Heuer-Jungemann, Amelie; Linko, Veikko

Engineering Inorganic Materials with DNA Nanostructures

Published in:
ACS Central Science

DOI:
10.1021/acscentsci.1c01272

Published: 22/12/2021

Document Version
Publisher's PDF, also known as Version of record

ACS central science

http://pubs.acs.org/journal/acscii

Outlook

Engineering Inorganic Materials with DNA Nanostructures

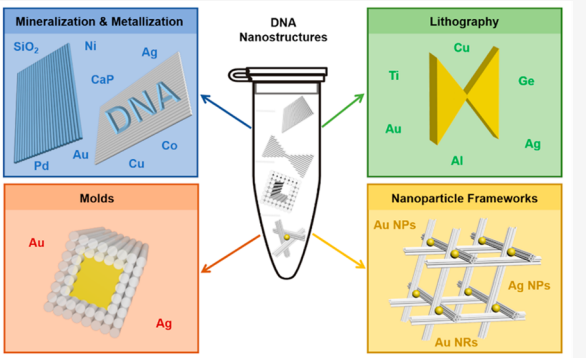
Amelie Heuer-Jungemann*,‖ and Veikko Linko*,‖

Cite This: https://doi.org/10.1021/acscentsci.1c01272

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Nucleic acid nanotechnology lays a foundation for the user-friendly design and synthesis of DNA frameworks of any desirable shape with extreme accuracy and addressability. Undoubtedly, such features make these structures ideal modules for positioning and organizing molecules and molecular components into complex assemblies. One of the emerging concepts in the field is to create inorganic and hybrid materials through programmable DNA templates. Here, we discuss the challenges and perspectives of such DNA nanostructure-driven materials science engineering and provide insights into the subject by introducing various DNA-based fabrication techniques including metallization, mineralization, lithography, casting, and hierarchical self-assembly of metal nanoparticles.



1. INTRODUCTION

The ability of precisely controlling the morphology of inorganic nanomaterials and metals is an essential feature for a wide variety of applications including nanophotonics, light harvesting, and biomaterials.[1] It is well-known that the properties of these substances are strongly dependent on their composition, size, and shape.[2] For example, a solution of spherical gold nanoparticles (Au NPs) appears red in color, while a suspension of gold nanorods (Au NRs) can vary in color from purplish-blue to green to brownish red, depending on the aspect ratio of the particles.

The ability of precisely controlling the morphology of inorganic nanomaterials and metals is an essential feature for a wide variety of applications including nanophotonics, light harvesting, and biomaterials.

While many wet-chemical approaches allow shape control to a certain extent—for instance, reaction conditions can be adjusted to create, among others, spherical, rod, or cubic shapes on the nanoscale—there always exists a degree of polydispersity. Additionally, more complex 3D shapes with programmable functions are often not accessible via conventional bottom-up wet-chemical methods. On the other hand, top-down methods, such as lithography, may produce more complex structures but are usually limited to larger feature sizes. Therefore, scientists have long sought out ways to overcome these issues posed by traditional fabrication methods.

One of the most promising approaches is to template inorganic materials such as minerals and metals using DNA nanostructures. DNA nanotechnology, and most noteworthy the DNA origami technique,[3] allows for unprecedented control over the shape and size of the resulting object, which is also fully site-specifically addressable. In the DNA origami technique, first reported by Paul Rothemund in 2006,[4] a long circular DNA "scaffold" strand, derived from the M13mp18 bacteriophage genome, is folded into any desired 2D or 3D shape with the aid of dozens of short, synthetic "staple" oligonucleotides. As a result, the helix domains within the DNA origami structure are held together by staple or scaffold crossovers. Each staple strand is modifiable and has its own well-defined spatial location in the DNA origami design, and therefore, the customizable DNA origami template may serve as a modular platform or a "nanobreadboard" for directing, positioning, and anchoring numerous biomolecular components, such as proteins,[5−7] RNA and CpG motifs,[8] drugs,[9] enzymes,[10,11] and aptamers,[12,13] thus manifesting the technique's substantial potential in biomedicine, diagnostics, and therapeutics.[14] Nevertheless, and besides the above-mentioned bioimplementations, ingenious contributions to materials science engineering have also been introduced. As an example, molecular-scale field-effect transistors for nano-

Received: October 15, 2021

electronics can be built by aligning carbon nanotubes with DNA origami analogues of circuit boards.[15,16] Recently, a burgeoning tendency to employ various DNA nanostructures with ever-increasing complexity[17,18] in the modulation of the morphology and functions of other inorganic and metallic nanomaterials has rapidly emerged.

In this Outlook, we briefly summarize and explore recent advances in the fabrication of metal, metal oxide, semiconducting, and inorganic nonmetallic nano-objects, templated by DNA nanostructures (Figure 1). We acknowledge that there

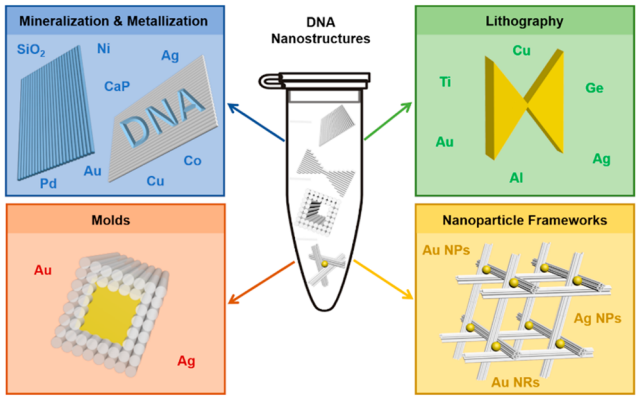


Figure 1. Programmable DNA nanostructures pave the way for engineering new types of hybrid and inorganic nanomaterials for a plethora of applications.

are many studies where DNA is used to position individual metal NPs to create discrete hybrid architectures as well as nanophotonic and plasmonic structures. Nevertheless, to narrow the scope of this Outlook to the synthesis of novel inorganic materials using DNA nanostructures, the interested reader is referred to recent review articles covering these topics.[19−21] Here, we furthermore discuss the emerging applications as well as the foreseeable challenges and potential solutions in using DNA nanostructures as a nanoscaffolding material and provide an outlook to future implementations.

2. METALLIZATION—SYNTHESIS AND ACHIEVED PROPERTIES

The metallization of linear or branched DNA strands has long been utilized for the formation of electrically conducting nanowires.[22] However, DNA nanostructures have also more recently been used as templates for the synthesis of different metal shapes not obtainable through wet-chemical or lithographic techniques.[23−32] In this section, we will discuss the recent progress in DNA nanostructure-templated metallization. DNA nanostructures have also been employed as molds to grow metal nanostructures within. Such systems will be discussed in Section 4.

Currently, two main strategies for DNA nanostructure-templated metallization exist. The first one involves the conjugation of small metal NPs (mainly Ag or Au, spheres or rods) to the nanostructure, followed by a further "overgrowth" step using a metal salt and reducing agent to fuse particles and obtain a larger, more complex single metallic nanostructure (Figure 2a).[24,31,32] As such, Aryal et al. conjugated Au NRs to DNA origami tiles in different arrangements in order to create Au nanowires for electrical applications, demonstrating that DNA origami templating of metal nanowires presents a promising path toward the creation of bottom-up nanofabrication of nanoelectronics (Figure 2b).[26] Uprety et al. used a similar approach to fabricate continuous metal nanostructures of various shapes such as T-shaped, rectangular, or square.[25] These structures grown from Au NRs showed highly improved shape specificity compared to similar structures grown from spherical Au NPs.[24] Importantly, the authors found that DNA-functionalized Au NRs exhibit an anisotropic growth, with

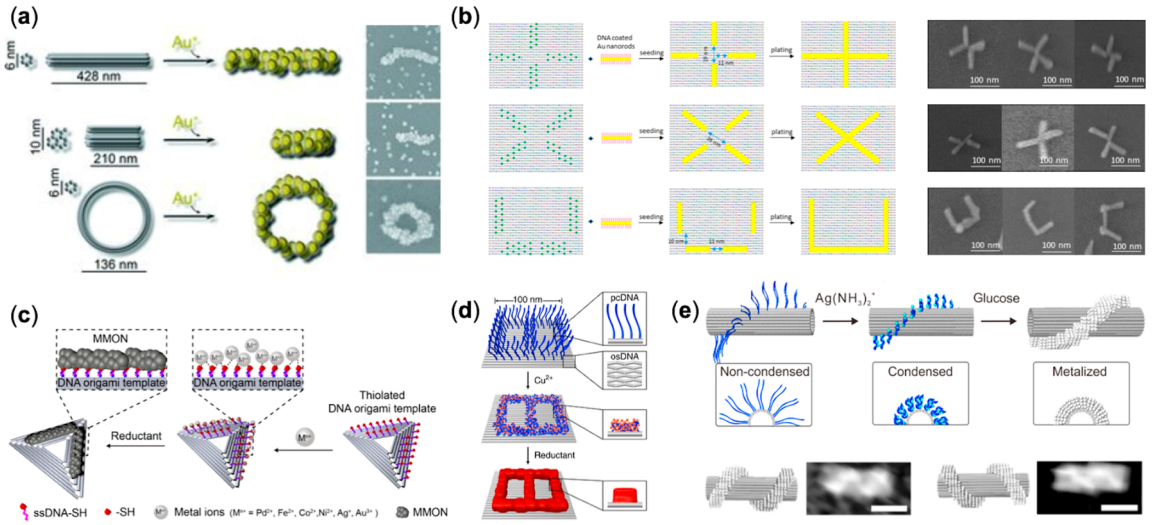


Figure 2. Metallization of DNA nanostructures. (a) (left) DNA origami serves as a template for the growth of Au NPs. (right) SEM images of the corresponding structures. (b) (left) Approach to form directed gold nanowires on DNA origami tiles. (right) SEM images of the corresponding structures. (c) Metal and metal oxide nanoclusters are formed on DNA origami templates equipped with thiolated strands. (d) DNA origami patterning with noncanonical DNA-based metallization reactions. (e) (top) DNA origami facilitates chiral silver patterns. (bottom; from left to right) Chiral left- and right-handed silver patterns and the corresponding AFM images. The scale bars are 50 nm. Panel a is reprinted with permission from ref 32. Copyright 2011 John Wiley & Sons. Panel b is reprinted with permission from ref 26. Copyright 2018 American Chemical Society. Panel c is reprinted with permission from ref 28. Copyright 2019 American Chemical Society. Panel d is reprinted with permission from ref 27. Copyright 2019 Springer Nature Ltd. Panel e is reprinted with permission from ref 29. Copyright 2021 American Chemical Society.

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

increased growth speed along the long axis during electroless deposition, allowing the diameter of resulting nanostructures to remain as small as 10 nm.[25]

The second technique involves the direct reduction of metal salts on (modified) single-stranded DNA (ssDNA) strands (Figure 2c).[28−30] This approach might be viewed as somewhat more straightforward and precise, as metal growth occurs directly on the DNA and does not require prior conjugation of DNA-modified Au NPs or Au NRs, which in itself can often be more challenging than expected. Additionally, this method does not suffer from the bottleneck of being able to use only those metal NPs which are dispersed in an aqueous solution and can easily be functionalized with DNA (i.e., mostly Au and Ag NPs). For example, Jia et al. could show that low-valency (less than three) metal cations, such as Cu^{2+}, could site-specifically condense protruding clustered ssDNA handles on DNA origami structures (Figure 2d).[27] The metallization reaction then occurred almost exclusively on these condensed DNA clusters, resulting in nm precise Cu nanostructures. Importantly, the length and number of the ssDNA handles to be clustered were found to be critical parameters for efficient metallization, since short strands (<10 nucleotides) did not support metallization. Making use of this effect, the authors used two lengths of ssDNA and could thus carry out bimetallic plating of DNA origami with both Cu and Ag site-specifically.[27]

On the other hand, Ding and co-workers utilized thiolated DNA handles hybridizing to protruding staple strands on a triangular origami in order to cluster metal ions. It is well-known that thiols display a strong affinity toward metals.[33] Making use of this affinity, the authors formed metal and metal oxide nanoclusters (MMONs) in predefined patterns on the DNA origami template using Ag^{+}, Au^{3+}, Co^{3+}, Fe^{2+}, Ni^{2+}, or Pd^{2+} as precursors. A great advantage of this method is a near quantitative yield of the target pattern, not requiring any purification. With the complete addressability of DNA origami, this method allows for the formation of nearly arbitrary 2D and 3D metal and metal oxide nanostructures with customized features such as prescribed chirality of the metal patterns (Figure 2e).[29]

3. MINERALIZATION—SYNTHESIS AND ACHIEVED PROPERTIES

While metallization approaches of DNA have been performed for many years, DNA mineralization is in fact a biological process that has occurred for millennia in the form of fossilization. Nevertheless, the successful application of such mineralization to designer DNA nanostructures in the laboratory is still in its infancy. However, the complete shape control over DNA nanostructures makes them extremely attractive templates for biomineralization.[34] Pioneering work in the biomimetic mineralization of biomolecules was carried out especially by the research groups of Shinkai,[35] Mann,[36] Brinker,[37] and Che.[38] However, adapting such processes designed for ssDNA or double-stranded DNA (dsDNA) molecules to DNA nanostructures—and DNA origami in particular—is far from trivial due to charges and buffer stability requirements. In this section, we discuss the successful biomineralization strategies for DNA origami nanostructures using $CaCO_3$, $Ca_3(PO_4)_2$, and SiO_2.

3.1. Silica. In 2018, Fan and co-workers reported the first successful mineralization of DNA origami nanostructures on surfaces (Figure 3a).[39] In their approach,[39,40] DNA nanostructures adsorbed on a solid support (TEM grid or mica) served as the template to create designer silica structures. Thereby, complex geometric information on a wide range of different DNA origami templates could be transferred to silica nanostructures with a controllable shell thickness. By employing the cationic co-structure directing agent *N*-trimethoxysilylpropyl-*N*,*N*,*N*-trimethylammonium chloride (TMAPS) in combination with tetraethoxysilane (TEOS), silica could be controllably grown only on the DNA nanostructure via TMAPS−phosphate backbone interactions. To overcome the competing interactions of Mg^{2+} ions used to stabilize the DNA nanostructures, the authors initially formed preclusters from TMAPS and TEOS. Molecular dynamics simulations revealed that, under high ionic strength conditions—usually required for DNA origami stability—at least three TMAPS molecules were required for efficient adsorption onto the DNA backbone, thus overcoming the electrostatic potential barrier. These silicified DNA nanostructures showed highly increased structural stability and toughness with forces of more than 3 nN being required to damage the structures.

Applying this approach, Mao and co-workers also demonstrated the formation of DNA−silica hybrid networks by organizing small silica particles, which were prepared *in situ*, along the phosphate backbone of a preformed DNA nanostructure network.[41] Besides pure DNA nanostructures, Liu et al. also demonstrated that DNA origamis conjugated to Au NRs could equally be encapsulated and, due to the increased stability, could be observed free-standing in 3D without any structural deformation. This feature has recently also been achieved by lyophilization of DNA origami on TEM grids in the presence of UO_2^{2+}.[42] As-prepared structures could withstand 1 nN of force before showing signs of deformation.

While the silicification approach by Liu et al. could only be carried out on a solid support with high-ionic-strength buffers, Nguyen et al. soon after evolved the approach toward DNA nanostructures in solution, at high concentrations (>100 nM) (Figure 3b).[43] Here, to avoid competing reactions between TMAPS and Mg^{2+} ions necessary for DNA origami stability, the authors used very low concentrations of Mg^{2+}, which had been recently shown by Kielar et al. to suffice for DNA origami stability in the absence of ethylenediaminetetraacetic acid (EDTA).[44] Kuzyk and co-workers developed the silica coating process further to also be applicable to very low concentrations of DNA origami (pM range) and with ultrathin silica shells by using $MgAc_2$ to fold DNA origami structures.[45] While both Liu et al. and Kuzyk and co-workers only showed successful silicification of single DNA origamis as well as 2D lattices, Nguyen et al. showed that not only relatively simple DNA origami structures, such as 14 helix bundles (14HBs), but also very complex 3D DNA origami lattices could be coated in a silica shell, thereby highly increasing their thermo- and mechanostability and thus allowing for a full structural analysis of these crystal lattices in a dry state without structural collapse of the lattices.[43]

Recently, Gang and co-workers demonstrated that a silicification of such 3D DNA origami lattices connected by Au NPs at low temperatures results in a smooth silica shell and lattice replicas which remained stable even when exposed to extreme conditions such as $T > 1000$ °C or $p > 8$ GPa.[46] The authors later also transformed silica-coated 3D DNA origami lattices into silicon carbide (SiC) lattices.[47] Such SiC lattices may be important new materials for optical, mechanical, and electronic applications. For their preparation, silicified DNA origami lattices were exposed to a Mg reduction reaction at a

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

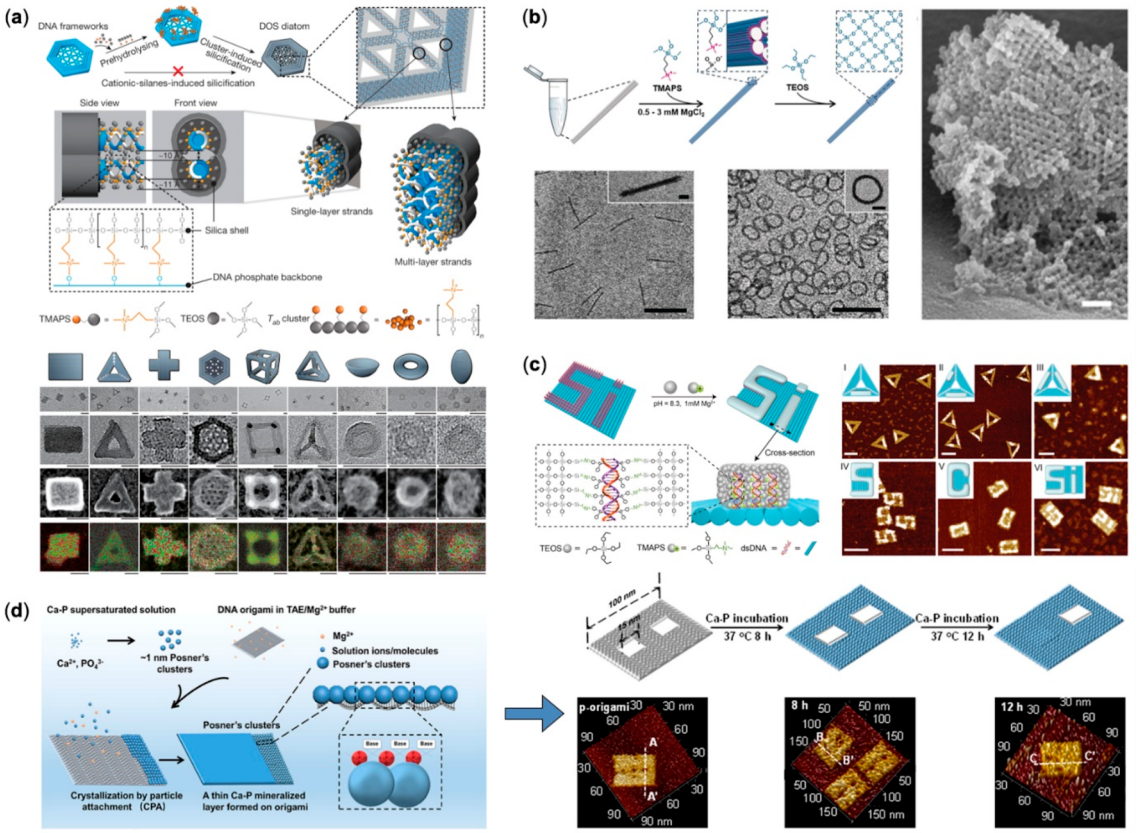


Figure 3. Mineralization of DNA nanostructures. (a) (top) DNA origami silicification (DOS) process with a DOS diatom-mimicking structure. (bottom; from top to bottom) Models, TEM, SEM, and EDS mapping images (Si in red, O in green, and P in blue) of the silica nanoparticles. The scale bars are 100 and 50 nm for zoomed-out and zoomed-in images, respectively. (b) (top−left) Silica formation on top of DNA origami. (bottom−left) Unstained TEM images of silica-encapsulated DNA origami (the scale bars are 300 nm; for insets, 30 nm). (right) SEM image of silica-coated crystals after a short Au/Pd sputtering (the scale bar is 200 nm). (c) (left) Site-specific silica formation on a DNA origami template. (right) AFM images of the synthesized silica nanoparticles. The scale bars are 100 nm. (d) (left) DNA origami template mineralization through a particle attachment strategy. (right) Mineralization of DNA origami with pores at different incubation times and the corresponding AFM images. Panel a is reprinted with permission from ref 39. Copyright 2018 Springer Nature Ltd. Panel b is reprinted with permission from ref 43. Copyright 2019 John Wiley & Sons. Panel c is reprinted with permission from ref 49. Copyright 2020 John Wiley & Sons. Panel d is reprinted with permission from ref 53. Copyright 2021 American Chemical Society.

high temperature (T < 700 °C) in order to form SiC. The SiC lattices retained the size and shape of the templating DNA lattice. Furthermore, they displayed a highly reduced resistivity compared to the silicified DNA lattices or conventional sol−gel silica. The same group also used silicified DNA origami lattices as precursors to create superconducting lattices by additional coating with niobium, thereby creating 3D arrays of Josephson junctions.[48] According to Gang and co-workers, their approach could be used for the formation of 3D superconducting quantum interference devices (SQUIDs), superconducting quantum interference filters (SQIFs), or parametric amplifiers for quantum information systems.[48]

In contrast to the aforementioned reports on complete encapsulation of the DNA origami nanostructure in a silica shell, Ding and co-workers observed that dsDNA overhangs showed stronger silica accumulation compared to the DNA origami itself when reaction conditions were adjusted to low Mg^{2+} Tris-HCl buffer at pH 8.3, 25 °C, and optimized TMAPS to TEOS ratio (Figure 3c).[49] Making use of this feature, the authors could form site-specific silica patterns on the DNA origami template, analogous to the metal and metal oxide patterns discussed previously. Silica only formed on the protruding dsDNA strands forming the pattern, while the DNA origami itself did not become encapsulated.

3.2. Calcium Phosphate and Calcium Carbonate.

Besides SiO_2, one of the first minerals used in mineralization reactions with DNA was calcium carbonate ($CaCO_3$). He et al. could already show in 2007 that DNA cross tiles could template the formation of $CaCO_3$ nanowires.[50] Hexagonal lattices were formed in the presence of Mg^{2+} ions, but nanowires were formed in the presence of Ca^{2+} ions. Further exposure of these Ca^{2+}-stabilized nanowires to CO_2 then resulted in the formation of $CaCO_3$ nanowires.

More recently, calcium phosphate was used to encapsulate DNA nanostructures. First reported by Zhang et al., the authors encapsulated drug-loaded DNA origami structures into pH-responsive calcium phosphate shells.[51] However, in this case, particles appeared to be quasispherical and were not templated by the DNA origami shape. Liu et al. soon after reported another strategy to coat DNA nanostructures with calcium phosphate.[52] In this study, the authors used Ca^{2+} instead of Mg^{2+} to fold DNA origami structures as Mg^{2+} had been shown to inhibit calcium phosphate crystallization. Purified DNA origami structures dispersed in a phosphate buffer could then be coated with calcium phosphate by the addition of $CaCl_2$ within 3 h at 37 °C,

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

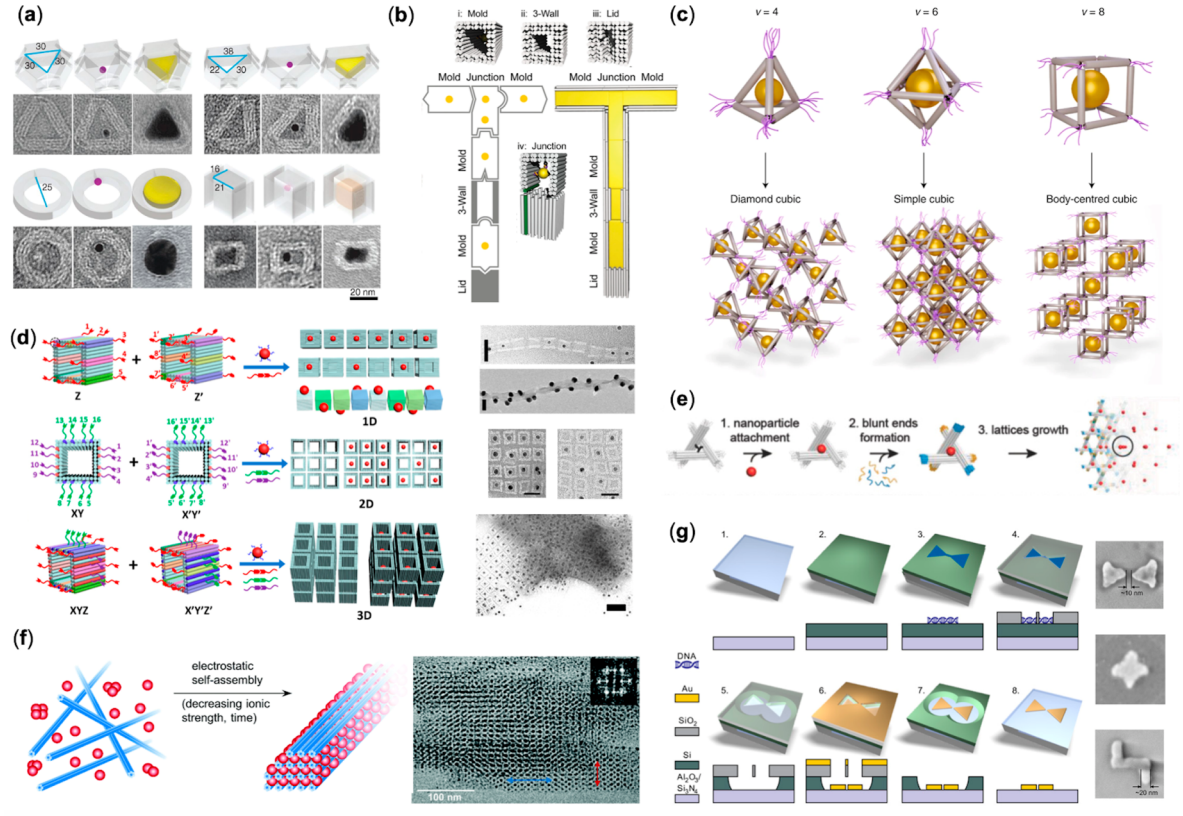


Figure 4. Metal NPs, lattices, and crystals from DNA nanostructure frameworks. (a) Casting of various metal NP shapes using DNA origami molds and the corresponding TEM images of each procedure step. (b) Complex and specific metal objects/geometries through a combination of different DNA origami molds. (c) (top) DNA frameworks equipped with Au NPs serve as "material voxels". (bottom) These material voxels form ordered lattices through vertex-to-vertex connection governed by the valence and the shape of the DNA cage. (d) (left) Programmable and modular DNA nanochambers for prescribed 1D, 2D, and 3D NP conformations. (right) Corresponding TEM images of the assemblies. The scale bars are 50 nm in all images, except 100 nm in the bottom image. (e) Au NP-equipped DNA origami tensegrity triangles assemble into a 3D rhombohedral crystalline lattice. (f) (left) Negatively charged six-helix bundles and positively charged Au NPs form ordered lattices through electrostatic interactions. (right) TEM image of the corresponding tetragonal superlattice. (g) (left) Parallel DNA-assisted lithography (DALI) method and the procedure steps. (right) SEM images (150 nm × 150 nm) of DALI-produced DNA origami-shaped metal nano-objects. Panel a is reprinted with permission from ref 55. Copyright 2014 The American Association for the Advancement of Science. Panel b is reprinted with permission from ref 58. Copyright 2021 John Wiley & Sons. Panel c is reprinted with permission from ref 67. Copyright 2020 Springer Nature Ltd. Panel d is reprinted with permission from ref 68. Copyright 2020 American Chemical Society. Panel e is reprinted with permission from ref 70. Copyright 2018 John Wiley & Sons. Panel f is reprinted with permission from ref 72. Copyright 2019 Royal Society of Chemistry. Panel g is reprinted with permission from ref 79. Copyright 2018 The American Association for the Advancement of Science.

making this reaction much quicker than the silicification reaction, which generally requires growth over several days. Nevertheless, the downside of this faster crystallization along with a larger diameter of Posner's cluster (1 nm for $Ca_9(PO_4)_6$ vs 3.2 Å for silica tetrahedral unit) resulted in a reduced precision of calcium phosphate mineralization compared to silica mineralization, and thus, shapes were not conserved very well. The authors then improved upon this synthetic strategy by slowing down and controlling the crystallization speed and thus achieved calcium phosphate structures templated by DNA origami with complete shape preservation (Figure 3d).[53] In this method, the authors used a dispersion of DNA nanostructures in a separately prepared metastable, supersaturated solution of calcium phosphate. This allowed the growth of a thin layer of calcium phosphate nanoclusters along the DNA phosphate backbone resulting in calcified DNA nanostructures with increased mechano- and thermostability. An important aspect of this technique was the preservation of accessibility of prepositioned functional molecules on the nanostructure. The authors showed that streptavidin, conjugated at predesigned positions to the DNA origami before calcification, remained active and could be conjugated with biotinylated moieties after calcification, thus overcoming one of the greatest challenges in the biomineralization of DNA nanostructures—the loss of addressability of the template—and allowing for downstream site-specific, post-synthetic modification of the inorganic nanostructure.

4. DNA MOLDS, NANOPARTICLE LATTICES, AND MOLECULAR LITHOGRAPHY

4.1. Casting Inorganic Nanoparticles with DNA Origami Molds. The examples of conventional DNA nanostructure metallization schemes were discussed in Section 2. However, DNA origami nanostructures can be ingeniously employed as "casting molds" for guiding and framing metal NP growth into desired shapes. In 2014, Seidel and co-workers[54] as well as Yin and colleagues[55] (Figure 4a) demonstrated techniques based on DNA origami for the casting of inorganic NPs. These methods rely on the chemical growth of a small "seed" Au NP into a larger metal (Au or Ag) NP in a confined space governed by a prescribed DNA origami cavity. In this way,

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

the grown Au NP accurately—advantageously down to sub-5 nm resolution—replicates the shape of the DNA origami "mold". As the DNA mold itself remains intact in the casting process, it may serve as a further functionalization platform, thus enabling fabrication of multimers, junctions, and composites such as quantum dot (QD)-Ag NP-QD sandwich structures.[55] Along these lines, Seidel and co-workers used the DNA "mold" method to create conducting gold nanowires,[56] metal nanoobjects with programmable lengths and patterns,[57] as well as multicomponent complex shapes, geometries, and superstructures (Figure 4b).[58] It is noteworthy, however, that nanostructures grown from such "seed" particles often show a lower degree of uniformity compared to NPs grown by standard solution-based protocols, which will be discussed in more detail in Section 5.

4.2. Prescribed Nanoparticle Lattices from DNA Origami Building Blocks. Since the dawn of applied DNA nanotechnology, the programmable nature of the DNA bond has been widely employed in assembling various well-ordered NP lattices and other hierarchical constructs.[59] These include lattices where flexible sequence- and length-adjustable DNA strands have been employed as NP surface ligands, thus allowing directed or guided crystal formation.[60−63] Besides DNA-assisted NP crystals, DNA nanostructures have recently been harnessed as templates for the fabrication of versatile and arbitrary valence-programmable NP clusters thus opening up new avenues in customizing NP cluster geometry, composition, and application-specific properties.[64]

Notwithstanding the above-mentioned progress, here, we focus on the DNA origami-controlled assembly of NP (super)lattices that can be considered as a completely new type of programmable material. One of the most striking implementations of such techniques was recently demonstrated by Gang and co-workers[65] (Figure 4c), who showed how 3D crystals of various nanomaterials could be formed using simple DNA origami cages as a scaffolding material. Similar to Pauling's principles that govern ionic crystal formation,[66] in this approach, the valency, shape, and coordination of the chosen DNA cage defined the produced lattice geometry. These prescribed tetrahedral, octahedral, or cubic DNA voxels could essentially be transformed into "material voxels" by equipping the cage with the selected cargo, such as Au NPs (Figure 4c, top panel), QDs, and proteins. Subsequently, these "material voxels" could be stitched together through vertex-to-vertex connections facilitated by the vertex-protruding ssDNA sequences (Figure 4c, bottom panel). The possibility to create arbitrary NP lattices with a great material and geometrical freedom paves a way for, e.g., various optical applications and may allow a detailed analysis of collective interparticle interactions of metal and semiconducting NPs.[67]

Soon after the introduction of the valence-controlled assembly of DNA cages, Gang and colleagues presented yet another route to programmable NP patterning.[68] In this alternative strategy, they employed modular and hollow DNA origami cuboids, i.e., "DNA nanochambers", which were functionalized with directional, differentiated, and "polychromatic" strand sets, thus allowing for the formation of 1D, 2D, and 3D arrays (Figure 4d, left panel). They demonstrated the feasibility of the approach by creating homologous nanochamber multimers, heteropolymers, helical polymers, and 2D and 3D lattices with and without Au NPs (Figure 4d, right panels).

Besides the hybridization of complementary sequences, i.e., sticky-end cohesion, as in vertex-to-vertex connections and differentiated polychromatic bonds, there also exist other efficient techniques to assemble DNA frameworks into higher-order architectures, which could be utilized for precise NP organization. Inspired by the small DNA tensegrity triangle molecules that served as the building blocks for the very first demonstration of 3D periodic DNA lattices,[69] Zhang et al. designed analogous, but larger, "tensegrity triangle" DNA origami structures that could similarly assemble into a 3D rhombohedral crystalline lattice (Figure 4e).[70] Instead of sticky-ends, Zhang et al. used blunt-end stacking interactions[71] to stack the triangular DNA origami monomers with 3-fold rotational symmetry together. The precision placement capability of the lattice was demonstrated by anchoring 10- and 20-nm Au NPs at the center of each origami monomer, resulting in rhombohedral Au NP lattices.

In contrast to the techniques discussed above, Julin et al. applied purely electrostatic interactions to organize cationic Au NPs with negatively charged six-helix bundle (6HB) DNA origami structures (Figure 4f, left panel).[72] The alkyl-oxy-ethylene ligand (including a positively charged quaternary ammonium group)-modified Au NPs (core size 2.5 nm) and 6HBs assembled into tetragonal superlattices (Figure 4f, right panel) upon dialysis against decreasing ionic strength. This method may equally enable a feasible assembly route for other DNA shapes and NP sizes, and it appears rather straightforward as the common ssDNA-functionalization of the Au NPs is not required. In other words, in this approach, the NPs are not merely anchored to the prescribed DNA frames, but they play a crucial role as "gluing" components in the lattice assembly. This may also provide intriguing implementations in dynamic NP lattice systems, as the NP arrays can be reversibly assembled and disassembled upon small changes in the environmental conditions, such as a minor tweak in the ionic strength of the solution.

4.3. DNA in Molecular Lithography. In the present-day industrial and technological world, the inextinguishable desire to miniaturize electronic components and hence to achieve a continuously higher packing density of the integrated circuits has pushed device manufacturing to the scale of a few nanometers, with cutting-edge consumer products assembled with 10−20 nm resolution.[73] To tackle these challenges, advanced methods such as electron beam lithography (EBL, provides a one-to-one fabrication scheme with relatively slow processing times) or (extreme ultraviolet) photolithography (fast and parallel manufacturing) are required. However, as this miniaturization paradigm becomes more and more demanding and pragmatically incremental, alternative routes have been sought out intensively.

One of the solutions for modern nanoengineering could be to harness the unsurpassed spatial addressability and the parallel bottom-up schemes of DNA nanostructures. Indeed, currently there exist several ways to make use of DNA nanotechnology and the exceptional properties of DNA nanostructures in device fabrication onto substrates: (1) DNA as a stencil tool in chemical vapor deposition (CVD) and etching and/or (2) a combination with conventional top-down nanopatterning such as lithography and physical vapor deposition (PVD). For example, DNA nanoassemblies can be used in CVD by modulating the deposition rate of inorganic oxides (SiO_2 and TiO_2)[74] as well as in reactive ion etching (RIE) masks, thus transferring the spatial information on DNA ensembles to a

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

silicon substrate in a "DNA molecular epitaxy" process with high resolution.[75] On the other hand, with the help of lithographic patterning, fluorescent DNA origami platforms can be precisely organized into predefined nanoarrays that may elicit optically intriguing properties.[76,77]

Yet another route to create inorganic nanopatterns with DNA nanostructure shapes is to combine the above-mentioned CVD growth of oxides, RIE, wet etching, and PVD with DNA origami. Shen et al. first adopted and further developed the selective oxide formation procedure[74] to create silicon oxide layers with "DNA origami silhouette"-type openings.[78] By a conventional etching of the silicon underneath the grown SiO_2 layer and the subsequent PVD of metals, the authors demonstrated DNA origami-shaped Au, Ag, and Cu NPs on bowl-like silicon wells.[78] This method was then upgraded to DNA-assisted lithography (DALI)-based production by first depositing a silicon layer on the target surface, repeating the other steps from the previous protocol, and finally etching the silicon completely away using hydrofluoric acid (HF) (Figure 4g, left panel).[79] This allowed the manufacturing of a handful of different Au and Ag nanoshapes on flat and transparent sapphire surfaces (Figure 4g, right panel), from which the antenna structures were also shown to act as surface-enhanced Raman spectroscopy (SERS)-based substrates for rhodamine 6G and 2,2-bipyridine molecules.[79]

Recently, the authors introduced additional sacrificial layers in the molecular lithography scheme and therefore generalized the method to biotemplated lithography of inorganic nanostructures (BLIN, which can also utilize virus capsids for the mask formation).[80] As BLIN circumvents the relatively harsh HF etching, the improved method allows the fabrication of plasmonic (Au and Ag), semiconducting (Ge), and metallic (Al and Ti) NPs on a wide variety of substrate materials such as common optical glass. As these techniques are highly parallel, they allow for the formation of billions of nanostructures on the chosen substrates in one go, thus providing a cost-effective alternative to, e.g., EBL in wafer-scale manufacturing.

5. CHALLENGES AND PERSPECTIVES

5.1. DNA Nanostructure Stability. One of the biggest challenges when working with DNA nanostructures is to ensure their stability under the required reaction conditions. DNA origami, for example, is thought to generally require high concentrations of Mg^{2+} (~10 mM) in order to maintain stability. However, as briefly mentioned earlier, Kielar et al. recently discovered that, by carefully adjusting buffer conditions (e.g., no EDTA) for the respective DNA nanostructure, the Mg^{2+} concentrations could be reduced to the low μM range.[44] Nevertheless, low concentrations of Mg^{2+} are not the only stability challenge to be overcome. In many cases, it is necessary to chemically increase the stability of DNA nanostructures in order to ensure their survival under certain reaction conditions necessary for, e.g., metallization approaches.

One potential solution to the stability hurdle is the cross-linking of DNA strands using chemical agents such as psoralen[23] or 3-cyanovinylcarbazole,[81] where the former can be added to the DNA strand as an external cross-linker, while the latter must first be integrated into the DNA strand, and cross-linking is reversible. Such photo-cross-linked structures could be heated to 70 °C without the loss of structural integrity.[81] Another method, not involving chemical cross-linking agents, was recently developed by Dietz and co-workers. Their "UV welding" approach made use of the naturally occurring formation of thymidine dimers upon UV irradiation.[82] By placing thymidines inside a DNA nanostructure in close proximity, covalent cross-linking via the formation of cyclobutene pyrimidine dimer bonds in response to UV irradiation can be achieved. Such "welded" DNA nanostructures were shown to be stable in water, in the absence of any cations, and could be heated to 90 °C without any notable signs of degradation. This type of cross-linking therefore shows great promise for synthesizing DNA nanostructures that are stable under conditions that would under normal circumstances result in their disassembly or deformation. Other methods, such as coating with lipids,[83,84] block co-polymers,[85,86] oligolysines,[87,88] proteins,[89,90] and peptoids,[91] may provide significantly enhanced stability to DNA nanostructures in biological settings (e.g., increased protection against degradation by nucleases). However, on many occasions (but not always[92]), these types of coatings are not suitable for templating reactions, which require direct DNA−material interactions.

5.2. Crystallinity and Uniformity of Inorganic Nanomaterials. Another great challenge when templating inorganic materials with DNA nanostructures is to obtain sufficient levels of crystallinity and uniformity of the inorganic nanostructure. This is especially true with respect to biomedical or photonic applications, where the shape and size of the nanostructure are key to their function. Of course, starting off with a well-defined DNA nano-object is key; however, additionally, crystallization conditions must be tuned carefully; e.g., in the case of biomineralization, slowing down reaction kinetics through adjustments of temperature, pH, movement during the reaction, or precursor concentrations can give better control over the crystallinity and uniformity of the mineralized nanostructure.

Arguably, casting various types of NPs using DNA origami molds has proven to be an attractive approach for custom inorganic NP synthesis, but alas, a well-justified concern of the particle uniformity and fabrication yields remains. For example, in the original article by Sun et al.,[55] the yield of the barrel-shaped DNA mold synthesis was only 20%, success in lid formation 12%, and closure of the box 31%. Although the seeding decoration yield was relatively high (86%), the casting yield, i.e., the NP growth success rate of correctly seeded molds, was just 6−40% depending on the employed metal and the target NP shape. Therefore, considering all of the fabrication steps—and despite the unsurpassable spatial resolution and versatility of the method—there is still plenty of room for improvement. The very recent application of DNA origami mold casting by Ye et al.[58] describes complex metal "superstructures" that have been organized through the conjugation of multiple molds. Using diligent optimization, they report that the mold assemblies can be formed at high efficiencies, with linear chains up to 90%. Although there is indeed significant progress in the synthesis yield, the crystallinity of the Au nanowires created through the linear assembly of molds is rather poor, thus complicating their use in real-world applications, e.g., in nanoelectronics.

5.3. Retaining DNA Template Addressability. Furthermore, one downside of coating DNA nanotemplates with inorganic materials is often the loss of addressability. Therefore, one challenge will be to develop novel methods that allow both the formation of an inorganic coating to achieve more durable structures as well as a retained addressability of the nanostructure after the encapsulation process. A step toward this direction was already made by Liu et al.[53] for calcium phosphate coating as already discussed in Section 3.2, and also

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

by Ding and co-workers,[49] who could show that during the silicification process, silica was predominantly accumulating on dsDNA, potentially suggesting that longer ssDNA handles protruding from a silicified DNA structure with a reasonably thin silica shell may allow for retained addressability. On the other hand, the incorporation of uncharged linkers, such as polyethylene glycol (PEG), or even proteins like neutravidin, may be able to result in less or no mineral deposition due to the lack of electrostatic interactions.

5.4. Precision Placement of DNA Nanostructures on Substrates. In substrate nanopatterning, one rather obvious obstacle arises when highly ordered DNA masks for potential downstream applications are required. For example, the current version of DNA-based lithography for metal nanostructures is demonstrated only with randomly deposited DNA nanostructures,[79] and the DNA origami-templated optical nanocavities require predeposition lithography to allow their fine-tuned organization.[76,77] Nevertheless, lithography for precision placement may be remarkably simplified by a recently developed cleanroom-free benchtop technique for straightforward substrate-processing through the self-assembled colloidal NP monolayer.[93] Another feasible route to macroscopic wafer-scale assembly is to scale up the facile surface- and cation-assisted formation of DNA origami lattices.[94] This strategy could serve as an alternative to lattices used in the "DNA molecular epitaxy" approach,[75] where the repeatable units were formed through stitching together unique sets of 32 nt DNA bricks.[95]

6. CONCLUSION AND OUTLOOK

Since its first report, DNA nanotechnology has evolved to an enabled state, where the design and assembly of objects exhibiting arbitrary shapes with sub-nanometer accuracy, complete addressability, and high stability toward various reaction conditions lie within the realms of possibility. These properties endow DNA frameworks with the ability to form inorganic nanostructures. Such structures could be assembled directly on DNA origami, using the whole design as a shape template for the fabrication of inorganic nanostructures not attainable through conventional wet-chemical methods. Alternatively, only selected domains of the origami could be used as templating motifs, thus making use of its site-specific addressability. This feature could be harnessed, e.g., in the formation of chiral plasmonic structures and in the shape-controlled growth of metallic NPs.

Since its first report, DNA nanotechnology has evolved to an enabled state, where the design and assembly of objects exhibiting arbitrary shapes with sub-nanometer accuracy, complete addressability, and high stability towards various reaction conditions lie within the realms of possibility.

The ways in which DNA nanostructures can be used to engineer inorganic nanomaterials is manifold, and potential applications of resulting structures are currently being explored. For example, mineralized DNA nanostructures will not only allow for implementations in harsh environments such as vacuum or organic solvents but may also pave the way for novel bone or dental replacements/grafts. As such, DNA nanostructures could also serve as scaffolds for the direct growth of biominerals *in vivo*.[96] For this, however, biomineralization procedures would have to be adapted to be nontoxic to the patient, and DNA nanostructures would need to be grown to a large enough size. Although this may not be straightforward, with the power of a hierarchical assembly and milligram-scale production of DNA origami structures,[97] it may well be possible in the future.

Mineralized DNA nanostructures will not only allow for implementations in harsh environments such as vacuum or organic solvents but may also pave the way for novel bone or dental replacements/grafts.

Mesoporous silica nanostructures have shown great promise in drug delivery; however, in many cases, only spheres and rudimental rods can be formed. Nevertheless, the size and shape of inorganic NPs play a crucial role in their interaction with cells and tissues. Therefore, forming custom silica NPs for each specific application (intracellular, intratumoral, targeted to specific organs, etc.) through DNA nanostructure templating could result in tremendous advancements in biomedicine. Additionally, currently, the level of potential "porosity" of the mineral shells remains unknown, but being able to tune pore sizes controllably, analogous to mesoporous silica particles, combined with complete control over shape and size, could open up completely new avenues in targeted drug delivery.

On the other hand, combining DNA self-assembly with top-down manufacturing could provide a step toward cost-efficient wafer-scale production of advanced metasurfaces[98] with active and nonlinear optical effects. Meanwhile, QD-based applications, such as QD optoelectronics and smart display technologies,[99] could benefit from the extremely accurate (periodical) DNA framework-assisted spatial organization of QDs.[65]

Combining DNA self-assembly with top-down manufacturing could provide a step towards cost-efficient wafer-scale production of advanced metasurfaces with active and nonlinear optical effects.

Overall, transferring the exceptional assembly power of DNA to robust inorganic compounds will ultimately lead us to the territory of inorganic materials science with a cornucopia of unique applications waiting to be discovered.

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Authors

Amelie Heuer-Jungemann − *Max Planck Institute of Biochemistry, 82152 Martinsried, Germany; Center for Nanoscience, Ludwig-Maximilians University, 80539 Munich, Germany;* orcid.org/0000-0003-3630-6389; Email: heuer-jungemann@biochem.mpg.de

Veikko Linko − *Biohybrid Materials, Department of Bioproducts and Biosystems, Aalto University, 00076 Aalto, Finland;* orcid.org/0000-0003-2762-1555; Email: veikko.linko@aalto.fi

Complete contact information is available at: https://pubs.acs.org/10.1021/acscentsci.1c01272

Author Contributions

‖A.H.-J. and V.L. contributed equally. The manuscript was written through contributions of both authors. The authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

V.L. acknowledges financial support by the Emil Aaltonen Foundation, the Sigrid Jusélius Foundation, the Jane and Aatos Erkko Foundation, and the Vilho, Yrjö, and Kalle Väisälä Foundation of the Finnish Academy of Science and Letters. A.H.-J. acknowledges funding from the Deutsche Forschungsgesellschaft (DFG) through the Emmy Noether program (project 427981116) and the SFB1032 "Nanoagents for the spatiotemporal control of cellular functions" (A06).

DEDICATION

In memory of Ned Seeman, founding father of DNA nanotechnology, who showed us that DNA has a place in the material world.

REFERENCES

(1) Yang, L.; Zhou, Z.; Song, J.; Chen, X. Anisotropic Nanomaterials for Shape-Dependent Physicochemical and Biomedical Applications. *Chem. Soc. Rev.* **2019**, *48*, 5140−5176.

(2) Heuer-Jungemann, A.; Feliu, N.; Bakaimi, I.; Hamaly, M.; Alkilany, A.; Chakraborty, I.; Masood, A.; Casula, M. F.; Kostopoulou, A.; Oh, E.; et al. The Role of Ligands in the Chemical Synthesis and Applications of Inorganic Nanoparticles. *Chem. Rev.* **2019**, *119*, 4819−4880.

(3) Dey, S.; Fan, C.; Gothelf, K. V.; Li, J.; Lin, C.; Liu, L.; Liu, N.; Nijenhuis, M. D. A.; Saccà, B.; Simmel, F. C.; et al. DNA Origami. *Nat. Rev. Methods Primers* **2021**, *1*, 13.

(4) Rothemund, P. W. K. Folding DNA to Create Nanoscale Shapes and Patterns. *Nature* **2006**, *440*, 297−302.

(5) Sprengel, A.; Lill, P.; Stegemann, P.; Bravo-Rodriguez, K.; Schöneweiß, E.-C.; Merdanovic, M.; Gudnason, D.; Aznauryan, M.; Gamrad, L.; Barcikowski, S.; et al. Tailored Protein Encapsulation into a DNA Host Using Geometrically Organized Supramolecular Interactions. *Nat. Commun.* **2017**, *8*, 14472.

(6) Aghebat Rafat, A.; Sagredo, S.; Thalhammer, M.; Simmel, F. C. Barcoded DNA Origami Structures for Multiplexed Optimization and Enrichment of DNA-Based Protein-Binding Cavities. *Nat. Chem.* **2020**, *12*, 852−859.

(7) Berger, R. M. L.; Weck, J. M.; Kempe, S. M.; Hill, O.; Liedl, T.; Rädler, J. O.; Monzel, C.; Heuer-Jungemann, A. Nanoscale FasL Organization on DNA Origami to Decipher Apoptosis Signal Activation in Cells. *Small* **2021**, *17*, 2101678.

(8) Ijäs, H.; Shen, B.; Heuer-Jungemann, A.; Keller, A.; Kostiainen, M. A.; Liedl, T.; Ihalainen, J. A.; Linko, V. Unraveling the Interaction between Doxorubicin and DNA Origami Nanostructures for Customizable Chemotherapeutic Drug Release. *Nucleic Acids Res.* **2021**, *49*, 3048−3062.

(9) Grossi, G.; Jepsen, M. D. E.; Kjems, J.; Andersen, E. S. Control of Enzyme Reactions by a Reconfigurable DNA Nanovault. *Nat. Commun.* **2017**, *8*, 992.

(10) Ijäs, H.; Hakaste, I.; Shen, B.; Kostiainen, M. A.; Linko, V. Reconfigurable DNA Origami Nanocapsule for pH-Controlled Encapsulation and Display of Cargo. *ACS Nano* **2019**, *13*, 5959−5967.

(11) Liu, S.; Jiang, Q.; Zhao, X.; Zhao, R.; Wang, Y.; Wang, Y.; Liu, J.; Shang, Y.; Zhao, S.; Wu, T.; et al. A DNA Nanodevice-Based Vaccine for Cancer Immunotherapy. *Nat. Mater.* **2021**, *20*, 421−430.

(12) Douglas, S. M.; Bachelet, I.; Church, G. M. A Logic-Gated Nanorobot for Targeted Transport of Molecular Payloads. *Science* **2012**, *335*, 831−834.

(13) Li, S.; Jiang, Q.; Liu, S.; Zhang, Y.; Tian, Y.; Song, C.; Wang, J.; Zou, Y.; Anderson, G. J.; Han, J. Y.; et al. A DNA Nanorobot Functions as a Cancer Therapeutic in Response to a Molecular Trigger In Vivo. *Nat. Biotechnol.* **2018**, *36*, 258−264.

(14) Keller, A.; Linko, V. Challenges and Perspectives of DNA Nanostructures in Biomedicine. *Angew. Chem., Int. Ed.* **2020**, *59*, 15818−15833.

(15) Maune, H. T.; Han, S.-p.; Barish, R. D.; Bockrath, M.; Goddard III, W. A.; Rothemund, P. W. K.; Winfree, E. Self-Assembly of Carbon Nanotubes into Two-Dimensional Geometries Using DNA Origami Templates. *Nat. Nanotechnol.* **2010**, *5*, 61−66.

(16) Sun, W.; Shen, J.; Zhao, Z.; Arellano, N.; Rettner, C.; Tang, J.; Cao, T.; Zhou, Z.; Ta, T.; Streit, J. K.; et al. Precise Pitch-Scaling of Carbon Nanotube Arrays within Three-Dimensional DNA Nanotrenches. *Science* **2020**, *368*, 874−877.

(17) Nummelin, S.; Kommeri, J.; Kostiainen, M. A.; Linko, V. Evolution of Structural DNA Nanotechnology. *Adv. Mater.* **2018**, *30*, 1703721.

(18) Heuer-Jungemann, A.; Liedl, T. From DNA Tiles to Functional DNA Materials. *Trends Chem.* **2019**, *1*, 799−814.

(19) Pilo-Pais, M.; Acuna, G. P.; Tinnefeld, P.; Liedl, T. Sculpting Light by Arranging Optical Components with DNA Nanostructures. *MRS Bull.* **2017**, *42*, 936−942.

(20) Kuzyk, A.; Jungmann, R.; Acuna, G. P.; Liu, N. DNA Origami Route to Nanophotonics. *ACS Photonics* **2018**, *5*, 1151−1163.

(21) Zhao, Y.; Shi, L.; Kuang, H.; Xu, C. DNA-Driven Nanoparticle Assemblies for Biosensing and Bioimaging. *Top. Curr. Chem.* **2020**, *378*, 18.

(22) Vittala, S. K.; Han, D. DNA-Guided Assemblies toward Nanoelectronic Applications. *ACS Appl. Bio Mater.* **2020**, *3*, 2702−2722.

(23) Liu, J. F.; Geng, Y. L.; Pound, E.; Gyawali, S.; Ashton, J. R.; Hickey, J.; Woolley, A. T.; Harb, J. N. Metallization of Branched DNA Origami for Nanoelectronic Circuit Fabrication. *ACS Nano* **2011**, *5*, 2240−2247.

(24) Pearson, A. C.; Liu, J.; Pound, E.; Uprety, B.; Woolley, A. T.; Davis, R. C.; Harb, J. N. DNA Origami Metallized Site Specifically to Form Electrically Conductive Nanowires. *J. Phys. Chem. B* **2012**, *116*, 10551−10560.

(25) Uprety, B.; Jensen, J.; Aryal, B. R.; Davis, R. C.; Woolley, A. T.; Harb, J. N. Directional Growth of DNA-Functionalized Nanorods to Enable Continuous, Site-Specific Metallization of DNA Origami Templates. *Langmuir* **2017**, *33*, 10143−10152.

(26) Aryal, B. R.; Westover, T. R.; Ranasinghe, D. R.; Calvopiña, D. G.; Uprety, B.; Harb, J. N.; Davis, R. C.; Woolley, A. T. Four-Point Probe Electrical Measurements on Templated Gold Nanowires Formed on Single DNA Origami Tiles. *Langmuir* **2018**, *34*, 15069−15077.

(27) Jia, S.; Wang, J.; Xie, M.; Sun, J.; Liu, H.; Zhang, Y.; Chao, J.; Li, J.; Wang, L.; Lin, J.; et al. Programming DNA Origami Patterning with Non-Canonical DNA-Based Metallization Reactions. *Nat. Commun.* **2019**, *10*, 5597.

(28) Li, N.; Shang, Y.; Xu, R.; Jiang, Q.; Liu, J.; Wang, L.; Cheng, Z.; Ding, B. Precise Organization of Metal and Metal Oxide Nanoclusters into Arbitrary Patterns on DNA Origami. *J. Am. Chem. Soc.* **2019**, *141*, 17968−17972.
(29) Zhang, Y.; Qu, Z.-b.; Jiang, C.; Liu, Y.; Pradeep Narayanan, R.; Williams, D.; Zuo, X.; Wang, L.; Yan, H.; Liu, H.; et al. Prescribing Silver Chirality with DNA Origami. *J. Am. Chem. Soc.* **2021**, *143*, 8639−8646.
(30) Pal, S.; Varghese, R.; Deng, Z.; Zhao, Z.; Kumar, A.; Yan, H.; Liu, Y. Site-Specific Synthesis and In Situ Immobilization of Fluorescent Silver Nanoclusters on DNA Nanoscaffolds by Use of the Tollens Reaction. *Angew. Chem., Int. Ed.* **2011**, *50*, 4176−4179.
(31) Pilo-Pais, M.; Goldberg, S.; Samano, E.; LaBean, T. H.; Finkelstein, G. Connecting the Nanodots: Programmable Nanofabrication of Fused Metal Shapes on DNA Templates. *Nano Lett.* **2011**, *11*, 3489−3492.
(32) Schreiber, R.; Kempter, S.; Holler, S.; Schüller, V.; Schiffels, D.; Simmel, S. S.; Nickels, P. C.; Liedl, T. DNA Origami-Templated Growth of Arbitrarily Shaped Metal Nanoparticles. *Small* **2011**, *7*, 1795−1799.
(33) Xue, Y.; Li, X.; Li, H.; Zhang, W. Quantifying Thiol−Gold Interactions Towards the Efficient Strength Control. *Nat. Commun.* **2014**, *5*, 4348.
(34) Athanasiadou, D.; Carneiro, K. M. M. DNA Nanostructures as Templates for Biomineralization. *Nat. Rev. Chem.* **2021**, *5*, 93−108.
(35) Van Bommel, K. J.; Friggeri, A.; Shinkai, S. Organic Templates for the Generation of Inorganic Materials. *Angew. Chem., Int. Ed.* **2003**, *42*, 980−999.
(36) Mann, S. Self-Assembly and Transformation of Hybrid Nano-Objects and Nanostructures Under Equilibrium and Non-Equilibrium Conditions. *Nat. Mater.* **2009**, *8*, 781−792.
(37) Brinker, C. J.; Lu, Y.; Sellinger, A.; Fan, H. Evaporation-Induced Self-Assembly: Nanostructures Made Easy. *Adv. Mater.* **1999**, *11*, 579−585.
(38) Che, S.; Liu, Z.; Ohsuna, T.; Sakamoto, K.; Terasaki, O.; Tatsumi, T. Synthesis and Characterization of Chiral Mesoporous Silica. *Nature* **2004**, *429*, 281−284.
(39) Liu, X.; Zhang, F.; Jing, X.; Pan, M.; Liu, P.; Li, W.; Zhu, B.; Li, J.; Chen, H.; Wang, L.; et al. Complex Silica Composite Nanomaterials Templated with DNA Origami. *Nature* **2018**, *559*, 593−598.
(40) Jing, X.; Zhang, F.; Pan, M.; Dai, X.; Li, J.; Wang, L.; Liu, X.; Yan, H.; Fan, C. Solidifying Framework Nucleic Acids with Silica. *Nat. Protoc.* **2019**, *14*, 2416−2436.
(41) Liu, L.; Zheng, M.; Li, Z.; Li, Q.; Mao, C. Patterning Nanoparticles with DNA Molds. *ACS Appl. Mater. Interfaces* **2019**, *11*, 13853−13858.
(42) Zhou, F.; Sun, W.; Zhang, C.; Shen, J.; Yin, P.; Liu, H. 3D Freestanding DNA Nanostructure Hybrid as a Low-Density High-Strength Material. *ACS Nano* **2020**, *14*, 6582−6588.
(43) Nguyen, L.; Döblinger, M.; Liedl, T.; Heuer-Jungemann, A. DNA-Origami-Templated Silica Growth by Sol−Gel Chemistry. *Angew. Chem., Int. Ed.* **2019**, *58*, 912−916.
(44) Kielar, C.; Xin, Y.; Shen, B.; Kostiainen, M. A.; Grundmeier, G.; Linko, V.; Keller, A. On the Stability of DNA Origami Nanostructures in Low-Magnesium Buffers. *Angew. Chem., Int. Ed.* **2018**, *57*, 9470−9474.
(45) Nguyen, M.-K.; Nguyen, V. H.; Natarajan, A. K.; Huang, Y.; Ryssy, J.; Shen, B.; Kuzyk, A. Ultrathin Silica Coating of DNA Origami Nanostructures. *Chem. Mater.* **2020**, *32*, 6657−6665.
(46) Majewski, P. W.; Michelson, A.; Cordeiro, M. A. L.; Tian, C.; Ma, C.; Kisslinger, K.; Tian, Y.; Liu, W.; Stach, E. A.; Yager, K. G. Resilient Three-Dimensional Ordered Architectures Assembled from Nanoparticles by DNA. *Sci. Adv.* **2021**, *7*, eabf0617.
(47) Michelson, A.; Zhang, H.; Xiang, S.; Gang, O. Engineered Silicon Carbide Three-Dimensional Frameworks through DNA-Prescribed Assembly. *Nano Lett.* **2021**, *21*, 1863−1870.
(48) Shani, L.; Michelson, A. N.; Minevich, B.; Fleger, Y.; Stern, M.; Shaulov, A.; Yeshurun, Y.; Gang, O. DNA-Assembled Superconducting 3D Nanoscale Architectures. *Nat. Commun.* **2020**, *11*, 5697.
(49) Shang, Y.; Li, N.; Liu, S.; Wang, L.; Wang, Z.-G.; Zhang, Z.; Ding, B. Site-Specific Synthesis of Silica Nanostructures on DNA Origami Templates. *Adv. Mater.* **2020**, *32*, 2000294.
(50) He, Y.; Tian, Y.; Chen, Y.; Ye, T.; Mao, C. Cation-Dependent Switching of DNA Nanostructures. *Macromol. Biosci.* **2007**, *7*, 1060−1064.
(51) Zhang, H.; Qu, X.; Chen, H.; Kong, H.; Ding, R.; Chen, D.; Zhang, X.; Pei, H.; Santos, H. A.; Hai, M.; et al. Fabrication of Calcium Phosphate-Based Nanocomposites Incorporating DNA Origami, Gold Nanorods, and Anticancer Drugs for Biomedical Applications. *Adv. Healthcare Mater.* **2017**, *6*, 1700664.
(52) Liu, X.; Jing, X.; Liu, P.; Pan, M.; Liu, Z.; Dai, X.; Lin, J.; Li, Q.; Wang, F.; Yang, S.; et al. DNA Framework-Encoded Mineralization of Calcium Phosphate. *Chem.* **2020**, *6*, 472−485.
(53) Wu, S.; Zhang, M.; Song, J.; Weber, S.; Liu, X.; Fan, C.; Wu, Y. Fine Customization of Calcium Phosphate Nanostructures with Site-Specific Modification by DNA Templated Mineralization. *ACS Nano* **2021**, *15* (1), 1555−1565.
(54) Helmi, S.; Ziegler, C.; Kauert, D. J.; Seidel, R. Shape-Controlled Synthesis of Gold Nanostructures Using DNA Origami Molds. *Nano Lett.* **2014**, *14*, 6693−6698.
(55) Sun, W.; Boulais, E.; Hakobyan, Y.; Wang, W. L.; Guan, A.; Bathe, M.; Yin, P. Casting Inorganic Nanoparticles with DNA Molds. *Science* **2014**, *346*, 1258361.
(56) Bayrak, T.; Helmi, S.; Ye, J.; Kauert, D.; Kelling, J.; Schönherr, T.; Weichelt, R.; Erbe, A.; Seidel, R. DNA-Mold Templated Assembly of Conductive Gold Nanowires. *Nano Lett.* **2018**, *18*, 2116−2123.
(57) Ye, J.; Helmi, S.; Teske, J.; Seidel, R. Fabrication of Metal Nanostructures with Programmable Length and Patterns Using a Modular DNA Platform. *Nano Lett.* **2019**, *19*, 2707−2714.
(58) Ye, J.; Aftenieva, O.; Bayrak, T.; Jain, A.; König, T. A. F.; Erbe, A.; Seidel, R. Complex Metal Nanostructures with Programmable Shapes from Simple DNA Building Blocks. *Adv. Mater.* **2021**, *33*, 2100381.
(59) Jones, M. R.; Seeman, N. C.; Mirkin, C. A. Programmable Materials and the Nature of the DNA Bond. *Science* **2015**, *347*, 1260901.
(60) Macfarlane, R. J.; Lee, B.; Jones, M. R.; Harris, N.; Schatz, G. C.; Mirkin, C. A. Nanoparticle Superlattice Engineering with DNA. *Science* **2011**, *334*, 204−208.
(61) O'Brien, M. N.; Jones, M. R.; Lee, B.; Mirkin, C. A. Anisotropic Nanoparticle Complementarity in DNA-Mediated Co-Crystallization. *Nat. Mater.* **2015**, *14*, 833−839.
(62) Lu, F.; Yager, K. G.; Zhang, Y.; Xin, H.; Gang, O. Superlattices Assembled Through Shape-Induced Directional Binding. *Nat. Commun.* **2015**, *6*, 6912.
(63) Julin, S.; Nummelin, S.; Kostiainen, M. A.; Linko, V. DNA Nanostructure-Directed Assembly of Metal Nanoparticle Superlattices. *J. Nanopart. Res.* **2018**, *20*, 119.
(64) Sun, S.; Yang, S.; Xin, H. L.; Nykypanchuk, D.; Liu, M.; Zhang, H.; Gang, O. Valence-Programmable Nanoparticle Architectures. *Nat. Commun.* **2020**, *11*, 2279.
(65) Tian, Y.; Lhermitte, J. R.; Bai, L.; Vo, T.; Xin, H. L.; Li, H.; Li, R.; Fukuto, M.; Yager, K. G.; Kahn, J.; et al. Ordered Three-Dimensional Nanomaterials Using DNA-Prescribed and Valence-Controlled Material Voxels. *Nat. Mater.* **2020**, *19*, 789−796.
(66) Pauling, L. The Principles Determining the Structure of Complex Ionic Crystals. *J. Am. Chem. Soc.* **1929**, *51*, 1010−1026.
(67) Linko, V.; Kostiainen, M. A. De Novo Nanomaterial Crystals from DNA Frameworks. *Nat. Mater.* **2020**, *19*, 706−707.
(68) Lin, Z.; Emamy, H.; Minevich, B.; Xiong, Y.; Xiang, S.; Kumar, S.; Ke, Y.; Gang, O. Engineering Organization of DNA Nano-Chambers through Dimensionally Controlled and Multi-Sequence Encoded Differentiated Bonds. *J. Am. Chem. Soc.* **2020**, *142*, 17531−17542.
(69) Zhang, T.; Hartl, C.; Fischer, S.; Frank, K.; Nickels, P.; Heuer-Jungemann, A.; Nickel, B.; Liedl, T. 3D DNA Origami Crystals. *Adv. Mater.* **2018**, *30*, 1800273.
(70) Zheng, J.; Birktoft, J. J.; Chen, Y.; Wang, T.; Sha, R.; Constantinou, P. E.; Ginell, S. L.; Mao, C.; Seeman, N. C. From

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX

Molecular to Macroscopic *via* the Rational Design of a Self-Assembled 3D DNA Crystal. *Nature* **2009**, *461*, 74−77.
(71) Gerling, T.; Wagenbauer, K. F.; Neuner, A. M.; Dietz, H. Dynamic DNA Devices and Assemblies Formed by Shape-Complementary, Non-Base Pairing 3D Components. *Science* **2015**, *347*, 1446−1452.
(72) Julin, S.; Korpi, A.; Nonappa; Shen, B.; Liljeström, V.; Ikkala, O.; Keller, A.; Linko, V.; Kostiainen, M. A. DNA Origami Directed 3D Nanoparticle Superlattice *via* Electrostatic Assembly. *Nanoscale* **2019**, *11*, 4546−4551.
(73) Lithography, 2020 Edition. In *IEEE International Roadmap for Devices and Systems (IRDS)*; IEEE, 2020; https://irds.ieee.org/editions/2020/lithography (accessed 10−12−2021).
(74) Surwade, S. P.; Zhou, F.; Wei, B.; Sun, W.; Powell, A.; O'Donnell, C.; Yin, P.; Liu, H. Nanoscale Growth and Patterning of Inorganic Oxides Using DNA Nanostructure Templates. *J. Am. Chem. Soc.* **2013**, *135*, 6778−6781.
(75) Shen, J.; Sun, W.; Liu, D.; Schaus, T.; Yin, P. Three-Dimensional Nanolithography Guided by DNA Modular Epitaxy. *Nat. Mater.* **2021**, *20*, 683−690.
(76) Gopinath, A.; Miyazono, E.; Faraon, A.; Rothemund, P. W. K. Engineering and Mapping Nanocavity Emission *via* Precision Placement of DNA Origami. *Nature* **2016**, *535*, 401−405.
(77) Gopinath, A.; Thachuk, C.; Mitskovets, A.; Atwater, H. A.; Kirkpatrick, D.; Rothemund, P. W. K. Absolute and Arbitrary Orientation of Single-Molecule Shapes. *Science* **2021**, *371*, eabd6179.
(78) Shen, B.; Linko, V.; Tapio, K.; Kostiainen, M. A.; Toppari, J. J. Custom-Shaped Metal Nanostructures Based on DNA Origami Silhouettes. *Nanoscale* **2015**, *7*, 11267−11272.
(79) Shen, B.; Linko, V.; Tapio, K.; Pikker, S.; Lemma, T.; Gopinath, A.; Gothelf, K. V.; Kostiainen, M. A.; Toppari, J. J. Plasmonic Nanostructures Through DNA-Assisted Lithography. *Sci. Adv.* **2018**, *4*, eaap8978.
(80) Piskunen, P.; Shen, B.; Keller, A.; Toppari, J. J.; Kostiainen, M. A.; Linko, V. Biotemplated Lithography of Inorganic Nanostructures (BLIN) for Versatile Patterning of Functional Materials. *ACS Appl. Nano Mater.* **2021**, *4*, 529−538.
(81) Tagawa, M.; Shohda, K.-i.; Fujimoto, K.; Suyama, A. Stabilization of DNA Nanostructures by Photo-Cross-Linking. *Soft Matter* **2011**, *7*, 10931−10934.
(82) Gerling, T.; Kube, M.; Kick, B.; Dietz, H. Sequence-Programmable Covalent Bonding of Designed DNA Assemblies. *Sci. Adv.* **2018**, *4*, eaau1157.
(83) Perrault, S. D.; Shih, W. M. Virus-Inspired Membrane Encapsulation of DNA Nanostructures To Achieve In Vivo Stability. *ACS Nano* **2014**, *8*, 5132−5140.
(84) Julin, S.; Nonappa; Shen, B.; Linko, V.; Kostiainen, M. A. DNA-Origami-Templated Growth of Multilamellar Lipid Assemblies. *Angew. Chem., Int. Ed.* **2021**, *60*, 827−833.
(85) Kiviaho, J. K.; Linko, V.; Ora, A.; Tiainen, T.; Järvihaavisto, E.; Mikkilä, J.; Tenhu, H.; Nonappa; Kostiainen, M. A. Cationic Polymers for DNA Origami Coating − Examining Their Binding Efficiency and Tuning the Enzymatic Reaction Rates. *Nanoscale* **2016**, *8*, 11674−11680.
(86) Agarwal, N. P.; Matthies, M.; Gür, F. N.; Osada, K.; Schmidt, T. L. Block Copolymer Micellization as a Protection Strategy for DNA Origami. *Angew. Chem., Int. Ed.* **2017**, *56*, 5460−5464.
(87) Ponnuswamy, N.; Bastings, M. M. C.; Nathwani, B.; Ryu, J. H.; Chou, L. Y. T.; Vinther, M.; Li, W. A.; Anastassacos, F. M.; Mooney, D. J.; Shih, W. M. Oligolysine-Based Coating Protects DNA Nanostructures from Low-Salt Denaturation and Nuclease Degradation. *Nat. Commun.* **2017**, *8*, 15654.
(88) Anastassacos, F. M.; Zhao, Z.; Zeng, Y.; Shih, W. M. Glutaraldehyde Cross-Linking of Oligolysines Coating DNA Origami Greatly Reduces Susceptibility to Nuclease Degradation. *J. Am. Chem. Soc.* **2020**, *142*, 3311−3315.
(89) Mikkilä, J.; Eskelinen, A.-P.; Niemelä, E. H.; Linko, V.; Frilander, M. J.; Törmä, P.; Kostiainen, M. A. Virus-Encapsulated DNA Origami Nanostructures for Cellular Delivery. *Nano Lett.* **2014**, *14*, 2196−2200.
(90) Auvinen, H.; Zhang, H.; Nonappa; Kopilow, A.; Niemelä, E. H.; Nummelin, S.; Correia, A.; Santos, H. A.; Linko, V.; Kostiainen, M. A. Protein Coating of DNA Nanostructures for Enhanced Stability and Immunocompatibility. *Adv. Healthcare Mater.* **2017**, *6*, 1700692.
(91) Wang, S.-T.; Gray, M. A.; Xuan, S.; Lin, Y.; Byrnes, J.; Nguyen, A. I.; Todorova, N.; Stevens, M. M.; Bertozzi, C. R.; Zuckermann, R. N.; et al. DNA Origami Protection and Molecular Interfacing Through Engineered Sequence-Defined Peptoids. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 6339−6348.
(92) Eklund, A. S.; Comberlato, A.; Parish, I. A.; Jungmann, R.; Bastings, M. M. C. Quantification of Strand Accessibility in Biostable DNA Origami with Single-Staple Resolution. *ACS Nano* **2021**, in press. DOI: 10.1021/acsnano.1c05540.
(93) Shetty, R. M.; Brady, S. R.; Rothemund, P. W. K.; Hariadi, R. F.; Gopinath, A. Bench-Top Fabrication of Single-Molecule Nanoarrays by DNA Origami Placement. *ACS Nano* **2021**, *15*, 11441−11450.
(94) Xin, Y.; Shen, B.; Kostiainen, M. A.; Grundmeier, G.; Castro, M.; Linko, V.; Keller, A. Scaling Up DNA Origami Lattice Assembly. *Chem. - Eur. J.* **2021**, *27*, 8564−8571.
(95) Ong, L. L.; Hanikel, N.; Yaghi, O. K.; Grun, C.; Strauss, M. T.; Bron, P.; Lai-Kee-Him, J.; Schueder, F.; Wang, B.; Wang, P.; et al. Programmable Self-Assembly of Three-Dimensional Nanostructures from 10,000 Unique Components. *Nature* **2017**, *552*, 72−77.
(96) Athanasiadou, D.; Carneiro, K. M. M. DNA Nanostructures as Templates for Biomineralization. *Nat. Rev. Chem.* **2021**, *5*, 93−108.
(97) Praetorius, F.; Kick, B.; Behler, K. L.; Honemann, M. N.; Weuster-Botz, D.; Dietz, H. Biotechnological mass production of DNA origami. *Nature* **2017**, *552*, 84−87.
(98) Shalaev, V. M. Optical Negative-Index Metamaterials. *Nat. Photonics* **2007**, *1*, 41−48.
(99) Choi, M. K.; Yang, J.; Hyeon, T.; Kim, D.-H. Flexible Quantum Dot Light-Emitting Diodes for Next-Generation Displays. *npj Flex. Electron.* **2018**, *2*, 10.

https://doi.org/10.1021/acscentsci.1c01272
ACS Cent. Sci. XXXX, XXX, XXX−XXX