A survey of advancements in nucleic acid-based logic gates and computing for applications in biotechnology and biomedicine

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Nucleic acid-based logic devices were first introduced in 1994. Since then, science has seen the emergence of new logic systems for mimicking mathematical functions, diagnosing disease and even imitating biological systems. The unique features of nucleic acids, such as facile and high-throughput synthesis, Watson–Crick complementary base pairing, and predictable structures, together with the aid of programming design, have led to the widespread applications of nucleic acids (NA) for logic gate and computing in biotechnology and biomedicine. In this feature article, the development of in vitro NA logic systems will be discussed, as well as the expansion of such systems using various input molecules for potential cellular, or even in vivo, applications.

1. Introduction

Based on their ever-increasing computing and storage capability on a miniaturized scale, silicon semiconductor-based intelligent computing systems have impacted every aspect of daily life. At the same time, however, the capabilities of traditional silicon chips are becoming increasingly limited.1 This has prompted researchers to explore alternatives to semiconductor-based computational systems, even at the molecular level. Molecules can be rationally designed, synthesized, and further integrated into Boolean operations, providing unprecedented potential for developing the basic components of molecular computing devices. More significantly, molecular assemblies that function as different modules, although not yet able to rival silicon-based computing devices, can, to some extent, emulate or mimic digital logic circuits.2

Several unique aspects characterize the design of molecular logic systems. First, the logic device input and the subsequent output to the next device must be considered. Second, a
semiconductor device typically relies on electrical input and output signals transported through mechanical wires on the silicon chips. In contrast, the input/output of a molecular logic system is not limited to electrical circuitry. For example, the diffusion of molecules in solution can be used as the input and light emission as the output of a molecular logic device. Third, molecular computational devices do not have to be as durable as their semiconductor counterparts, especially when used in live biosystems that only require active function for hours to days. Finally, molecular computational devices, albeit relatively simple, can still be utilized in various fields, ranging from in vitro sensing and diagnosis to cellular drug delivery, and even gene expression regulation in vivo.

Nucleic acids (NA), as the significant carriers of genetic information, have recently displayed unprecedented potential in practical, high-capacity and low-maintenance digital information storage because of their predictable structures, high-throughput synthesis and sequencing techniques. NA-based logic gate operation was first reported by Adleman and Lipton to solve the directed Hamiltonian path problem and the “SAT” question in computer science with single-stranded DNA sequences and enzymes. After that, researchers sought to design and create various DNA/RNA-based logic systems for feedback and cascading, mimicking mathematical function, diagnosing disease, and even imitating the neural network and the memory system. Although NA-based logic and computing is still in its infancy, these attempts to substitute NA-based logic devices for conventional silicon chips and utilize them for cellular or in vivo applications have become the driving force behind a new generation of molecular logic systems.

This feature article first focuses on the in vitro design of NA-based logic and computational systems, followed by a review of recent progress in sensing and diagnosis with initial inputs of ions, small molecules and proteins. Finally, biological applications with NA-based logic platforms will be surveyed.

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Weihong Tan, Distinguished University Professor and V. T. and Louis Jackson Professor of Chemistry at the University of Florida, earned his PhD (1993) from the University of Michigan. Dr Tan's research interests include Chemical Biology and Bioanalytical Chemistry. His group developed the cell-SELEX technique to screen nucleic acid aptamers for specific recognition of diseased living cells. They further used these aptamers for identification of early disease diagnosis, targeted drug delivery, and cancer cell enrichment and separation. In addition, the Tan group has engineered a variety of DNA nanostructures to be used as drug carriers, biosensors and nanomotors.
2. Rational design of the nucleic acid molecular logic system

The basic construction modules of NA-based logic devices include input (DNA/RNA, ions, small molecules or proteins), computational “hardware” (double-stranded DNA/RNA), and output (DNA/RNA, or other readable signals). Thus, while it is easy to envision single-stranded DNA as input to double-stranded DNA computing “biohardware,” the output depends on triggering a readable signal, and in a NA-based logic network, this is typically achieved by a toehold-mediated displacement reaction. More specifically, the ssDNA input hybridizes to a specific domain (toehold) of the dsDNA, initiating the displacement process and releasing another ssDNA sequence as the output. Three basic steps are involved in this procedure: toehold binding, branch migration and strand dissociation (see Fig. 1). It is worth noting that the length of toehold in a logic circuit quantitatively determines the rate constant of a strand-displacement reaction, which can vary by six orders of magnitude. Using this basic principle, Seelig et al. reported the implementation of DNA-based digital logic circuits to perform a series of functions, such as AND, OR and NOT gates. Moreover, this enthalpy-driven displacement reaction was also utilized in signal amplification, feedback, cascading and pattern transformation.

Since nucleic acids can be easily modified in the laboratory, either individual nucleotides or the entire sequence, unique properties and applications can be achieved. In addition, a double-stranded DNA (dsDNA) chain can provide long-range hole transport, which is caused by the ordered π-electron system of the bases, and different DNA pairs have distinct efficiency expression results. To build AND/OR logic gates, it is easy to modify the DNA bases and sequences with specific pairing, which can apparently affect the long-range hole transport efficiency. Thus, the Boolean results can be expressed by comparing the ratio of the measured long-range hole transport efficiencies of the normal and modified base pairs. Okamoto et al. reported a DNA logic gate system which employed MDA (methoxybenzodeazaadenine) paired to T base, instead of the displacement reaction was also utilized in signal amplification, strand cleavage at GGG sites by PAG E (polyacrylamide gel electrophoresis) analysis upon hot piperidine treatment of reaction products. It is worth noting that the length of toehold in a logic circuit quantitatively determines the rate constant of a strand-displacement reaction, which can vary by six orders of magnitude. Using this basic principle, Seelig et al. reported the implementation of DNA-based digital logic circuits to perform a series of functions, such as AND, OR and NOT gates. Moreover, this enthalpy-driven displacement reaction was also utilized in signal amplification, feedback, cascading and pattern transformation.

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The photon is one of the most useful and popular tools used in the construction of logic gates since light can be considered as the output signal. Saghateian et al. used DNA-based photonic logic gates to provide AND, NAND and INHIBIT Boolean operations (Fig. 3A). The NAND gate (NOT AND) is a logic gate which produces an output that is false only if all its inputs are true; thus its output is complementary to that of the AND gate. A LOW (0) output results only if both the inputs to the gate are HIGH (1); if one or both inputs are LOW (0), a HIGH (1) output results. It is made using transistors. The NAND gate is significant because any Boolean function can be implemented...
by using a combination of NAND gates. This property is called functional completeness. Four possible input DNA strands (0,0; 1,0; 0,1; 1,1) are presented in the “AND” and “NAND” gates, in which the fluorescence signals are recognized by DNA strands labeled with different fluorophores based on fluorescence resonance energy transfer (FRET). For the AND gate, only having “1” at both inputs (1,1) can induce the FRET signal with two fluorophores on each oligonucleotide. This provides the maximum fluorescence intensity, in contrast to the low fluorescence signals for the other three input types. For the NAND gate, a (1,1) input results in a low fluorescence signal, while the other combinations provide strong signals, simply because the AND gate is also called an inverting buffer, which stresses its ability to amplify. If we hook two NOT gates together we will now have a YES gate or non-inverting buffer) consists of an inactive deoxyribozyme module (ST) and another attached beacon module. The output signal can be realized when the ST region is cleaved based on the following steps. First, the input sequence opens the loop of the beacon module and releases its stem. Second, the activated stem allows the ST module to form the active state by hybridizing with the substrate labeled with a fluorophore (TAMRA) and a quencher (BH2). Finally, cleavage, which occurs in the active ST module, results in the restoration of the fluorescence output signal. Because of the facile modification of the beacon module incorporated in the ST region, multiple input beacon modules can be precisely used with deoxyribozyme for different types of complex gates, such as “YES”, “AND” and “NAND” (Fig. 4B and C).

3. Functional nucleic acid logic system involving metal ions and biomolecules

DNA not only forms a duplex structure, but it also interacts with ions, small molecules or proteins through a variety of mechanisms. Inspired by these properties, many researchers have designed logic gates by combining strand displacement with ion or molecule binding, thus largely expanding the scope...
of nucleic acid logic gate application. Moreover, some designs can not only detect the analyte, but also realize the control and manipulation of biological molecules in vitro with involvement of the DNA logic gate.

3.1 NA logic systems mediated by metal ions and small molecules

Based on the interactions between DNA and metal ions, DNA logic gates can be mediated by the input of different ions that employ such mechanisms as mismatch base pairing by metal ions, 44–47 ion-mediated catalytic deoxyribozyme 48–52 and tetrad structure formation, such as G-quadruplexes and i-motifs. 53–55 For example, mercury ions (Hg$^{2+}$) can interact with the thymine–thymine (T–T) mismatch in DNA double strands, thus increasing the stability of the duplex. 41 A similar phenomenon also occurs between the Ag$^{+}$ ion and cytosine–cytosine (C–C) mismatch. 56 Taking advantage of this property, Park et al. developed a logic gate in which the output is the PCR product of a double-stranded DNA. 57 They deliberately put the T–T or C–C mismatches at the 3′ ends of both primers and templates, making elongation to occur only when Hg$^{2+}$ or Ag$^{+}$ is present, respectively. They established different gate systems using this property. Take the AND gate as an example. T–T and C–C mismatches were deliberately inserted on the forward and reverse primers with the substrates, respectively (Fig. 5A). With the mismatch at the end, the polymerase enzyme cannot work. Thus only with both the input ions (Ag$^{+}$ and Hg$^{2+}$) present can the 3′ end base pair with each other, which induce the polymerase reaction.

While numerous techniques that have been developed for ion detection exploiting DNA logic gates, most of the output formats are fluorescence and colorimetric, which result in tedious management procedures, as well as difficulties in transferring the output signal into nonmolecular-based systems. Zhang et al. tried to solve this problem by utilizing the change in Faradaic current as the output signal (Fig. 5B). The T-/C-rich DNA strands on a modified gold electrode surface hybridize with T-/C-rich DNA strands with ferrocenecarboxylic acid (Fc) labeled at the end. 58 For AND gate operation, T–T and C–C separately pair to form the duplex, but only with input of both Hg$^{2+}$ and Ag$^{+}$ ions. This brings Fc close to the surface of the gold electrode and produces a Faradaic current as the output. They also constructed NAND and NOR gates using similar strategies.

DNAzymes, which were first identified in 1994, are single DNA strands that show catalytic ability for certain chemical reactions. 40 Often they need metal ions as cofactors. 59 Taking advantage of this property, researchers have developed many strategies to detect ions. In addition, many DNA logic gate biosensing techniques have been established based on DNAzymes, using ions as inputs and DNA/RNA strands produced by the catalytic reactions as reporters, which will produce fluorescence, electronic, colorimetric or other kinds of signals. 48 Bi et al., for instance, developed a set of logic gates, including AND, OR, INHIBIT, XOR, XNOR, NOR, and NAND, with colorimetric output. 60 Basically, they designed a series of supramolecular circular DNA strands containing certain patterns of repeated units, as well as the cleavage sites for DNAzymes.
As shown in Fig. 6A, by inputting the cofactor ions (Mg\(^{2+}\) and Pb\(^{2+}\)), the two DNAzymes are activated, and the substrate is cleaved, resulting in overhung segments. When two hybridization overhangs are generated on one strand of DNA, gold nanoparticles modified with complementary oligonucleotides are brought close to each other upon hybridization. This aggregation induces a color change from red to purple as the output. By rationally modifying the patterns of the circular DNA substrate, various logic gates can be realized.

Screened through an in vitro process called systematic evolution of ligands by exponential enrichment (SELEX), aptamers are single-stranded oligonucleotides which fold into unique secondary and tertiary structures with binding affinity to biological small molecules, proteins or even cells.\(^{59,61-63}\) As an analog to antibodies, aptamers have many advantages, such as facile synthesis, good reproducibility, and thermal endurance. Most importantly, however, as DNA strands, aptamers can be incorporated into logic gate circuitry easily and effectively. Many logic gate systems have been designed utilizing the targets as inputs and binding-induced structural transformations of DNA strands as responses.\(^{24,64-70}\) Yin et al., for example, developed a colorimetric logic gate system based on aptamer-crosslinked hydrogels.\(^{71}\) By modifying DNA molecules onto polymer chains, hybridization behavior with crosslinker strands induces hydrogel formation. Since the aptamer sequences of ATP and cocaine are incorporated into the DNA strands, the hydrogel dissociates upon target recognition. As output, the authors trapped BSA-modified gold nanoparticles in the hydrogel, and monitored particle release for detection. For the AND gate (Fig. 6B), each strand partially hybridizes two others, forming a Y-shaped structure. Thus, one input can interrupt hybridization between two of them, but since the three strands remain linked together, no breakdown of the hydrogel occurs. For the OR gate, the crosslinker hybridizes with both DNA strands modified on a polymer, while between the two strands there is no interaction. As such, either one of the molecules can decompose the hydrogel and release the gold nanoparticles.

### 3.2 Protein-mediated NA logic systems

Monitoring biological systems depends on the accurate detection of proteins. For that reason, many researchers have focused on making detection methods simple and effective including, for example, strip platforms,\(^{72}\) photoinduced electron transfer (PET),\(^{73}\) nanomaterials,\(^{74,75}\) and electrochemiluminescent devices.\(^{76}\)

When compared with the most popular protein detection method, enzyme-linked immunosorbent assay (ELISA), which utilizes an antibody and an enzyme, aptamers need a less rigid environment. In addition, some aptamers can both recognize proteins and regulate protein functions upon recognition. For instance, thrombin aptamer TA-29 can target the protein without interference, while TA-15 that binds to the fibrinogen exosite of thrombin strongly inhibits blood coagulation.\(^{77}\) Taking this feature into consideration, Han et al. developed a logical molecular circuit that can realize programmable and autonomous manipulation of thrombin function via a set threshold.\(^{78}\)

As shown in Fig. 7A, the process includes three stages. In the input convertor, upon addition of thrombin, TA-29 binds to its target position and releases the partially complementary strand as the DNA-input. In the normal input range, the process stops at the threshold controller step, and the DNA input hybridizes to one strand of the threshold duplex with the other strand as waste. However, if thrombin input exceeds the threshold, the inhibitor generator step is activated, and following strand displacement, inhibitor TA-15 is generated by recognizing thrombin, and blood coagulation is impeded.

While previous methods have used proteins as inputs, Deiters et al. have recently engineered a set of DNA logic operations with proteins as outputs.\(^{79}\) Compared to typical outputs, such as oligonucleotides or fluorescent signals, direct control of protein activation enables the immediate triggering of enzyme functions. In this work, they exploited zinc-finger proteins AaRT and E2C, which are able to easily fuse with the split-protein component of luciferase, as well as bind to DNA with recognition ability. AaRT, which recognizes a guanine-rich sequence, and E2C, which binds to an adenine-rich group, are used as a proof-of-concept (Fig. 7B). The two halves of the split-luciferase enzyme are separately modified with the two zinc finger proteins to generate a luminescence readout. Integrated luciferase is formed and a signal produced only when
the two zinc proteins are brought close together through binding to the DNA scaffold. Several gates, such as AND, OR and NOR, can be constructed. In addition to the single gates, more complex devices which integrate multiple logic gates can be fabricated. Fig. 7B shows a combined AND/NOR gate. In this construct, the presence of both B and C strands activates the AND gate, and the output strand, as well as the A strand, acts as one of the inputs for the next NOR gate. Either input of the NOR gate releases the zinc protein binding strand from the scaffold, inducing luminescence quenching.

4. Nucleic acid logic systems for cancer theranostics

A key goal of NA-based logic systems is the ultimate translation of these devices for applications in vivo, for smart sensing, regulating, and even rewiring of biological systems. However, considering the complex environment of a biological system, a successful design of the buffer system may have totally different results when applied in vivo, usually failing because of the unstable nature of nucleic acids, the lack of robustness of the designed hybridization reaction, or vulnerability of nucleic acids when exposed to enzymatic digestion. Scientists worldwide are trying to solve these problems. The effort includes those working on modifications of existing natural DNA, such as phosphorothioate replacing DNA, locked nucleic acid (LNA), 2\textsuperscript{-}site-modified nucleic acids, or enantiomers of natural DNA. Efforts to introduce artificial nucleotides into DNA will largely overcome the shortfalls of natural DNA and will endow nucleic acid logic systems with more building blocks and higher information density.

Among all biological applications, cancer-related research undoubtedly spurs most attention. The images of building smart nucleic acid logic systems for cancer detection and therapy are indeed intriguing. Although this logic gate concept was proposed as early as in 1994, only recently has research in living cells advanced, and cancer-related research has followed. Although reaching the goal of applying logic systems
in vivo may still stretch far into the future, many excellent research results have already been published.

In 2007, the Benenson group constructed a molecular computing core implementing general Boolean logic using RNA interference (RNAi). In human kidney cells, this evaluator could directly evaluate any Boolean expression based on endogenous molecular inputs. In another work, this group built another RNAi-based logic circuit that could sense the expression levels of certain types of preinstalled endogenous microRNA (miRNA) and, as a consequence, classify the cell type for a predetermined response. That is, whenever the expression level matches the default profile, the logic circuit correspondingly triggers a cellular response to induce apoptosis (Fig. 8A). Deiters et al. reported the engineering of an AND gate to sense specific miRNA inputs in living cells with a fluorescence signal as the output. This system could expand the potential of nucleic acid logic systems to monitor, image and respond to cell-specific markers. Very recently, Cai et al. designed a series of CRISPR-Cas9-based modular AND gate circuits that activate the output gene only if two promoter inputs are active in the tested cells. The designs exploit output genes, including the luciferase reporter for bladder cancer cell detection and cellular functional genes to inhibit bladder cancer cell growth, and inducing apoptosis or decrease cell motility.

Besides the successful work focusing on logic gate-based miRNA detection or gene regulation, other studies have targeted cancer-related biomarkers. To achieve successful cancer detection and therapy, a biomarker makes it possible to distinguish cancer cells from normal cells or other types of cells and can largely enhance specificity and increase efficiency. As natural binding molecules, antibodies are the most useful binders in biomedicine today. Stojanovic et al. developed antibody-nucleic acid conjugates that can analyze cells by sensing surface biomarkers CD45 and CD20 (Fig. 8B). These devices can detect the existence of two to three biomarkers in a logical pattern and give a corresponding fluorescence signal, thus avoiding the steps of transfecting oligonucleotides into cells. This capability largely extends the use of logic systems, thereby prompting operations directly on the surfaces of native cells.

As alternative binders, aptamers are excellent tools for incorporation with NA logic gates for cancer marker detection and targeted therapy. As noted above, cell-SELEX technology was first developed in Tan group and has been utilized to generate over 300 aptamers targeting many kinds of cancer cells. Those aptamers are now being widely used in biomedical research as probes for cancer cell molecular recognition. In 2012, Douglas et al. reported pioneering work by developing a DNA nanorobot that could intelligently recognize cancer cells via biomarkers on cell membranes. They used DNA origami to build a hexagonal barrel-shaped nanostructure, with a dimension of 35 nm × 35 nm × 45 nm. This structure can release its payload only when combinations of cell surface biomarkers match the aptamers fixed on the nanorobots, working much like combination locks where all the tumblers must fall into place. Amir et al. recently designed nanorobots capable of dynamically interacting with each other to generate logical outputs in live animals. Depending on the outputs, the molecular payloads could be switched either on or off. These origami robots have now been used in live cockroaches for controlling a molecule targeting their cells.

In Tan group, DNA-based logic systems have also been developed for cancer marker detection and targeted cancer therapy, using aptamers binding either to proteins or living cells. The first example utilized the special properties of gold
nanoparticles (AuNP) to develop AND and OR logic gates for soluble biomarker detection (Fig. 9). As a model to show the strategy, two important proangiogenic factors commonly used for cancer diagnosis and treatment, platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), were tested. In the absence of both PDGF and VEGF, fluorescence from each probe is quenched by AuNPs, and the AuNPs are monodispersed as surrounded by DNA probes, showing a red color in solution. However, when either one of these proteins is present in the solution, one type of duplex opens, restoring fluorescence, which is the output of the OR logic gate. When both targets are present, both types of duplexes open, and the AuNPs aggregate by the complementary design of the connecting DNA. The solution becomes purple as the reporter output of the AND logic gate.

Later, a logic circuit was engineered on the surface of the cells to achieve targeted and amplified photodynamic cancer therapy (PDT). In this work, a photosensitizer, Chlorin e6 (Ce6), was used as the killing module in the cell-surface sensing logic circuit (Fig. 10A). In the absence of target cells, the two hairpin structures are stable. Upon introduction of the target cells, the aptamers selectively recognize them and bind specifically to the cell-surface targets. The overhanging catalyst sequence on the aptamer catalyzes the hybridization reaction between A1 and A2 to form A12, which further reacts with the R12 module to release the quencher-labeled strand and activate Ce6, which generates singlet oxygen to kill cancer cells by irradiation at 404 nm.

As aptamers become available against more cell types, programmable analysis of multiple biomarkers on the cell surface will be necessary for the clinician to establish a comprehensive disease profile and conduct a more accurate intervention. To apply logic gates to cancer cell targeting and therapy, at least two aspects must be addressed. First, all modules need to be integrated into a single nanodevice to allow the use of logic systems as therapeutics. Second, logic gates more sophisticated than either AND or OR need to be developed to satisfy different biomedical criteria.

The Tan group has made progress towards meeting both of these requirements. To integrate all modules into one piece, a nanodevice termed “nano-claw” was designed for autonomous analysis of multiple cancer cell-membrane markers, yielding a diagnostic signal or targeted PDT response (Fig. 10B). The structures were designed into either ‘X’ or ‘Y’ shapes, depending on the number of biomarkers to be tested. Either of these two types is composed of an oligonucleotide backbone as the scaffold, several modified switchable aptamers as “capture toes”, and a logic-gated DNA duplex as the “effector toe”. The “capture toes” recognize and bind to cell-surface targets, while, at the same time, generating “barcode strands”. The signal is released only if all “barcode strands” match the information stored at the “effector toe.” Using this strategy, both ON and INH gates were designed and tested successfully. Although this is only a preliminary attempt, it shows the potential of integrating logic gates into nanostructure assemblies.

Another effort involved the development of a programmable and universal platform to meet the requirement of screening for different complex conditions on cell membranes (Fig. 10C).

5. Concluding remarks

During the two decades since NA-based computational devices were first proposed, newly emerging logic systems have preliminarily demonstrated applications both in vitro and in vivo. The construction of NA-based logic devices can be integrated with DNA, RNA, small molecules, proteins, enzymes and even live cells with large variability, in contrast to conventional semiconductor-based computing systems. Also, the operation of NA-based logic devices is more flexible and diverse since they can be either static or oscillatory with various output generation modes. More significantly, the highly regulated and predictable properties of nucleic acids coupled with auxiliary programming software make molecular logic devices easy to control. All these unique features have advanced NA-based logic devices over the last ten years. However, many challenges must be overcome before these devices will see practical use. First, the relatively slow reaction kinetics between NA bases, or other interaction molecules, and the...
transport and output yield of scale-up NA logic devices could impede practical implementation. Second, the leak reaction and spurious binding between nucleic acid sequences may slow down the desired reaction rates and decrease the effectiveness of NA logic devices.8,10 Third, NA-based logic systems are more dependent on the diffusion among different nucleic acid gates, which may produce some unexpected spurious interactions.10 Moreover, current NA-based logic devices still cannot rival silicon chips in computational speed and capacity. These are critical issues in the future design of next-generation NA-based computing devices.

Nonetheless, the advantages of NA-based logic systems still offer tremendous opportunities for both in vitro and in vivo applications. From a fundamental point of view, NA logic circuitry must be scaled up to designs that can effectively substitute for semiconductor-based computing devices. For instance, the reversible strand displacement process was designed for DNA cascade reaction and introduced to construct a sophisticated biochemical circuit.10 In biomedicine, NA-based biological circuitry will facilitate personalized medicine by acquiring multiplexed physiological information inside the human body, then performing logical operations for analysis, and finally releasing loaded drugs, or even regulating the expression of specific disease genes.97–100 With further improvement of DNA/RNA nanotechnology and programming, more sophisticated artificial devices or systems based on NA and other biomolecules will be designed and created to satisfy growing needs in biotechnology and biomedicine.

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**Fig. 10** (A) Principle of the specific cancer cell-surface aptamer circuit for enhanced photodynamic therapy (reprinted by permission from ref. 94, Copyright 2013, American Chemical Society). (B) Construction of DNA-based “nano-claw”: two-input trivalent “Y”-shaped nano-claw and three-input tetravalent “X”-shaped nano-claw (reprinted by permission from ref. 95, Copyright 2014, American Chemical Society). (C) Schematic of the aptamer-based cell-surface “AND” logic gate for diagnosis and treatment of a specific cancer cell type in the presence of two biomarkers (reprinted by permission from ref. 96, Copyright 2014, American Chemical Society).

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Notes and references


