# Nanoparticles Caged with DNA Nanostructures

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## Abstract

Nanoparticles (NPs) offer many benefits in biotechnology because of their small size and unique properties. However, many applications require precise positioning of the NPs or biological targeting molecules on their surfaces. DNA cages constructed from DNA tile, origami, or wireframe nanostructures offer a promising path forward because of their simplicity and programmability that can be used to generate complex, dynamic 2D and 3D geometries. Such materials can be used to pattern DNA on NP surfaces and organize NPs into specific supramolecular structures. DNA-caged NPs can be implemented in biosensing and drug delivery applications with cavities precisely designed to encapsulate specific biomolecules. Ultimately, such approaches provide a springboard for future DNA robot designs that will enable controlled interactions with biological systems.

## Introduction

Inorganic nanoparticles (NPs) have unique properties because of their small size, which allows access to features of the quantum regime and increases atomic behaviors associated with surface states at their high surface to volume ratio. Properties such as surface plasmon resonance (SPR), surface enhanced Raman scattering (SERS), size-dependent fluorescence, and superparamagnetism have been exploited in biotechnology for sensing, bioseparations, drug discovery and therapeutic interventions [1]. Nucleic acid-NP hybrid materials in particular offer great promise in the burgeoning genomics and gene therapy fields. For example, gold nanoparticles (AuNPs) are abundantly used as quenchers in molecular beacon assays for nucleic acid detection, as delivery agents for gene therapy, and in Förster Resonance Energy Transfer (FRET)-based theranostics that combine sensing and delivery [2].

Concomitant with the advance of NPs in nucleic acid detection and therapies, deoxyribonucleic acid (DNA) nanotechnology has emerged as a powerful force in realizing materials with diverse and programmable architectures. Composed of only four repeating bases that pair via a defined number of hydrogen bonds, DNA is a simple, but powerful, structural material. DNA displays different stiffness in its double- vs. single- stranded forms, enabling regional tuning of material properties and local flexibility. DNA nanostructures can be used to strengthen materials [3], form complex geometries [4], and template NP growth [5,6]. Dynamic DNA nanostructures can be realized through incorporation of more flexible single-stranded regions and “toe-holds” that detach from neighboring strands to hybridize to a more complimentary added strand [7].

In the last decade, the convergence of these two fields has sparked research in DNA-NP composites. DNA has been used to organize NPs [8], control their separation distance [9], and actuate their presentation to external targets [10]. These enabling technologies are opening new doors in sensing [11] and treatment [12]. DNA nanostructure-NP hybrid materials have been reviewed elsewhere [13,14]. However, within the last five years, there has been increasing emphasis on hybrids in which DNA nanostructures are used to encapsulate, or “cage”, NPs (for an excellent review on DNA nanostructures cage materials see [15] or [16]**. Caging offers several advantages to traditional DNA bioconjugation methods (reviewed in [17]) in that DNA can be precisely patterned on the NP surface. The use of complex nanostructures also enables reconfigurable materials in which NPs can be selectively presented to the external environment. This review will examine types of DNA cage nanostructures, methods of integrating DNA cages with NPs and biomolecules to form hybrid materials, and application of those materials in DNA patterning, and biomedical sensing, delivery, and theranostics.

**DNA Nanostructures**

Integration of DNA and NPs emerged from initial studies pioneered by Shultz [18] and Mirkin [8] in which short single-stranded DNA (ssDNA) sequences were used to form NP composites through duplexing (Figure 1A). However, the assemblies generated were limited by the short sequence length employed and lack of ability to pattern DNA on NP surfaces. Reconfiguration primarily focused on assembly and disassembly functions. In contrast, DNA nanostructures comprised of DNA tiles, origamis, or wireframes provide much greater control. DNA tiles, originally conceived by Seeman [19], are small repeating units that assemble into a larger structure (Figure 1B). DNA origami, originally realized by Rothemund [4], involves folding a circular DNA strand into specific shapes using shorter “staple” strands (Figure 1C). DNA wireframes are a specialized form of DNA origami in which designs are generated computationally using a mesh to represent the shape and then routing scaffolding to achieve that shape through specialized algorithms (Figure 1D). All of these approaches can be used to generate DNA caging nanostructures.

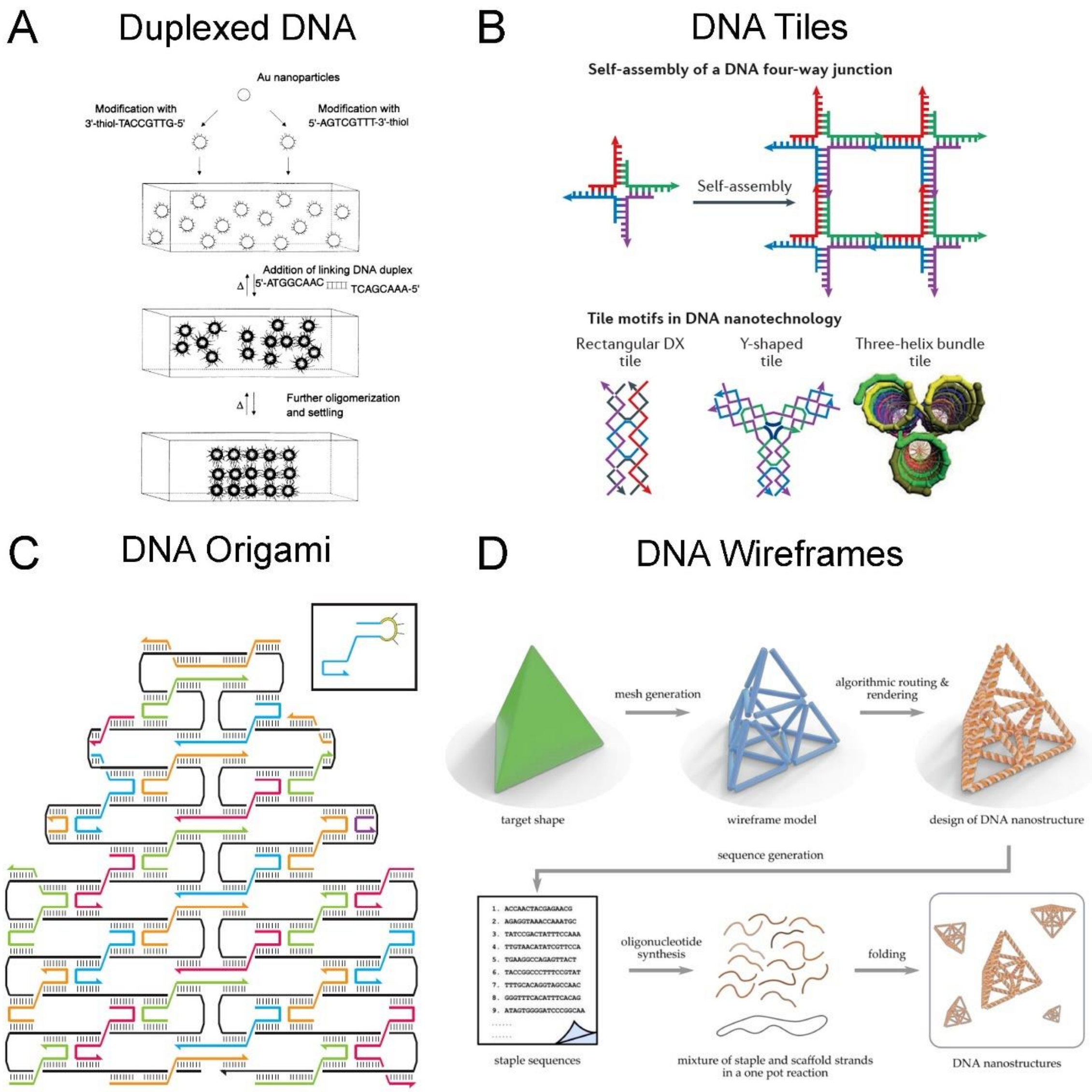


**Figure 1:** Methods of interfacing DNA nanostructures with NPs. A) Duplexed DNA is used to form NP aggregates whose organization is controlled by thermodynamic considerations, nanoparticle packing, and DNA distribution on the NP surface. B) DNA tile nanostructures are formed from multiple DNA strands that interact. Repeating tiles can be assembled to form larger 2D and 3D structures. (C) DNA origami is constructed from a circular DNA strand that is folded using multiple staples into complex geometries. D) DNA wireframe technology extends DNA origami designs using computational mesh generation and algorithms to map specific designs that can achieve complex geometries. Structures shown in (B-D) can be attached to NPs or used to cage them in

their interior. *A) Reprinted by permission from* [8] *B) Reprinted by permission from* [19]. *C) Reprinted by permission from* [4]. *D) Reprinted from Piskunen et al., Increasing Complexity in Wireframe DNA Nanostructures, Molecules, 25(8), 1823, 2020 under Creative Commons license.*

**DNA Caged-Nanoparticle Hybrid Material Designs**

DNA cages (Figure 1B-D) offer significant advantages compared to duplexing methods (Figure 1A) for generating DNA-NP hybrid materials because of their design flexibility and compatibility with many types of NPs. The most popular NPs employed are AuNPs and quantum dots (QDs). AuNPs in particular are well studied since they can be easily modified with DNA through Au-thiol affinity, permitting easy integration with DNA nanostructures. Some of the simplest structures formed using DNA scaffolds are AuNP clusters (Figure 2A) [20,21]. Organizing NPs using such scaffolds enables study of the effects of spacing, placement, and size on plasmonic or other emergent interactions.

A slightly more complicated architecture employs DNA origami well and slit designs with precisely-sized channels can capture NPs in specific patterns. For example, wells designed by Kuzuya et al. [22] resembling a belt with regularly spaced holes were used to capture either unconjugated AuNPs or streptavidin molecules. AuNPs could be captured with high efficiency (50-90%) and specificity (99.6%), with subsequent streptavidin capture. The two different types of wells were distinguished via AFM after additional gold growth at the NP sites. Other designs are also possible, such as a ladder-like structure. A vertical column of AuNPs was constructed using triangular DNA rungs programmed to accommodate NPs of specific sizes [23]. In a similar design, slits were generated from equally sized rows in a DNA square and used to capture up to five AuNPs sequentially [24]. It is also possible to organize the NPs in columns, diagonal lines, and “T” shapes. The controlled spacing and precise organization of NPs templated on DNA scaffolds allows for accurate measurements of plasmonic enhancement, useful in biosensing.

Additionally, this approach could be expanded to other NP types to induce proximity dependent emergent properties, such as fluorescence or magnetic effects. These advances could lead to future applications in templated material growth and drug delivery.

These designs have progressed to DNA nanostructures capable of caging individual NPs. For example, Kuzuya et al. [25] created a DNA origami box consisting of two halves that closed with the addition of ssDNA joining strands. The bottom interior face has a binding site for one AuNP, which must be captured before closing the box. NP cargoes are released via bar-coded strand invasion reactions that provide specificity. Although boxes are simple shapes, it should be noted that this presented some degree of difficulty in dynamic DNA nanostructure design. Boxes can be designed to bind proteins as well as NPs (Figure 2B) [26], and when combined, these designs afford endless possibilities for labeling and drug delivery. Also using DNA origami, Church et al. [10] created a barrel like structure that can hold AuNPs and antibody fragments. When the structure was opened, antibodies were able to bind their antigens, whereas AuNPs generated contrast for cellular level imaging.

In addition to boxes and barrels generated using DNA origamis, tile designs have also proven popular in caging NPs. Icosahedra have been generated from 5-way junction tiles to yield icosahedra halves (Figure 2C). When the halves were united, NPs could be encapsulated in the interior, including AuNPs [27] and [28]**, QDs [29], and small fluorescent molecules [30,31]. AuNP and QD cargoes enable cell imaging; AuNPs as a bright/dark field contrast and QDs as a fluorescent reporter. Additionally, both hybrid materials could be used for optoelectronic applications (e.g., plasmonics, FRET) with more precise organization. Further, although these icosahedra designs have primarily been implemented for non-specific cellular uptake, like barrels origamis [10], they too could be modified to promote specific interactions with cells.

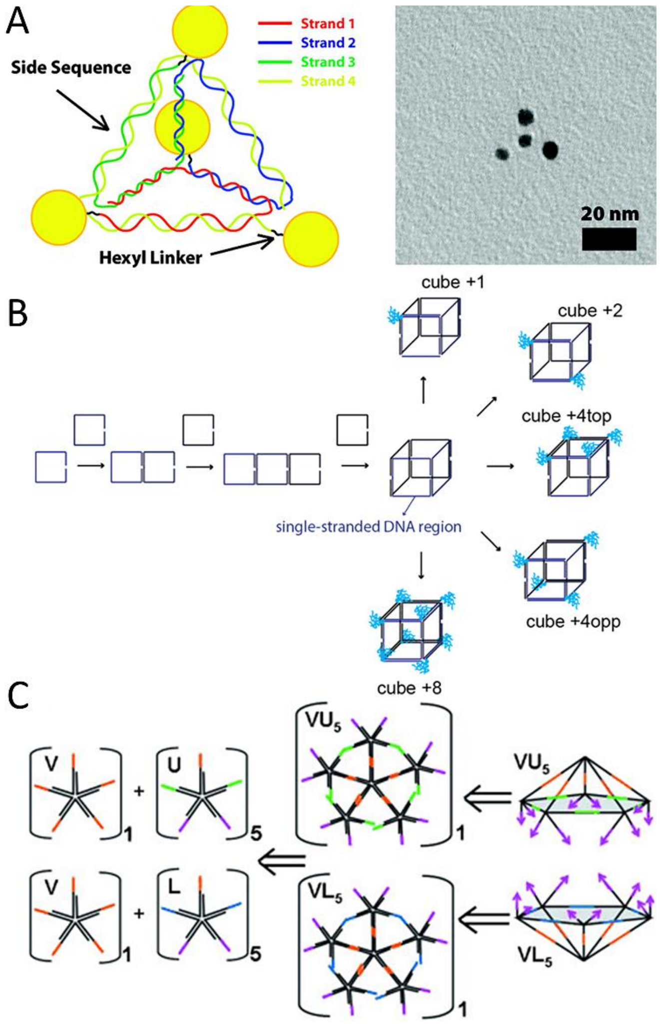


**Figure 2:** Representative DNA cages for NP organization and encapsulation. A) Pyramidal structures comprised of DNA duplexes constrain AuNPs for plasmonic applications. B) DNA origami boxes assembled with one or more protein binding strands enable capture of human albumin serum, increasing DNA stability. C) Icosahedra comprised of 5-way junction DNA tiles were made in two halves that come together to encapsulate AuNPs. *A) Reprinted (adapted) with permission from [20], B) Reprinted (adapted) with permission from [26], C) Reprinted from [27]***

## Applications of DNA-Caged Nanoparticles

*DNA Printing*

A fundamental requirement for NPs in genomic applications is the ability to interact with nucleic acids, often through surface modification with targeting nucleic acid molecules. Unfortunately, NP modification via traditional or even emerging bioconjugation methods can be challenging [17], resulting in reduced colloidal stability and loss of surface dependent properties. For these reasons, many genomic applications have been limited to AuNP materials because of their strong affinity for thiol groups that are easily added to nucleic acid sequences. Even for AuNPs, though, DNA conjugation can be challenging, necessitating specialized protocols, such as salt aging [32] and low pH [33]. In contrast, DNA caging offers a facile method for patterning DNA on NP surfaces, either through the cage itself or through DNA printing mechanisms [34]. For example, Xie et al. [28] designed DNA icosahedra with specific overhangs that capture and decorate AuNP surfaces with DNA in specific patterns. ssDNA attachment occurs after binding/encapsulation. The DNA template is then easily removed through dissolution or stand invasion, leaving behind highly specific DNA patterns that can be implemented with a variety of sequences. So far, however, this has been limited to shorter DNA sequences that lack secondary structure [34].

*Superlattices*

In addition to DNA patterning, DNA cages can be used to assemble NPs into specific superstructures that enable emergent properties, such as plasmonic signaling. For example, tetrahedron DNA cages have been used to generate AuNP assemblies resembling the methane molecule [35]. Such molecules can be used as “voxel” elements to template assembly of higher order structures, such as NPs patterned in a diamond lattice [36]. Voxels represent space in 3D arrays in the same way pixels do in 2D. Designs of this complexity are not easily achievable through thermodynamic self-assembly alone [37], and it is in this space that the power of DNA templating is realized. DNA-enabled voxels can be used to make programmable materials spanning to the micro-scale in 2D [38] and 3D [39]**. Such assemblies afford opportunities to investigate the effect of spatial proximity on biological behaviors, such as the role of co-localization in enzyme efficiency (Figure 3). For example, voxel elements were used to study coupled enzyme reactions between glucose oxidase (GOx, product $H_2O_2$) and horse radish peroxidase (HRP, product resofurin). The ability to pattern enzymes in precise orientation allowed the effect of distance between enzymes on these coupled reactions to be carefully observed. The researchers found that enzymes present in precisely ordered arrays were more efficient than enzymes in semi-ordered or disordered arrays, suggesting that diffusion is an important consideration in these processes. These results suggest potential design of chemical factories with programmable voxel elements to improve production of biologics. DNA cages uniquely enable these studies because of the precise control they afford over aggregate structure.

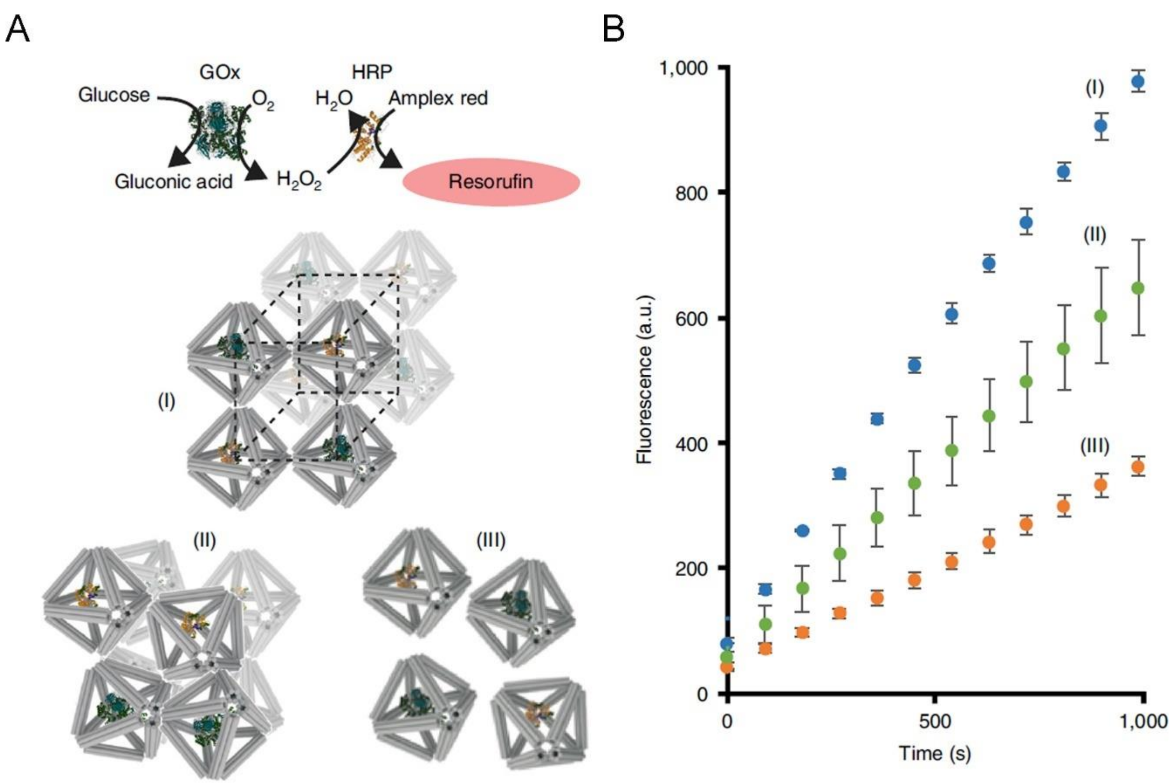

**Figure 3:** DNA-caged enzymes forming “voxel” elements were used to study proximity and cooperativity effects in enzyme-substrate conversion. Ordered enzymes (scheme I, blue) showed the greatest increase in activity compared to semi-ordered and disordered aggregates. *Reprinted by permission from* [39]**.

*Sensing*

Another prominent application of DNA caged materials is in biosensing. In addition to direct sensing of nucleic acids through ssDNA binding sequences or aptamers. For example, the DNA origami barrels described previously were ‘locked’ by aptamers that opened in response to analyte binding [10]. Binding initiated a conformation change that revealed AuNP and fluorescent antibody sensing elements. This allows for selective labeling and interaction of the DNA origami structures. This method can be employed using a variety of lock and key combinations, allowing for high specificity and accuracy.

*Drug delivery*

In addition to sensing, DNA caged materials have found increasing application in drug delivery applications. The versatile nature of DNA cages allows for a wide variety of biomolecules, including chemotherapeutics (i.e., doxorubicin, DOX [40-42]), sugars (dextran [30,43]), hormones (i.e., dehydroepiandrosterone, DHEA [30]), transcription factors (CAP [44]), and proteins (CASP3 [40]**) to be easily encapsulated. Encapsulation can occur through DNA hybridization, DNA interactions, or stochastic assembly. For example, CAP transcription factors (modified with 30 bp sequences) were encapsulated in DNA pyramids (similar to Figure 2A) displaying binding sites selected based on the CAP crystal structure. This approach and the flexibility of the DNA nanostructures increased probability of internalization [44]. Alternatively, many therapeutics interact with DNA, such as the popular chemotherapeutic molecule doxorubicin (DOX). DOX is a DNA intercalation agent that inhibits DNA synthesis, thus resulting in cell death. As such, DOX can also intercalate into DNA nanostructures that serve as drug carriers. DOX is released with DNA cage degradation [40,42,45]. Finally, biomolecules can be encapsulated non-specifically by controlling the nanostructure-to-drug ratio during assembly. DNA nanostructures, such as icosahedra, can be used to encapsulate any molecule that fits inside the cavity. In this case, modified dextran was encapsulated and delivered to live cells using non-specific endocytotic pathways [43]. Using modified dextran structures allows for the addition of therapeutics that can be released using photocleavable linkers [30].

An important factor for drug delivery applications is stability of cages in the biological environment. Cellular uptake of DNA cages and their cargoes depends on their size and shape (Figure 4). Among several choices, the optimal shape for DNA cages has been proposed as pyramidal based on animal screening studies using DNA wireframe structures [40]**. In this study, the researchers screen several DNA cage designs with different shape and composition. The designs were screened for *in vivo* uptake, permitting rapid analysis for a large engineering shape design space. Although the researchers used tumor-specific uptake as a model system, this approach is broadly translatable to other targeting investigations. Results were confirmed by using DNA caged therapeutics for tumor therapy. Additionally, the use of L-DNA rather than the naturally-occurring D-DNA was found to elicit greater biological stability in serum and less interaction with endogenous proteins [40,45]. Similarly, tetrahedral structures have been shown to remain in the cytoplasm for at least 48 hours without significant degradation [46].

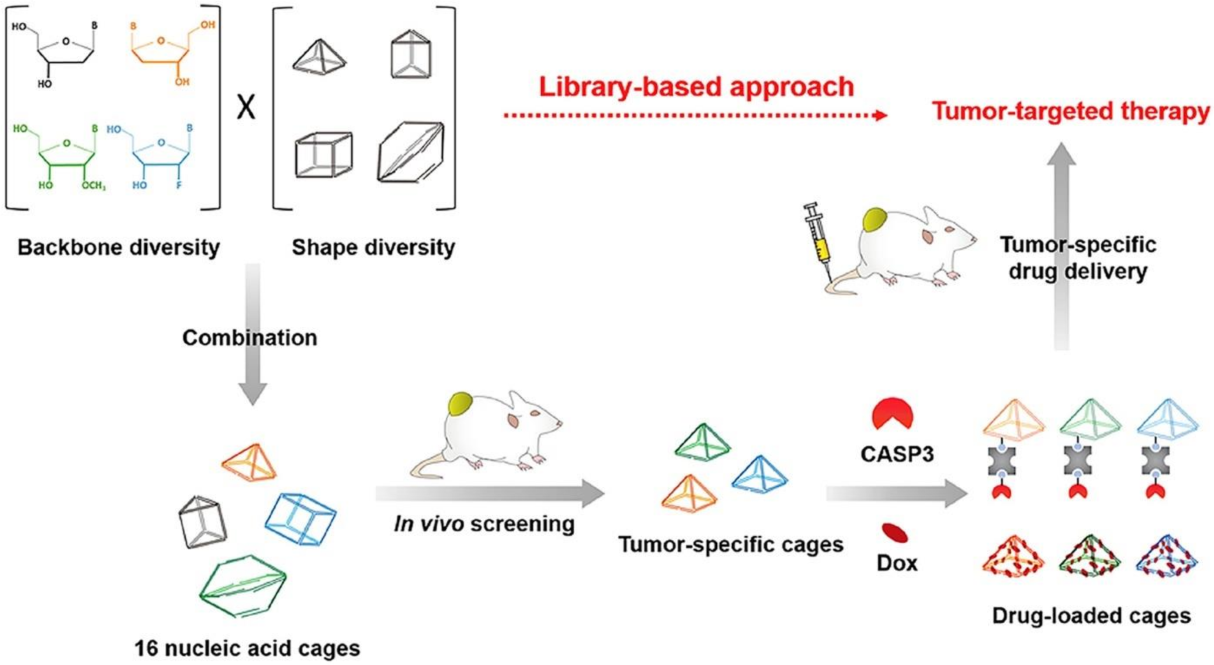


**Figure 4:** The composition and shape of DNA cages influences cellular uptake and tumor specificity. A screening library (top, left) was developed (bottom, left) and used to find the optimal shape and composition of DNA caged structures for tumor targeting through *in vivo* screening (middle). Results were then confirmed using doxorubicin (DOX) and caspase-3 (CASP3) anti-tumor agents, toward targeted therapy. This method can be used to explore a large experimental design space quickly, minimizing lengthy *in vivo* experiments. *Reprinted from [40]***.

**Conclusions and Future directions**

The partnership between DNA nanotechnology and NPs is a natural one. Many biomedical applications benefit from specific NP conformations or controlling access to the NP over space and time. DNA nanotechnology, with its inherent programmability, flexibility, and dynamic structures, can meet these needs. Further, DNA cages, which can be designed to intimately and precisely interface with NP elements, are ideal for this purpose. Current DNA-caged NP materials are being applied to control DNA presentation on NP surfaces. These composite materials can be applied for NP supramolecular assembly, toward bioactive materials with defined structures, and to applications in sensing, drug delivery, and theranostics.

As methods for the design and supramolecular assembly of DNA-caged NPs advance, new applications will continue to emerge. One exciting potential glimpse at the future is the concept of DNA robots that could operate in living environments. Arnon et al. [47] explored this concept by developing DNA-NP hybrid materials containing magnetic NPs that could be heated in an radio frequency-induced electromagnetic field (RFMF) to induce a conformation change in the hybrid structure (Figure 5A,B). Upon actuation, robots were able to bind hemocytes in an adult cockroach model. RFMF heating was induced in response to cognitive load detected using electroencephalogram (EEG) signals in a human test subject (Figure 5C). When cognitive load was achieved (i.e., a stress response), the RFMF field was applied, inducing nanorobots to alter their configuration to bind hemocytes. To confirm success, hemocytes were isolated from the test animals after the experiment and analyzed (Figure 5D,E). Although not a fully closed loop system, this study shows the potential of DNA-NP hybrid materials to perform robotic functions in living systems. More recently, this group has developed DNA robots that exhibit quorum sensing, similar to bacteria, by responding to and emitting chemical signals, toward closed loop processing [48]**. In the future, such research could be translated to applications in human health, with actuatable DNA nanostructures metering out the sensing and therapeutic capability of NPs in response to internal or external signals.

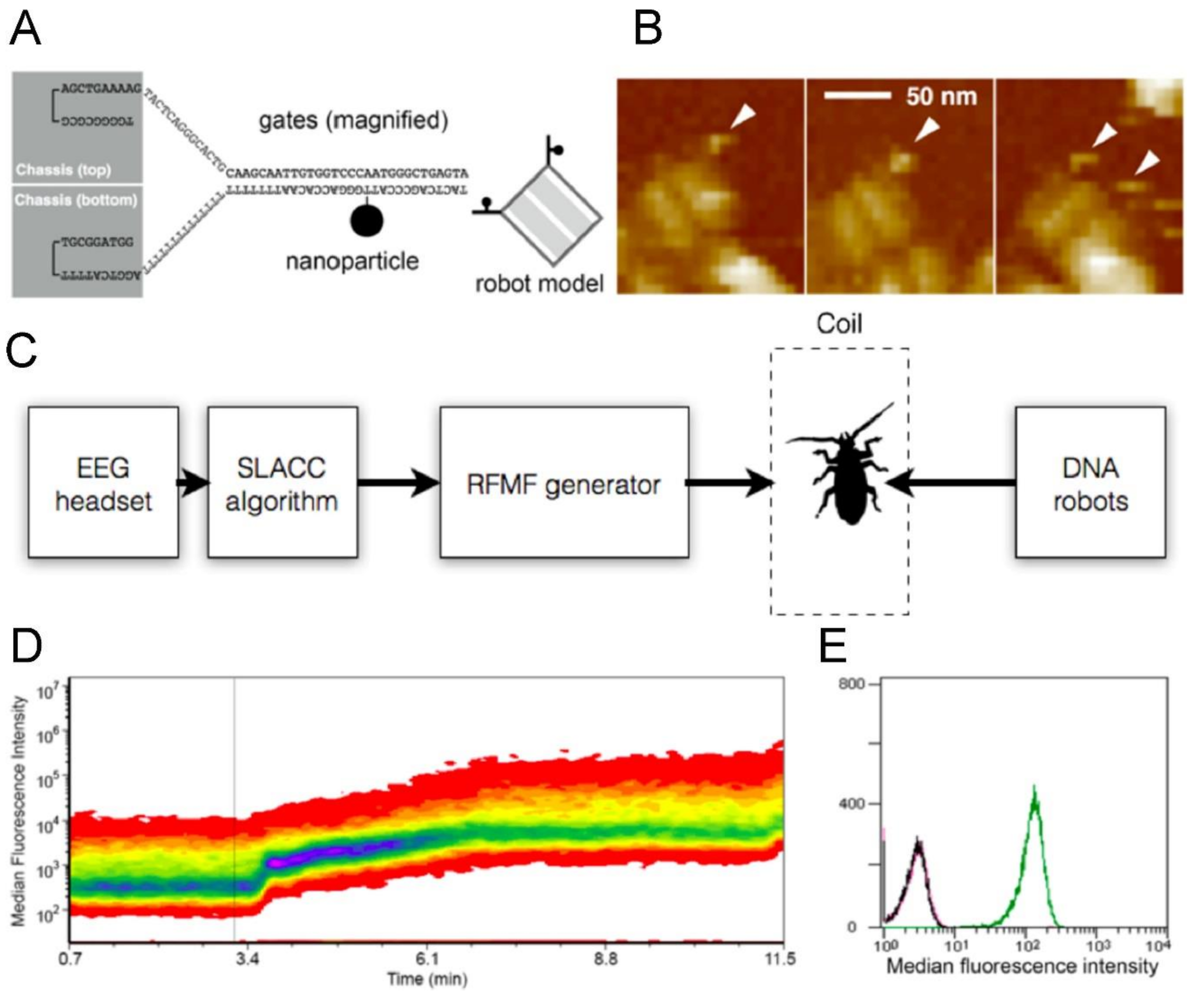


**Figure 5:** The possible future of DNA nanostructure-NP materials? (A-B) DNA nanostructures and magnetic NPs were combined to form robots that could open in response to radio frequency-induced magnetic fields (RFMF) as shown in (A) schematic and (B) in atomic force microscopy. (C) Robots injected in live cockroaches were actuated by RFMF fields generated based on signals detected from an electroencephalogram (EEG) in response to stress on a human subject. Robots were programmed to bind hemocytes in the cockroaches. (D,E) After the experiment was completed, hemocytes were collected and quantified using flow cytometry. The presence of the robots was confirmed by increased signal (D), which was higher than that of hemocytes without robots (E). *Reprinted from [47]*.

**Author Contributions**

EJ and JOW equally contributed to this article including researching, writing, and editing the materials.

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