission.\textsuperscript{[31]} Copyright 2013, American Chemical Society. h) Arbitrary Au/Ag NP were synthesized within DNA origami molds. Reproduced with permission.\textsuperscript{[32]} Copyright 2014, AAAS. i) Complex silica structures were deposited onto DNA origami templates. Reproduced with permission.\textsuperscript{[33]} Copyright 2018, Springer Nature.}
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in a cross geometry, whose chirality can be dynamically reversed using molecular triggers (Figure 3c). Fluorescent quantum dots (QDs) were attached onto a rod-shaped DNA template to form chain-like clusters (Figure 3d). The number and position of QDs were precisely controlled by varying the number and position of corresponding docking sites on the template. Reported by Zhang et al., superparamagnetic iron oxide (Fe₃O₄) NPs were assembled into large superlattice crystals with defined unit cell by programming the ssDNAs conjugated onto the NPs (Figure 3e). Similar to QDs, as demonstrated by Liedl and co-workers, fluorescent nanodiamonds were positioned onto DNA origami templates forming fluorescent clusters with prescribed configurations (Figure 3f). Lu and and co-workers developed a technique to conjugate ssDNAs onto upconversion nanoparticles (UCNPs), which were then linked with a number of small AuNP of complementary ssDNAs to form core-satellite hybrid assemblies (Figure 3g). In addition to guiding the assembly of presynthesized NPs, DNA structures may serve as molds or templates to direct in situ synthesis of inorganic materials. The geometry of the mold could be well translated to the final synthesized materials. Yin and co-workers designed a series of DNA origami structures with arbitrary internal cavities serving as molds for metallic NP synthesis (Figure 3h). Small AuNPs were first positioned within the mold as nucleation seeds to initiate metal growth until the cavity was filled. Au/Ag NPs with arbitrary sizes and shapes were synthesized using this method. Fan and co-workers fabricated complex silica materials on a variety of DNA origami templates including 2D/3D objects and 2D lattices (Figure 3i). The silica layer could drastically stabilize the internal DNA structures to strengthen its resistance against thermal, biological, or mechanical perturbations.

3.3. DNA-Guided Assembly of Biological Materials

In biology, functional components (e.g., proteins, nucleic acids) are generally integrated within a party to work synergistically or sequentially to complete assignments with high efficiency and accuracy. Well, it remains challenging to mimic these biological parties in vitro due to the lack of assembling tools. As demonstrated by various examples, DNA structures may hold great potential in this endeavor given its assembling capability and biocompatibility. For instance, glucose oxidase (GOx) and horseradish peroxidase (HRP) were placed on a DNA template in close proximity to realize cascade enzymatic reactions (Figure 4a). Enzyme cascade Dynamic reconstitution of EGFP (a) Nter-EGFP Cter-EGFP (b) Dynamic reconstitution of EGFP from two splits programmed by a DNA origami device. Reproduced with permission. Copyright 2012, American Chemical Society. Dynamic reconstitution of EGFP (b) Nter-EGFP Cter-EGFP (b) Dynamic reconstitution of EGFP from two splits programmed by a DNA origami device. Reproduced with permission. Copyright 2012, American Chemical Society. DNA template directed polymerization of curli. Reproduced with permission. Copyright 2019, Springer Nature. DNA-STV hybrid structure (d) DNA-STV hybrid structure Reproduced with permission. Copyright 2012, WILEY-VCH Verlag GmbH & Co. KGaA. Study interaction forces between two nucleosomes positioned on DNA origami hinge. Reproduced with permission. Copyright 2016, AAAS. Bispecific aptamer-induced artificial pairing of proteins could regulate cellular pathways. Reproduced with permission. Copyright 2019, American Chemical Society. Responsive delivery of thrombin by a DNA origami robot-induced significant tumor suppression. Reproduced with permission. Copyright 2018, Springer Nature. DNA structure-mediated delivery of siRNAs for cancer therapy. Reproduced with permission. Copyright 2017, WILEY-VCH Verlag GmbH & Co. KGaA. Delivery p53 gene by a triangular DNA origami. Reproduced with permission. Copyright 2018, American Chemical Society.

which exhibited significantly enhanced enzymatic efficiency comparing to freely dispersed enzymes in aqueous solutions or distally localized enzymes on DNA template. Proteins may also be reconstituted in a dynamic fashion. Ke et al. made a DNA clamp with two splits of an EGFP initially placed in distal positions (Figure 4b). Molecular fastener (a DNA molecule) was added to close the clamp so that EGFP splits were brought together and thus reconstituted to recover green fluorescence. Polymerization of curli was directed by a DNA origami protein complex that mimicking nucleation sites (Figure 4c). Mao et al. attached CsgB protein onto a DNA template serving as the starting point for curli polymerization, or as the ending point to dock freely polymerized curli approaching in vicinity. Mao and co-workers constructed three DNA nanocages (tetrahedron, octahedron, and icosahedron) with biotin handles at each face (Figure 4d). Streptavidin was then mounted onto the nanocages via binding to biotin handles, to form a DNA-streptavidin hybrid complex structure with fine control over number and positions of streptavidin. Dietz and co-workers used DNA template for biophysical studies of nucleosomes (Figure 4e), where they placed two nucleosomes within a DNA origami hinge to examine their interaction forces. DNA structures are versatile tools on regulating cellular pathways by interacting with cellular membrane proteins. Li and co-workers designed a bispecific aptamer that can bind to and thus pair two membrane proteins to specifically downregulate or upregulate corresponding cellular pathways (Figure 4f). DNA structures also hold potent delivery capability for biological therapeutics. Ding and co-workers constructed a DNA robot to load thrombin within its cavity (Figure 4g), which was sealed by aptamer AS1411. Upon recognition of nucleolin in tumor microenvironment by AS1411, DNA robot opened up to expose thrombin to induce blood clogging, leading to cancer cell starvation. The DNA robot can significantly suppress tumor growth in diverse xenograft and orthotopic tumor models. Wang and co-workers used DNA vehicles to deliver anticancer small interfering RNA (siRNA) against oncogene Bcl2 (Figure 4h). They showed that siRNA delivered by DNA vehicles can drastically suppress tumor growth in mice via knocking down Bcl2 proteins in cancer cells, as validated by molecular mechanistic studies. In addition to proteins and siRNAs, which have relatively small molecular weights, megadalton-sized genes can be delivered by DNA vehicles as well. For example, Ding and co-workers linked a number of p53 genes onto a triangular DNA origami vehicle, which was intercalated by doxorubicin (Figure 4i). This combinatory delivery system showed promising efficacy on cancer therapy.

3.4. DNA-Guided Assembly of Living Cells

Clustering of cells play important roles in cellular communications, stem cell differentiation, tissue formation, and so on, which was typically realized through interactions between natural proteins on cell membrane. Although there have been only a few reports, it has been demonstrated that DNA may act as a potent ligand to construct artificial cellular clusters or microtissues toward a variety of biological applications. Bertozzi and co-workers functionalized cells with short ssDNAs to impart specific adhesive properties on the cell. DNA structures also hold potent delivery capability for biological therapeutics. Ding and co-workers constructed a DNA robot to load thrombin within its cavity (Figure 4g), which was sealed by aptamer AS1411. Upon recognition of nucleolin in tumor microenvironment by AS1411, DNA robot opened up to expose thrombin to induce blood

![Figure 5. DNA-guided assembly of living cells. a) ssDNA-directed clustering of cells. Reproduced with permission. Copyright 2009, NAS. b) A 3D microtissue generated by layered assembly of multiple cell types controlled by DNA. Reproduced with permission. Copyright 2015, Springer Nature. c) DNA origami-induced hierarchical assembly of cells. Reproduced with permission. Copyright 2017, John Wiley & Sons Inc.](image-url)
the design of microtissues with defined cell composition and stoichiometry. The authors used this strategy to construct a paracrine signaling network in isolated 3D microtissues. Similarly, Gartner and co-workers used DNA to program and reconstitute the multicellular organization of organoid-like tissues with prescribed size, shape, composition, and spatial heterogeneity (Figure 5b). The authors generated a variety of microtissues having multiple and distinct epithelial and stromal compartments. These microtissues incorporated endothelial networks, fibroblasts, and epithelial cells using multiple-step DNA-programmed assembly of cells.

Instead of using ssDNAs to program the clustering of cells, Castro and co-workers first anchored DNA origami handles onto cell membrane (Figure 5c). By programming the interactions between DNA origami handles on cells, hierarchical assembly of multiple cellular types was realized.

It is anticipated by the authors that integration of DNA origami nanodevices may transform the cell membrane into

![DNA assembly-enabled molecular intelligent systems](https://example.com/fig6)

an engineered material that can mimic, manipulate, and measure biophysical and biochemical function within the plasma membrane of living cells.

3.5. DNA Assembly-Enabled Molecular Intelligent Systems

Molecular intelligent systems are advanced systems consisting of molecules that can perceive and respond to the surrounding world. The programmability of DNA molecules suits them a perfect material for designing molecular intelligent systems that are able to compute and execute sophisticated tasks. The most robust working mechanism to put DNA molecules in programmable motion is strand displacement reaction, where a DNA strand of low affinity is displaced by a strand of higher affinity to a specific target.\(^\text{[46]}\) As shown in Figure 6a, strand a\(^b\) would displace strand b\(^a\) from binding with strand ab since strands ab and a\(^b\) are fully complementary. The displacement is initiated from the single-stranded overhang region, also known as toehold. In addition to toehold-mediated strand displacement reaction, DNA molecules of specific sequences or chemical modifications may respond to certain molecular targets (small molecules, proteins, etc.) or environmental cues (ions, temperature, light, etc.), as shown in Figure 6b. For additional information regarding dynamic DNA assembly, one can refer to a recent review on this topic.\(^\text{[47]}\) Krishnan and co-workers designed a I-motif-based pH sensor (I-switch) to map internal pH changes of cellular organelles in living cells (Figure 6c).\(^\text{[48]}\) I-motif is a cytosine-rich DNA strand that can form a stable quadruplex structure under acid condition (e.g., pH = 5). Such conformational change within I-switch was able to be translated to fluorescent output based on a technique called fluorescence resonance energy transfer (FRET) between fluorophores. I-switch is an efficient reporter of pH from pH 5.5 to 6.8, with a high dynamic range between pH 5.8 and 7. To demonstrate its ability to function inside living cells, the authors used the I-switch to map spatial and temporal pH changes associated with endosome maturation. Yan and co-workers constructed a molecular spider that can achieve directional movement on a 2D DNA origami landscape (Figure 6d).\(^\text{[49]}\) By designing the landscape, the molecular spiders autonomously carry out a sequence of actions, including ‘start,’ ‘follow,’ ‘turn,’ and ‘stop.’ Intelligent walkers may behave like robots to conduct sophisticated tasks, including cargo sorting, picking, and transporting (Figure 6e).\(^\text{[50]}\) Qian and co-workers fabricated a DNA robot and docked it onto a DNA origami field, which is able to randomly walk along tracks to pick up molecular cargos and transport to designated sites. Apart from DNA robots, the same group developed a complex molecular neural circuit that can be trained to recognize molecular patterns (Figure 6f).\(^\text{[51]}\) Such neural network, after training, is able to recognize molecular patterns of arbitrary handwritten digits “1”–“9.” Furthermore, the network can classify test patterns with up to 30 of the 100 bits flipped relative to the digit patterns “remembered” during training, suggesting that molecular circuits can robustly accomplish the sophisticated task of classifying highly complex and noisy information on the basis of similarity to a memory. Fan and et al. showed that a DNA navigator was able to perform single-molecule parallel depth-first search on a 2D DNA platform (Figure 6g).\(^\text{[52]}\) A specific solution path connecting a given pair of start and end vertices can be easily extracted from the set of all paths taken by the navigators collectively. Recently, a complex DNA computing system was developed by Winfree and co-workers (Figure 6h).\(^\text{[53]}\) where they designed a set of 355 single-stranded tiles that can be reprogrammed to implement a wide variety of 6-bit algorithms. Using this set of tiles, they constructed a number of 21 circuits that can execute algorithms, including copying, sorting, random walking, electing a leader, simulating cellular automata, generating deterministic and randomized patterns, counting to 63, and so on, with an overall per-tile error rate of less than 1 in 3000, suggesting that molecular self-assembly may be a reliable algorithmic component within programmable chemical systems.

4. Conclusion

DNA nanotechnology has offered tremendous opportunities in fabricating functional assemblies through DNA-guided assembly of molecules, materials, and living cells. These functional assemblies exhibit a set of properties that stand them out from conventional materials, including a) precise controllability over functional components’ number and spatial locations; b) capability of sensing, computing, and responding to external stimuli. DNA-guided functional assemblies have demonstrated exciting applications in many fields, including nanofabrication, plasmonics, biophysics, tissue engineering, biosensing/bioimaging, drug delivery, data storage, molecular computing, and so on. Nevertheless, a large portion of these applications are solely based in the laboratory; there is still a long way to go toward practical applications given challenges such as production expense, stability in working environments, and so on. Technical breakthroughs in these categories may drastically boost its utility in addressing real-world problems.

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Conflict of Interest

The authors declare no conflict of interest.

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