Designer 3D DNA polyhedra for biomedical applications

Dhiraj Bhatia, PhD
Institute Curie, Centre de Recherche, U1143/UMR3666, INSERM/Curie/CNRS,
26 rue d'Ulm, 75248 Paris Cedex 05, France
Email: dhiraj.bhatia@curie.fr

Abstract: Structural DNA nanotechnology explores various nanoscale structural and functional properties of DNA to develop probes at nanoscale for diverse applications. Three dimensional architectures based on DNA like various polyhedra, boxes, and DNA-based dendrimers, have raised particular interest in biomedical applications. Some of these DNA architectures have been recently explored as nano containers for functional molecules and as molecular scaffolds to site specifically display biological ligands. Such DNA nanostructures have been demonstrated to interact with cell-surface markers and trigger signalling pathways in biological systems via specific targets. These recent studies highlight the emerging potential of DNA devices in biomedical applications that could enable targeted delivery of molecular payloads within living systems.
Keywords: DNA Nanotechnology, 3D polyhedra, bioimaging, biomedical applications

Introduction

The last decade witnessed the emergence of DNA in a new function — a scaffolding material that can be moulded into architectures on the nanoscale. DNA possesses key chemical properties that confer it with power to be used for nanoscale construction (1) DNA can be chemically produced using automated chemical methods by high throughput and combinatorial approaches; (2) it possesses chemical robustness that provides stability on the architectures, enabling their functionality under diverse environmental and cellular conditions; (3) DNA has uniform and periodic double helical nature independent of its primary sequence; (4) the thermal stability of different sequences of DNA can be easily predicted; (5) thus its possible and feasible to program interaction hierarchies into base pairing of DNA nucleotides resulting in site-specific molecular associations within a given architecture; (6) different biochemical and molecular biological tools are available to manipulate DNA sequences specifically; thus allowing controlled tailoring of various DNA sequences and structures; (7) DNA units are modular in nature; and (8) certain sequences of single-stranded DNA called aptamers can bind to a range of molecules with high specificity and affinities. Multiple DNA units can thus be combined in a programmed manner to construct various complex nanostructures both structurally and functionally. This science, which utilizes DNA as construction material for self-assembly at the nanoscale is termed as structural DNA nanotechnology (Modi et al. 2010).

Structural DNA nanotechnology creates nanoarchitectures like (a) static or rigid DNA scaffolds, 1D wires, tubes, 2D sheets, tiles and crystals, 3D polyhedra, DNA crystals, boxes and (b) dynamic DNA systems, nanomachines, robots, walkers, and sensors (Bhatia et al. 2011a, b; Krishnan and Simmel 2011). Most of these devices are assembled using short segments of DNA either directly or through smaller modules that undergo self-assembly in a programmed manner into a well-defined nano-architecture. Recent development in the field utilizes single long strand of DNA, such as a viral genome that folds into various shapes in presence of hundreds of shorter single strands called staple strands. This approach called DNA origami has been explored to construct panoply of complex and functional architectures (Sacca and

Neimeyer 2012) (**Fig. 1**). This review focuses on molecularly identical and structurally well-defined 3D designer nucleic acid-based devices for their applications in nanomedicine and biomedical applications.

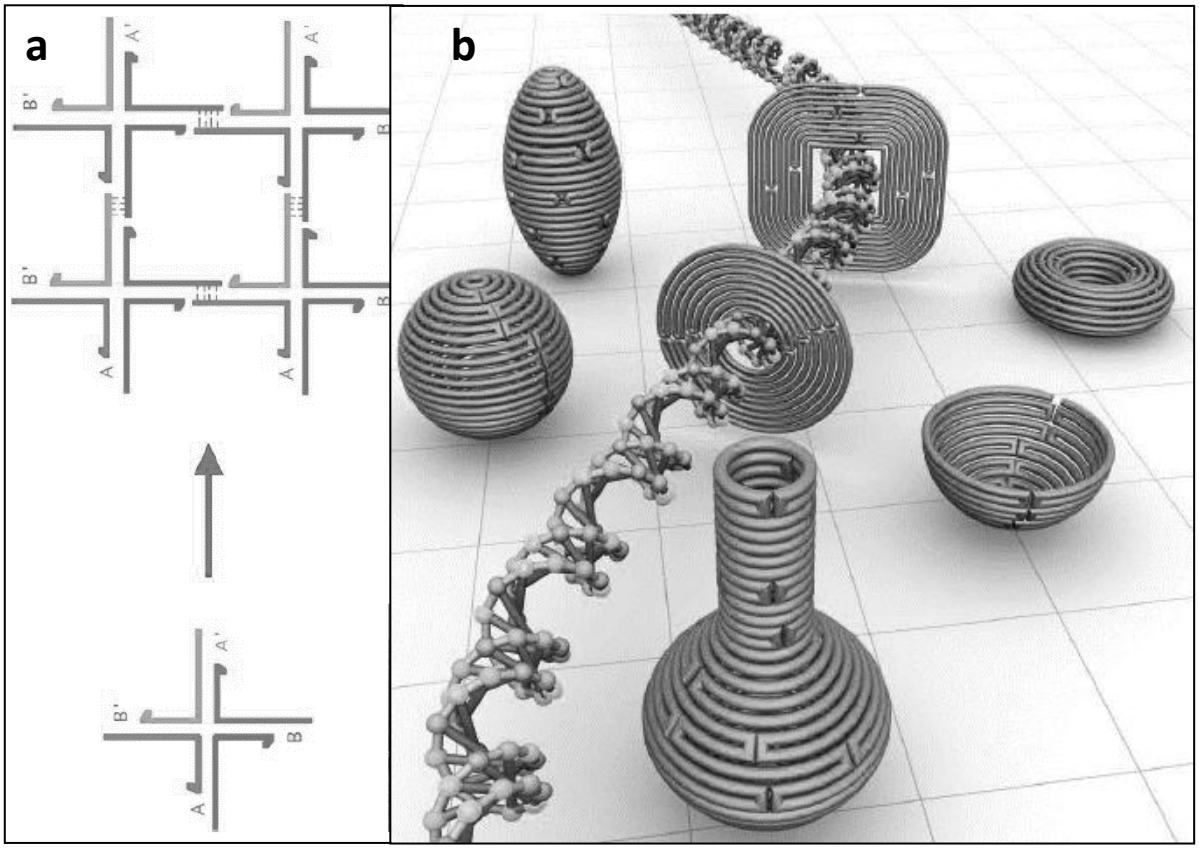

Fig. 1. Structural DNA Nanotechnology – DNA can act as rigid rod upto the distances of 50 nm and different sequences of DNA can self-assemble with each other by specific Watson-Crick base pairing (**a**). Exploring these properties, various nanoscale architectures can be created into 1, 2 and 3D respectively. An example of various 2D and 3D architectures built using DNA origami is represented in **1b**.

DNA based 3D Polyhedra

For any scaffold to be used for biomedical applications, it should possess the ability to create molecularly addressable, well-defined structures along with the capacity to be connected with other functional molecules Thus, a preliminary beginning of this aspect in this field was the creation of DNA-based structures that could entrap external useful cargo like drug molecules or therapeutic proteins within their cavity. In 1991, the first 3D polyhedron made from DNA was realized by Seeman and co-workers, who formed a complex using six strands of DNA that possessed the molecular connectivity of a cube, even though with extremely low yield (Chen and Seeman 1991). The main aim of this work was to create DNA based 3D periodic meshwork which could entrap protein molecules within its cavities and thus enhance 3D protein crystallography. This was followed by the creation of a truncated octahedron using similar strategy, thus failing to get these structures in higher yields (Zhang and Seeman 1994). A DNA tetrahedron was constructed in quantitative yields using a simple strategy of combining four DNA oligonucleotides to self-assemble together in one pot assembly in 2005. This structure was the first to be topologically characterized using AFM, providing visual evidence of the formation of DNA polyhedra (Goodman et al. 2005). Shih et al.

designed a DNA octahedron using a 1.8-kb DNA and smaller staple oligonucleotides. This approach served as a precursor to the more well-known DNA "origami" method, in which a long single strand of DNA is folded into well-defined shapes using several shorter DNA strands (Shih et al. 2004). DNA origami was later exploited to make 3D polyhedra like icosahedron (Douglas et al. 2009). The origami methodology was further explored to construct a cuboidal box by using six copies of the genomic DNA of M13 bacteriophage (Andersen et al. 2009). The controlled opening and release of internally attached molecules was also demonstrated using a DNA origami-based 3D robotic device (Douglas et al. 2012). All these techniques were based on folding of DNA oligonucleotides in 3D space to create polyhedra. An alternative approach was developed in 2007, which used small molecules as mimics of DNA junctions, the DNA strands were covalently conjugated together to form DNA–small molecule junctions, which are stable and prefolded in a defined confirmation. Using such small molecule-DNA based junctions, various DNA polyhedra like cubes, octahedra, and prisms were constructed (Aldaye and Sleiman 2007). In 2008, a general self-assembly based strategy was developed to programmably polymerize DNA junctions into symmetric polyhedra based on platonic solids (He et al. 2008) (**Fig. 2**).

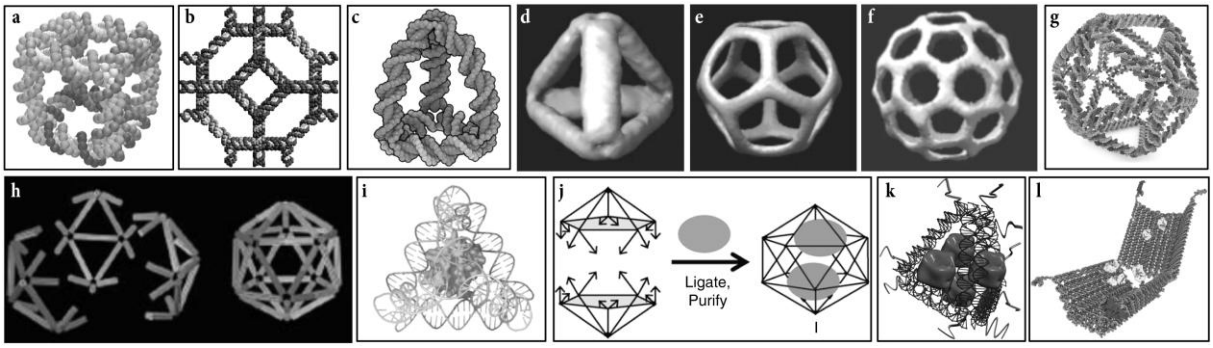

Fig. 2. *DNA based 3D polyhedra*. Various DNA based platonic solids like 3D polyhedra have been synthesized and characterized using various approaches and techniques (a. cube, b,e. octahedron, c,d. tetrahedron, f,g,h. icosahedron). Some of these polyhedra have been characterized in terms of their ability to encapsulate external cargo (i. protein encapsulated within DNA tetrahedron, j. nanoparticles encapsulated within DNA icosahedron, k. protein encapsulated within DNA tetrahedron) as well as surface conjugation to different ligands like CpG motifs (k) as well as antibodies (l).

DNA Polyhedra with functionalities

Most polyhedra postulated to have many applications in areas including drug delivery, biomolecular organization, bioreactors, etc. (Zhang et al. 2009; Aldaye et al. 2008). All these applications were based on two key properties of DNA polyhedra: they could encapsulate various cargos within their cavities, and that the surface of DNA can be modified with various tags at specific sites. Despite these properties of DNA, the applications of DNA polyhedra have been much less explored. Entrapment of molecular cargo within DNA polyhedra has been explored to some extent. A protein like cytochrome C was covalently attached to one arm of a DNA tetrahedron and it was demonstrated to be site specifically positioned on the tetrahedron in such a way that it faced the interior of the polyhedron and positioned itself in the internal cavity of a DNA tetrahedron (Erben et al. 2006). Using the same strategy, different antibodies and nanoparticles have been accommodated within a DNA origami box (Douglas et al.

2012). This strategy is extremely limited covalent attachment of the cargo to the host in such a way that the cargo is facing inwards and positioned in the inner cavity of these polyhedra. This strategy is limited by two major problems - the number of cargoes to be entrapped is restricted to the number of sites at DNA edges facing inwards, and more number of DNA strands need to be modified to maximize encapsulation efficiencies and yields. Release of such covalently encapsulated cargo also remains to be addressed.

The ability of any polyhedra to entrap external cargo lies in its capacity to trap freely diffusing cargo from external solution while polyhedron is formed, within its internal volume without chemical attachment of the cargo to the host. Such physical encapsulation of cargo without modifying its structure within a polyhedron can overcome all the previous limitations and can entrap different types of cargoes in high yields in bulk.

Using a modular self-assembly methodology, a DNA icosahedron was assembled in quantitative yields (Bhatia et al, 2009). This strategy of construction is much feasible than others since it offers several advantages - the icosahedron can be assembled from two halves, which resemble two prefolded cup-shaped half icosahedra. These two halves can be joined together in presence of excess of external cargo in solution, leading to formation of icosahedron with the cargo trapped inside the icosahedral cavity. It was shown that DNA polyhedra like icosahedra can entrap various cargoes like inorganic gold nanoparticles, or organic polymers like FITC-dextrans (Bhatia et al. 2009, 2011a, b).

Along with its applications in its utilization for delivery of encapsulated cargo cell type specifically, some parallel applications of cargo-loaded DNA icosahedra also emerged in terms of functional *in vivo* imaging. The latter ability can have many applications in nanomedicine and biomedical applications since it employs the like target detection and quantitative reporting. A range of cargo encapsulated within smart DNA polyhedra can be envisaged for various bioimaging applications such as paramagnetic nanoparticles, radioactive probes as along with fluorescent chemical probes. Polyhedra carrying imaging agents can be targeted to specific tissues *in vivo* and various techniques can be explored for functional and quantitative bioimaging like X-ray, MRI, CT, PET, SPECT, or fluorescence-based tomography. As an example, DNA tetrahedra carrying siRNAs and conjugated to folic acid, labelled with fluorophores when injected in mice were targeted to tumours with minimal accumulation in other bodily organs and tissues (Lee et al. 2012).

Apart from carrying cargoes within their encapsulable volumes, DNA polyhedra also possess well defined external 3D surfaces that can be modified at specific sites with various biomolecules, nanoparticles, etc. using chemical conjugation procedures (Martin et al.). This is extremely important and desired since DNA polyhedra carrying payloads can be surface modified by various targeting moieties that can target the cages along with encapsulated cargo to specific target tissues or organs in living organisms. As an example, DNA tetrahedron was realized with hairpins extending outwards from the edges of the tetrahedron. These hairpins can function as aptamers to recognize and bind various analytes (molecules or receptors) in solution or on the surface of cells (Zhang et al. 2010). Tetrahedra conjugated to CpG motifs inducing immune stimulatory response in cells were also extended outwards from each of the tetrahedral vertices (Li et al. 2011). Exploring a similar approach, an icosahedron was designed to carry at each of its vertices, aptamers against the MUC1 protein present on tumour cells (Chang et al. 2011). In a complimentary approach, Lee

et al. incorporated siRNA duplexes protruding outwards from the middle of a DNA tetrahedron (Lee et al. 2012) (**Fig. 2**).

Biological applications of 3D DNA polyhedra

The applications of DNA polyhedra, even though discovered in 1991, had not been explored to its full capacity. Cargo loaded DNA icosahedra were shown to be uptaken in living cells and *in vivo* by Bhatia et al. (2011a, b). A fluorescent biopolymer like FITC-dextran was encapsulated within DNA icosahedron and it was observed that these, host–cargo complexes were endocytosed by cellular systems like *Drosophila* hemocytes. These complexes were further microinjected into an *in vivo* model C. elegans, where they were taken up specifically by coelomocytes (Bhatia et al. 2011a, b). FITC-dextran is an established reagent for pH measurements in biological systems (Thomas et al. 1979). This work also demonstrated that the functionality of the encapsulated FITC-dextran remains unaffected in cells and in vivo, in terms of its pH sensing ability in the context of endosomal maturation. These initial findings have direct implications in delivery applications where drug-loaded DNA polyhedra can be targeted to tissues and organs in living organisms by modifying the surface properties of DNA polyhedra with targeting ligands.

Other DNA devices like DNA tetrahedra and nanotubes were similarly shown to be uptaken by cells like HEK (human embryonic kidney cells) and HeLa cells respectively (Walsh et al. 2011; Hamblin et al. 2012). A DNA icosahedron, surface modified with aptamers for MUC1 – a marker for tumor surfaces was realized. Doxorubicin was loaded within this polyhedron by nucleobase intercalation. These drug loaded, aptamer decorated icosahedra were uptaken by cancer cells and induced cell death (Chang et al. 2011). A complimentary strategy for delivery using DNA polyhedra was developed using CpG motif carrying therapeutic aptamers connected from the vertices of a DNA tetrahedron. Toll-like receptors present on the cell surface recognize these CpG motifs carrying aptamers, which induce immunostimulatory effects within cells (Li et al. 2011; Schuller et al. 2011). A significant breakthrough was achieved in terms of DNAs ability for delivery, when a DNA tetrahedra were developed for targeted siRNA delivery within living organisms like mice (Lee et al. 2012). The engineered tetrahedra carry extra siRNA containing duplex arms connected to tetrahedra and protruding from its edges. One strand on the duplex was the drug/siRNA while the other strand was conjugated to a targeting motif - folate. When injected within tumor carrying mice, these structures showed specific targeting to tumors without accumulation in other organs and the siRNA effect was seen. In order to develop DNA platform-based,

vaccines

the DNA tetrahedron was conjugated to streptavidin as an antigen and CpG deoxynucleotides as adjuvant. This complex when injected in mice showed the increase immune response toward streptavidin as compared to the immune response against free streptavidin as antigen (Liu et al. 2012) (**Fig. 3**).

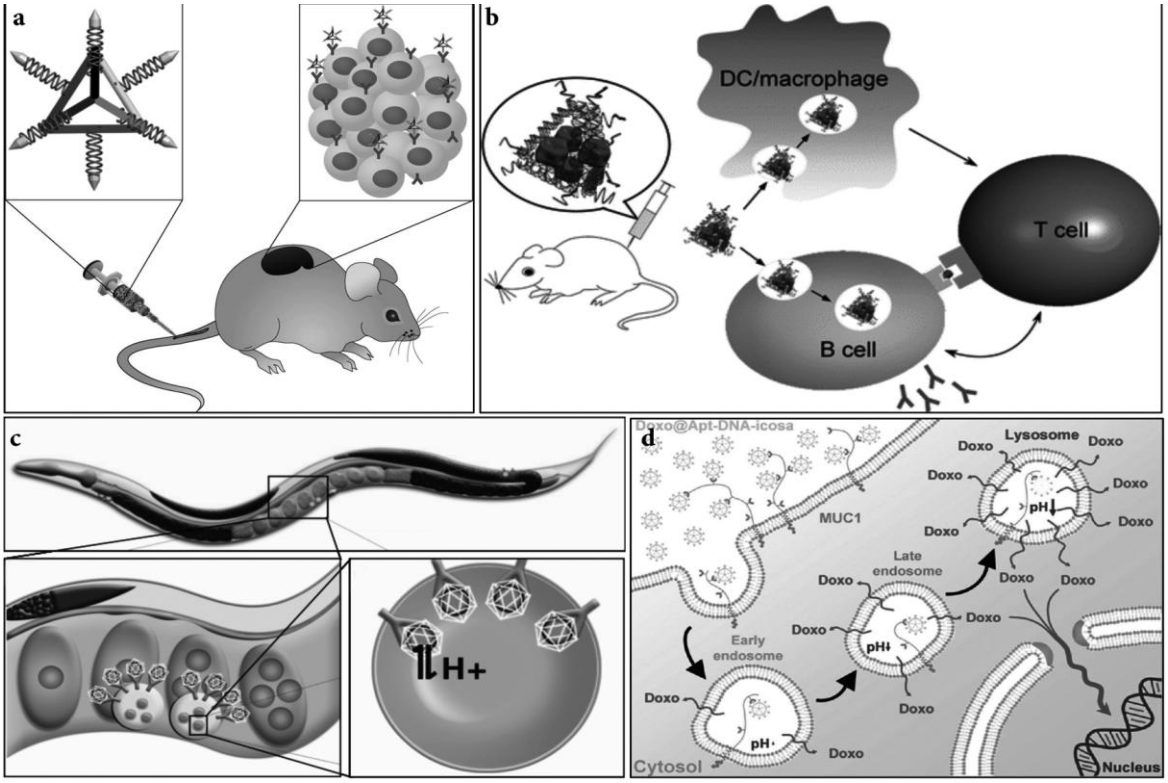

Fig. 3. *Biological applications of DNA polyhedra.* a, folate conjugated siRNA loaded DNA tetrahedra for targeted delivery of siRNA to tumours in mice. b, CpG motifs conjugated DNA tetrahedra carrying streptavidin to induce immune response in mice, c. FITC dextran encapsulated DNA icosahedra for functional pH bioimaging of coelomocytes in *C. elegans*, d. Doxorubicin loaded, aptamer conjugated DNA icosahedra for controlled drug delivery in cancer cells.

Conclusions and future perspectives

DNA-based designer nano-architectures hold substantive potential in nanomedicine and related biomedical applications (Pinheiro et al. 2011). The advantages offered by DNA in control over structure and the site-specific tailorability of the scaffold is generalizable to panoply of molecules and currently is unsurpassable by any other scaffolds. DNA nanodevices have very promising applications in biomedical sciences. However, there are still limitations before these are utilized for pharmaceutical scales i.e. there is a long journey to go before these devices can make up from bench side to bed side. The biggest limitation that restricts unlimited applications of DNA nanodevices in biology is that DNA is not targetable. The language of cells and tissues has been written in the codes of proteins and not DNA. Thus, DNA needs to be interfaced with various protein players to make them compatible for the biological applications. The chemistry of creating the interface between DNA and other biomolecules like proteins, lipids and sugars is still a biggest limitation of DNA devices in biomedical applications, which has been reflected by just a handful of publications of biological applications despite hundreds of reports of construction and characterization of DNA devices. The key challenges for DNA devices for being used as commercial delivery or diagnostic agents are: 1. The stability of DNA devices in biological systems – resistance to nucleases, 2. Strict control over targeting these devices to specific tissues without off target effects, 3. Control over release of entrapped cargo

at target sites, 4. Scaling up the synthesis of DNA components, 5. Costs of synthesis and alternatives to the backbones to increase flexibility and stability, 6. Immunogenic response from the DNA devices itself. Various alternative strategies are currently being developed to address these above challenges and to develop clean DNA devices for applications. For example, the scaling up of simple DNA structures was demonstrated by amplifying key DNA components from bacteria (Lin et al. 2008). The purified components were shown to self-assemble into well-defined polyhedra like tetrahedra in higher quantities (Li et al. 2009). Thus, using bacterial or cellular replication, it can be possible to scale up the synthesis of various components needed for DNA self-assembly into nanopolyhedra. Once internalized and targeted to the site of release in biological systems, the controlled release of a drug can be achieved by opening these polyhedra or by conformational change induced through an external stimulus. DNA polyhedra were shown to change their shapes in vitro in response to external DNA strands (Goodman et al. 2008; Aldaye and Sleiman 2007). Alternatively, DNA intercalating molecular drugs can either be intercalated within the DNA components of these structures or the DNA arms themselves can be used as drugs like siRNA (Schuller et al. 2011; Zhang et al. 2012). In this regard, the DNA pyramids with a loop in one of the arms were realized. The single-stranded region of the loop could function as siRNA against a target mRNA and its activity was demonstrated *in vitro* as well as in cells (Keum et al. 2011). Small cellular RNA molecules like microRNAs could function as structural transition triggers for such nanocarriers. A DNA box could be opened or closed upon addition of an external DNA strand (Andersen et al. 2009). This idea can be further exploited by utilizing cellular miRNAs as the keys to the opening of such boxes in cells. Similarly, Douglas et al. designed a DNA box with "aptamers keys," which could open the box upon sensing ligands on the cell surface (Douglas et al. 2012) leading to release of internal, encapsulated antibodies. The stability of DNA skeleton itself within the biological milieu is another major challenge, as most nucleic acids are prone to degradation by nucleases. DNA origami arrays were recently developed that are extremely stable in cell lysates, thus displaying the resistance of DNA polyhedra to nucleases in biological systems (Mei et al. 2011). Combined together, DNA-based nano-architectures offer an extremely powerful tool to develop targetable drug delivery systems for future applications not only in nanomedicine but for many closely related biomedical applications like sensing, diagnostics and immunotherapy. Given the reducing costs of DNA synthesis and the enhancement in efficiency and error free (homogeneous) formation of DNA nanostructures, the future offers interesting avenues for this bio-application of nanotechnology.

Acknowledgements

I thank Institute Curie and HFSP for long-term postdoctoral fellowships. Also, useful discussions with Prof. Yamuna Krishnan and Prof. Ludger Johannes are duly acknowledged.

References

• Aldaye FA, Sleiman HF (2007) Modular access to structurally switchable 3D discrete DNA assemblies. J Am Chem Soc 129:13376–13377 http://dx.doi.org/10.1021/ja075966q PMCid:PMC3092387

• Aldaye FA, Palmer AL, Sleiman HF (2008) Assembling materials with DNA as the guide. Science 321:1795–1799 http://dx.doi.org/10.1126/science.1154533 PMCid:PMC3092387

• Andersen FF, Knudsen B, Oliveira CL et al (2008) Assembly and structural analysis of a covalently closed nano-scale DNA cage. Nucleic Acids Res 36:1113–1119 http://dx.doi.org/10.1093/nar/gkm1124

• Andersen ES, Dong M, Nielsen MM et al (2009) Self-assembly of a nanoscale DNA box with a controllable lid. Nature 459:73–76 http://dx.doi.org/10.1038/nature07971

• Bhatia D, Mehtab S, Krishnan R et al (2009) Icosahedral DNA nanocapsules by modular assembly. Angew Chem Int Ed 48:4134–4137 http://dx.doi.org/10.1002/anie.200806000 PMid:19222079

• Bhatia D, Sharma S, Krishnan Y (2011a) Synthetic, biofunctional nucleic acid-based molecular devices. Curr Opin Biotechnol 22:475–484 http://dx.doi.org/10.1016/j.copbio.2011.05.004 PMid:21652202

• Bhatia D, Surana S, Chakraborty S et al (2011b) A synthetic icosahedral DNA-based host-cargo complex for functional in vivo imaging. Nat Commun 2:339 http://dx.doi.org/10.1038/ncomms1337 PMid:21654639

• Chang M, Yang CS, Huang DM (2011) Aptamer-conjugated DNA icosahedral nanoparticles as a carrier of doxorubicin for cancer therapy. ACS Nano 5:6156–6163 http://dx.doi.org/10.1021/nn200693a

• Chen J, Seeman NC (1991) Synthesis from DNA of a molecule with the connectivity of a cube. Nature 350:631–633 http://dx.doi.org/10.1038/350631a0

• Douglas SM, Dietz H, Liedl T et al (2009) Self-assembly of DNA into nanoscale three- dimensional shapes. Nature 459:414–418 http://dx.doi.org/10.1038/nature08165

http://dx.doi.org/10.1038/nature08016

• Douglas SM, Bachelet I, Church GM (2012) A logic-gated nanorobot for targeted transport of molecular payloads. Science 335:831–834 http://dx.doi.org/10.1126/science.1214081

• Erben CM, Goodman RP, Turberfield AJ (2006) Single-molecule protein encapsulation in a rigid DNA cage. Angew Chem Int Ed 45:7414–7417 http://dx.doi.org/10.1002/anie.200603392 PMid:17086586

• Goodman RP, Schaap IAT, Tardin CF et al (2005) Rapid chiral assembly of rigid DNA building blocks for molecular nanofabrication. Science 310:1661–1665 http://dx.doi.org/10.1126/science.1120367

• Goodman RP, Heilemann M, Doose S et al (2008) Reconfigurable, braced, three-dimensional DNA nanostructures. Nat Nanotechnol 3:93–96 http://dx.doi.org/10.1038/nnano.2008.3

• Hamblin GD, Carneiro KM, Fakhoury JF et al (2012) Rolling circle amplification-templated DNA nanotubes show increased stability and cell penetration ability. J Am Chem Soc 134:2888–2891 http://dx.doi.org/10.1021/ja301573b http://dx.doi.org/10.1021/ja2107492

• He Y, Ye T, Su M et al (2008) Hierarchical self-assembly of DNA into symmetric supramolecular polyhedra. Nature 452:198–201 http://dx.doi.org/10.1038/nature06597

• Keum JW, Ahn JH, Bermudez H (2011) Design, assembly, and activity of antisense DNA nanostructures. Small 7:3529–3535 http://dx.doi.org/10.1002/smll.201101804

• Ko S, Liu H, Chen Y et al (2008) DNA nanotubes as combinatorial vehicles for cellular delivery. Biomacromolecules 9:3039–3043 http://dx.doi.org/10.1021/bm800479e

• Krishnan Y, Simmel FC (2011) Nucleic acid based molecular devices. Angew

Chem Int Ed 50:3124–3156 http://dx.doi.org/10.1002/anie.200907223 PMid:21432950

•Lee H, Lytton-Jean AKR, Che Y et al (2012) Molecularly self-assembled nucleic acid nanoparticles for targeted in vivo siRNA delivery. Nat Nanotechnol 7:389–393 http://dx.doi.org/10.1038/nnano.2012.73

• Li Z, Wei B, Nangreave J et al (2009) A replicable tetrahedral nanostructure self-assembled from a single DNA strand. J Am Chem Soc 131:13093–13098 http://dx.doi.org/10.1021/ja903768f

• Li J, Pei H, Zhu B et al (2011) Self-assembled multivalent DNA nanostructures for noninvasive intracellular delivery of immunostimulatory CpG oligonucleotides. ACS Nano 5:8783–8789 http://dx.doi.org/10.1021/nn202774x

• Lin C, Rinker S, Wang X et al (2008) In vivo cloning of artificial DNA nanostructures. Proc Natl Acad Sci USA 105:17626–17631 http://dx.doi.org/10.1073/pnas.0805416105

• Liu X, Xu Y, Yu T et al (2012) A DNA nanostructure platform for directed assembly of synthetic vaccines. Nano Lett 12:4254–4259 http://dx.doi.org/10.1021/nl301877k

• Lo PK, Karam P, Aldaye FA et al (2010) Loading and selective release of cargo in DNA nanotubes with longitudinal variation. Nat Chem 2:319–328 http://dx.doi.org/10.1038/nchem.575 PMid:21124515

• Martin E, Herdewijn P, Matusda A et al (eds) Curr Protoc Nucleic Acid Chem. doi:10.1002/ 0471142700

• Mei Q, Wei X, Su F (2011) Stability of DNA origami nanoarrays in cell lysate. Nano Lett 11:1477–1482 http://dx.doi.org/10.1021/nl1040836

• Modi S, Bhatia D, Simmel FC et al (2010) Structural DNA nanotechnology: from bases to bricks, from structure to function. J Phys Chem Lett 1:1994–2005 http://dx.doi.org/10.1021/jz1004957

• Pinheiro V, Han D, Shih WM et al (2011) Challenges and opportunities for structural DNA nanotechnology. Nat Nanotechnol 6:763–772 http://dx.doi.org/10.1038/nnano.2011.187

• Sacca B, Neimeyer CM (2012) DNA origami: the art of folding DNA. Angew Chem Int Ed 51:58–66 http://dx.doi.org/10.1002/anie.201105846 PMid:22162047

• Schu¨ller VJ, Heidegger S, Sandholzer N et al (2011) Cellular immunostimulation by CpG- sequence-coated DNA origami structures. ACS Nano 5:9696–9702 http://dx.doi.org/10.1021/nn203161y PMid:22092186

• Shih WM, Quispe JD, Joyce GF (2004) A 1.7-kilobase single-stranded DNA that folds into a nanoscale octahedron. Nature 427:618–621 http://dx.doi.org/10.1038/nature02307

• Thomas JA, Buchsbaum RN, Zimniak A et al (1979) Intracellular pH measurements in Ehrlich ascites tumor cells utilizing spectroscopic probes generated in situ. Biochemistry 18:2210–2218 http://dx.doi.org/10.1021/bi00578a012

• Walsh AS, Yin H, Erben CM et al (2011) DNA cage delivery to mammalian cells. ACS Nano 5:5427–5432 http://dx.doi.org/10.1021/nn2005574

• Zhang J, Seeman NC (1994) Construction of DNA-trucated octahedron. J Am Chem Soc 116:1661–1669 http://dx.doi.org/10.1021/ja00084a006

• Zhang C, He Y, Su M et al (2009) DNA self-assembly: from 2D to 3D. Faraday Discuss 143:221–233 http://dx.doi.org/10.1039/b905313c

• Zhang C, Su M, He Y et al (2010) Exterior modification of a DNA tetrahedron. Chem Commun 46:6792–6794
http://dx.doi.org/10.1039/c0cc02363a
PMid:20730149

• Zhang C, Tian C, Guo F et al (2012) DNA-directed three-dimensional protein organization. Angew Chem Int Ed 51:3382–3385
http://dx.doi.org/10.1002/anie.201108710
PMid:22374892

• Zhao Z, Jacovetty EL, Liu Y et al (2011) Encapsulation of gold nanoparticles inside a DNA origami cage. Angew Chem Int Ed 50:2041–2044
http://dx.doi.org/10.1002/anie.201006818
PMid:21344547 PMCid:PMC3083863

• Zimmermann J, Cebulla MP, Mo¨nninghoff S et al (2008) Self-assembly of a DNA dodecahedron from 20 trisoligonucleotides with C(3 h) linkers. Angew Chem Int Ed 47:3626–3630
http://dx.doi.org/10.1002/anie.200702682
PMid:18383496