Int J Med Rev 2018 June;5(2):68-76

doi 10.29252/IJMR-050205

INTERNATIONAL JOURNAL OF MEDICAL REVIEWS

Narrative Review

Nano-Aptasensor: Strategies and Categorizing

Jamal Rashidiani[1], Khadijeh Eskandari[1], Seyed Jafar Mousavy[1], Ramezan Ali Taheri[1], Hamid Kooshki[1*]

[1]Nano Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

Corresponding Author: Hamid Kooshki, Nano Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran. Email: hmdkooshki@gmail.com

Received February 17, 2018; **Accepted** March 27, 2018; **Online Published** June 25, 2018

Abstract

The widespread use of nano-aptasensors is seen in various clinical areas, drug discovery, the development of human health, and biological research. Variety in design practices, detection strategies, and areas of application remind us of the need for review, comparison, and classification of this type of sensors. The aptasensors and the attractiveness of using nanotechnology, like a wonderland, have attracted researchers' attention. Furthermore, the application of these tools (rapid detection, quality control, and drug level assessment in the clinical and paraclinical settings) are of special importance. In this study, aptasensors have been reviewed and classified in terms of type, sensor approach, and transducer type, and in some cases, the advantages, disadvantages, and detectability of sensors have been described. To select, compare, and classify nano-aptasensors in the present research, the author sought to use nanotechnology, aptamer bioreceptor, and application field of these types of sensors, while considering the sensor's ability. Nanotechnology have the high potential to reduce costs, save time, and increase the accuracy of detecting agents. Diversification in strategy, precedence of studies, and type of nano-processes itself are not considered as advantages; rather the simplicity, accuracy, user-friendliness, accessibility, and competitive cost of the sensor lead to the superiority of the nano-aptasensor.

Keywords: ssDNA, Aptamer, Sensor, Nanotechnology, Biosensor

Citation: Rashidiani J, Eskandari K, Mousavy SJ, Taheri RA, Kooshki H. Nano-aptasensor: strategies and categorizing. Int J Med Rev. 2018;5(2):68-76. doi:10.29252/IJMR-050205.

Introduction

The rapid detection of agents, toxins, and disease markers is beyond the scope of traditional sampling and detection methods; however, it is possible to solve this problem using biosensors.[1] Aptamers are short fragments of oligonucleotides, peptides, and peptide nucleic acids (PNAs), which, specifically and with high affinity, bind to various biological, organic, and inorganic targets.[2] Aptamers act like pharmaceutical analogues for monoclonal antibodies and have high binding affinity with target molecules. They also have high potential for sensitive and accurate detection.[3] Over the past two decades, nano-biosensors have been widely used in various research and applied fields, including tracking bio-terrorist attacks, clinical diagnoses, drug discovery, human health development, and bio-research, increasingly consolidating their position. The important parts of biosensors include the bio-receptor, signal transducer, signal amplifier, and processor (Figure 1). Biosensors are highly diverse. An aptamer used in a bio-receptor is called an aptasensor, and it is called a nano-aptasensor if nano-methods and nano-materials are used in the construction of the aptasensor.[4-9]

A Quick Review of Detection Methods

Detection and measurement methods can be divided into three groups: traditional, novel, and hybrid. Traditional methods are based on the biological activity of an analyte or its physiological effects on living cells or animals and include methods of investigating animal behavior, animal feeding,[10] physiological responses,[11] the use of cell culture, and immunological methods.[12] Novel methods include radio immunoassay, immunodiffusion, ELISA, ELISA-ALIKA, PCR, etc.[13] These methods are not optimal now and have many shortcomings, e.g., low detection potential, high cost, complicated procedures, long processing times, and the need for space and skilled personnel.[3,14] Recently, more accurate and simpler sensing methods have emerged with advancements made in other fields and the scientific convergence created in the form of interdisciplinary sciences.[15,16]

Biosensors (Definitions and History)

A biosensor is a tool that uses specific biochemical interactions to measure an analyte. This reaction results in the production of a signal; if recorded, amplified, and read, the analyte can be tracked and measured (Figure 1).[17] The use of canaries by miners to detect contamination or lethal doses of carbon monoxide in mines is considered as the first application of biosensors. The idea of using a sensor to measure human bioanalytes was raised in the early twentieth century, but electrodes or probes were used until the 1970s. The first generation of biosensors measured analytes such as sugar in

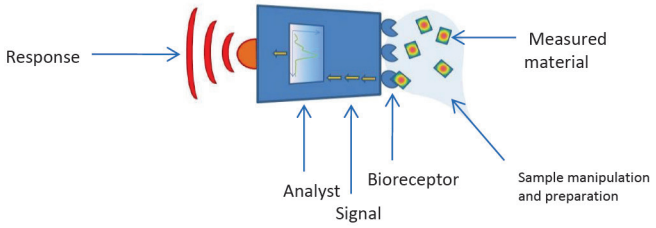

Figure 1. Schematic Structure of a Biosensor.[19]

human body liquids. Dr. Leland C. Clark first developed the concept of biosensing, and a biosensor is sometimes called a Clark electrode.[18] In the beginning of the 1990s, scientists began to think about using such sensors as tools. In addition to the issue of tracking analytes, ways to measure and quantify analytes were also sought. To this day, every sensor used to track, detect, and measure bioanalytes is considered a biosensor. However, scientists such as Professor Kissinger essentially disagree with this idea and consider biosensors as the only measurement tool comprised of biocomponents.[18] Some go even further and do not consider nanoparticles or quantum dots transmitted to cells or tissues to transmit the signals of intracellular interactions and extracellularly track the signal resulting from its labeling as biosensors. They also believe that the new generation biosensors are those made by researchers using biomaterial and components such as enzymes, proteins, cells, intracellular organelles, tissues, etc. to detect analytes that may not necessarily be of biological components.[18]

Widely diverse methods have been used to create biosensors, yet despite the apparent variety and differences, they are all comprised of sensing element parts (bioreceptor), a transducer (detector), and a processor.

Transducer: The transducer is the second part of the biosensor that converts the chemical or physicochemical signals generated through the binding of the sensing element to an analyte into a measurable output signal. This part of the biosensor can send the type and amount of reaction with different signals to the processor using different physicochemical methods and changes (electrochemical, optical, mass, or thermal before and after the reaction).[20,21]

Processor: Using one of the signal reading methods, this part receives (directly or indirectly), amplifies, and sends the signal from the changes in the bioreceptor. The message may be sent by changing the visible (changing the color of the sensors determining the shelf life of food products) or invisible frequency (e.g., electromagnetic waves) or by changing the 0 and 1 (zero/one) algorithms in the computer field.

Bioreceptor: A bioreceptor is a biological-element (antibodies, nucleic acids, enzymes, cells, and other biomaterials) which can selectively react with only a specific substance. The analyte molecules are transferred to the receptor in the following three ways: micro/nanofluidic or microcurrent concentration-dependent systems, filtration, and selection-dependent methods.[22] The bioreceptor part is of particular importance and is considered the major component of the biosensor, because it basically performs the biorecognition act. Bioreceptors used in biosensors include enzymes, antibodies, cell receptors, nucleic acids of DNA or RNA, microorganisms or whole cells, synthetic tissues, and receptors.[22,23]

Aptamer: The term aptamer is derived from Latin and Greek words (aptos) meaning "to fit". Aptamers are short fragments of oligonucleotides, peptides, and PNAs, which bind various biological, organic, and mineral targets specifically and with high affinity. Because of their folding ability, aptamers are able to form second and third structures that are expected to bind target structures at the picomole or nanomole unit.[24-26] The growing number of aptamer-related studies (Figure 2) indicates the importance of these macromolecules. Compared with monoclonal antibodies, these biomolecules not only have the advantages of antibodies, but also overcome many of their weaknesses.[27] These macromolecules have higher temperatures, greater environmental stability, and the ability to be denatured and renaturated.[28] The production and detection of aptamers are far simpler, less costly, and faster than the production of monoclonal antibodies.[29] They have an extraordinary repeatability,[5,6] less immunogenicity,[7,8] a variety of targets, and can be synthesized against a wide range of substances, molecules, and even toxic and non-immunogenic ions.[5] Some of the characteristics of these magic molecules along with antibodies are presented in Table 1.

The following benefits are mentioned for aptamers in comparison with antibodies[30-33]:

Apta-biosensors: As noted above, a biosensor is a sensor in which biological components are used to detect a particular analyte.[34] Aptamers are used for detection proposes according to different strategies, and aptamers can be classified accordingly. The apta-biosensors can be classified into label-free, label-dependent, or nano-apta-biosensor groups. Label-free aptasensors do not need a special label to detect an analyte, and the signal is directly amplified and recorded.[35] Sensors in this category can also be classified according to the type of message transmission system, such as:

Surface plasmon resonance aptasensors: Surface plasmon resonance (SPR) is a reference optical method. The resonance angle of the gold disk surface has been changed and is reported with the resonance unit (Ru) by stabilizing a ligand on the surface of a chip of plasmon-containing metals (for example, gold) and the introduction of the flow of liquid

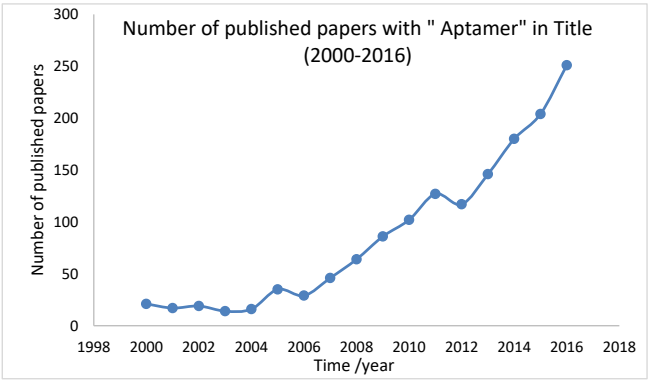

Figure 2. Statistics of Articles Published During the Years 2000-2016.

Table 1. Comparison of Antibodies and Aptamers in Terms of Different Indicators

Characteristics	Antibody	Aptamer
Binding affinity	µM-pM intervals	µM-pM intervals
Production Process	• The presence of contamination in the production process may affect the quality of the final product. • It is difficult to produce antibodies against a toxic substance that is not tolerated by an animal. • To produce antibodies against non-immunogenic targets, these targets should be conjugated or changed in some way.	• Chemical • Significant large-scale synthesizability • The need for repetitive cycles in the laboratory to isolate a specific aptamer against a detected target • Isolable against almost any target •Cost-effective
Immunization	• High immunogenicity	• Non/Less - immunogenic
Batch-to-batch variation	• The possibility of a large difference from one package to another	• The same activity in all synthesized batches
Stability	• Light-sensitive • Irreversible denaturation in the face of difficult conditions • Resistance to nuclease degeneration	• Heat-resistance • The ability to return to the main conformation at lower temperatures • Persistence against denaturation/renaturation cycles • Nuclease-sensitive
Shelf life	• Limited shelf life	• Easy storage in lyophilized powder form or storage solution in -20°C for an unlimited period.
Conformation	• Having a specific structure even without the presence of the ligand	• Having no structure in the solution space and folding into a 3-dimensional structure after binding
The possibility to apply chemical changes in a specific region	• Restrictions on the application of chemical changes	• Simple and easy process of making changes • Labeling/conjugation of chemicals both during and after synthesis
Stabilization	• Generally, antibody molecule orientations are randomly seen.	• Simple stabilization in '5 and '3 regions
Size	• Large size does not allow kidney filtration and limits the availability of antibodies to many of the biostructures.	• Small size allows the aptamer to easily enter into biological structures. • It is sensitive to kidney filtration and requires more modifications, such as PEG.

containing the target ligand at a constant and specified speed due to the ligand-target interaction. These units are increased proportionally to the concentration of the reactive component in the liquid phase.[36]

Quartz crystal microbalance aptasensors: Quartz crystal microbalance (QCM) is another technology used in combination with aptamers to detect various factors. In this method, a quartz piece is placed between two electrodes, and biomolecules (for example, an aptamer) are stabilized on electrodes. The quartz crystal frequency changes of this system are observed at the same time using a frequency meter; if the target molecule binds the bioreceptor, the mass changes and the frequency decreases.[36]

Surface acoustic wave aptabiosensors: Sensors that work based on short-acoustic waves have recently been used in combination with aptamers. In some studies, a sensitive surface is engraved using lithography. When the aptamer is stabilized by juxtaposing the analyte with a biochip, the acoustic-wave changes are recorded by a computer, and tracking and measurement are reported as compared to the base state.[37,38]

Cantilever aptasensors: There is a vibrational thin striped metal piece in this type of aptasensor, the upper plate of which is uniformly coated with aptamers, which bind to an electrochip from its narrow tip. These aptasensors are mainly used in the gas phase, but they are also used in solutions in practice and to measure the frequency variation of the quartz oscillator plate that occurs due to the surface mass absorption of the analyte in the oscillator. These sensors are subjected to the analyte, and the analyte-aptamer binding changes the pressure due to a mass increase in the vibration of the cantilever plate, which is transmitted to the electrochip and forms the basis of the tracking and measurement processes.[39]

Label-dependent aptasensors: To visualize and track the outcome of the aptamer-target reaction in this type of aptasensor, the analyte needs to be labeled. If the target component is labeled, the signal should be reported indirectly. That is, the analyte concentration is obtained by calculating the light or color changes and comparing the results with the base state. Some of these apta-biosensors include:

Optical aptasensors: Aptamers have been used as bio-receptors in biosensors based on optical signals which are often detectable using methods of measuring fluorescence signals, chemiluminescence, or optical methods with higher wavelengths (known as colorimetry).

Fluorescence-based aptasensors: Fluorescence-based aptasensors use fluorescence labels for ultimate tracking. In this method, for example, fluorescence caused by fluorescein isothiocyanate is altered by the establishment of an aptamer-target interaction which can be tracked and recorded. In a simple form, however, the aptamer should be labeled using both fluorescence and quencher. That is, the presence of a fluorophore-quencher pair is obligatory. The aptamer must have a definite shape; for example, it must be like a hairpin or consist of complementary components, and opened when binds the analyte, loop or a double-strand, and the signal is

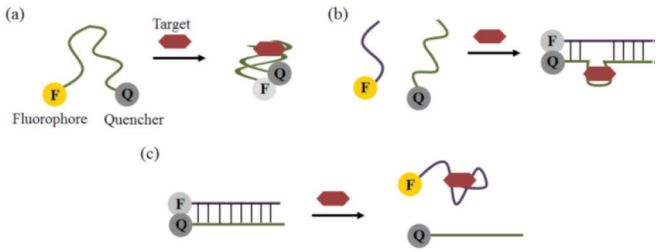

Figure 3. Fluorescence-Based Aptasensors.[40]

on or off (Figure 3). One study used a fluorescence-based aptasensor sample, and the Förster resonance energy transfer of cocaine was successfully detected at a detection limit ranging from 100 nmol to 900 µmol.[40,41]

Chemiluminescence aptasensor: Luminescence is a general term meaning that light is caused to be emitted from certain compounds based on the process of changing energy levels in a molecule. When the molecular is excited, it becomes energetic and releases its energy as light after returning to the base state. If the luminescence is caused by the excitation energy of a chemical or electrochemical reaction, it is called chemiluminescence. Nano-aptasensors, which produce or enhance the signal using a chemiluminescence process, have good competitive advantages because of their molecular nature.[15,42,43]

Colorimetric aptasensors: Materials or labels are either found in nature or made by researchers; in the presence of an analyte or a change in concentration, they cause color changes in the environment. These changes can be detected using colorimetric or photometric instruments or even the naked eye.

Nano-aptabiosensors: A nano-biosensor is referred to as a sensing system which has, at least, a nanostructure in its construction. The use of nanomaterials greatly increases the sensitivity of this system. The application of nanotechnology in molecular, atomic, and subatomic detection is a relatively new field of science that is also known as nano-detection. Nano-sensors which are based on biological sciences or applied in biological sciences are called nano-biosensors. However, this definition is not universally accepted, and some apply the use of bio-elements in the preparation of nano-sensors only as naming criteria. If an aptamer is used as a bioreceptor in the biosensor, it is called a nano-aptasensor.[9] Aptamers are compatible with different types of electrochemical, acoustic, fluorescence, and piezoelectric signals, and, while possessing excellent biodetection, they also have the ability to bind and combine with organic, inorganic, and mineral components as well as quantum dots and other components. They also play an important role in detecting biological agents in combination with these nanomaterials. The use of nano-aptasensors has led to the detection of very low levels of chemical (toxins and ions) and bio-contaminants (viruses, fungi, parasites, bacteria, molecules, and macromolecules) in the agricultural, food, and pharmaceutical industries as well as in military, police, and judicial areas.[36,44,45] The detectability of some of these sensors reaches 1 nmol in 15 minutes while reducing the sample size by 10 µL.[46] Nanomaterials are at the center of attention in most studies because of their characteristics, including their unique size-dependent optical properties, shape and chemical composition, high surface energy level, high surface-volume ratio, and adjustable surface properties. The contribution of nanomaterials and aptamers has improved signal detection, increased sensitivity, increased selectivity, extended linearity, and, in general, facilitates the better detection of various chemical and biological agents. In the last 10 years, nano-aptasensors have been used and investigated based on different sensing strategies such as colorimetric, fluorescence, electrochemical, current changes, surface properties changes, electromagnetic spectrum changes, etc, in various industrial, hygiene-health, defense-security, and research fields.[47]

The use of metal nanoparticles in nano-aptasensors: Metal nanoparticles may account for the highest number of nanomaterials used in sensors (Table 2). Gold, iron oxides, and silver nanoparticles are the most common metal nanoparticles used in this field.[47] Metal nanoparticles exhibit vast change in their properties, i.e. size and distance, and have a high surface-volume ratio which makes them suitable options to be used as colorimetric nano-biosensors.[48] The appropriate properties of sensors, detectors, and reporters are usually heavily size-dependent. In addition, the combination of metal nanoparticles (gold-silver) or special shapes of nanomaterials (gold nanorods) consist of two SPR bands proportional to their length-to-width ratios, which in turn paves the way for their more widespread use.[49] These properties have led to the use of metal nanomaterials in the fabrication of nano-biosensors based on various sensing methods (Table 2).[50-52]

Use of quantum dots for the production of nano-aptasensors: Quantum dots are defined as small semiconductor crystals. An electromagnetic field emits light at different wavelengths by controlling the dimensions of the quantum dots. Since quantum dots can produce light with particular wavelengths, these fine crystals are used in optical devices. In this field, quantum dots can be used to make infrared detectors and light emitting diodes.[53-58]

The use of nanotubes in the production of nano-aptasensors: Single-walled and multi-walled carbon nanotubes, due to their unique mechanical and electronic properties, have recently been used in the variety of applications, including their use as highly-precise and fast sensors for detection of substances at very low concentrations. These sensors are highly sensitive in detecting very small concentrations of gas molecules at room temperature. These nanomaterials have been used in different fields due to their high electrical conductivity. These properties have important implications for detection applications. Maehashi et al used a sample of nano-aptasensors mixed with single-walled carbon nanotubes to detect immunoglobulin E (IgE), which has a nanomolar detection limit.[71]

The use of nano-tools in the production of nano-aptasensors: Studies on nano-tools are part of the up-to-date scientific research in the world. Research results published in *Biosensor and Bioelectronics* in 2009 reported a biosensor gold electrode surface that was modified in such a way that gold nanoparticles were deposited electrochemically on a smooth electrode surface. The electrode was then immersed

Table 2. Use of Metal Nanoparticles in the Fabrication of Various Types of Nano-Aptasensors[58-70]

Probe	Target	Strategy	Detection Time	LOD
Apt-Au NPs	Adenosine	Colorimetric	10 s	0.1 mM
Apt-Au NPs	Adenosine	Colorimetric	5 min	20 µM
Apt-Au NPs	Adenosine	Colorimetric	1 min	10 µM
Apt-Au NPs	Adenosine	Colorimetric	10 min	20 µM
Apt-Au NPs	Adenosine	SPR	30 min	1 nM
Apt-Au NPs	Adenosine	Electrochemical	90 min	180 pM
Apt-QD & Au NPs	Adenosine	Fluorescence	1 min	50 µM
Apt-Au NPs	Cocaine	Colorimetric	10 min	20 µM
Apt-Au NPs	Cocaine	Colorimetric	10 s	25 µM
Apt-Au NPs	Cocaine	Colorimetric	5 min	10 µM
Apt-QD	Cocaine	Fluorescence	1 min	120 µM
Apt-QD & Atto 590	Cocaine	Fluorescence	15 min	1 µM
Apt-QD & Cy5 & Iowa Black RQ	Cocaine	Fluorescence	-	0.5 µM
Au NPs & Fc-Apt	Cocaine	Electrochemical	5 min	0.5 µM
Apt-Au NPs	ATP	Colorimetric	30 min	0.6 µM
Apt-Au NPs	ATP	Colorimetric	30 min	10 nM
Apt-Au NPs & Au NPs	ATP	SALDI-MS	10 min	0.48 µM
Apt-QD & Cy5	ATP	Fluorescence	-	24 µM
Apt-SiO2@Fe3O4	AMP	Fluorescence	-	0.1 µM
Apt-Au NPs & DNA-Au NP-Hg2+ aggregates	Cysteine	Colorimetric	-	100 nM
Apt-Au NPs	Hg2+	Colorimetric	-	100 nM
Apt-Au NPs	Hg2+	Colorimetric	30 min	10 nM
Apt-Au NPs	Hg2+	Colorimetric	10 min	25 nM
Apt-Au NPs	Hg2+	Colorimetric	5 min	0.6 nM
Apt-Au NPs	Hg2+	Colorimetric	-	1 µM
Apt-Au NP	Hg2+	Colorimetric	-	250 nM
Apt-Au NPs & DNAzyme	Hg2+	Colorimetric	-	1 nM
Au NPs & Dye-Apt	Hg2+	Fluorescence	30 min	40 nM
Apt-Au NPs	K+	Colorimetric	4 min	1 mM
Apt-Au NPs	K+	Colorimetric	10 min	0.5 mM
Apt-Au NPs & DNAzyme	Pb2+	Colorimetric	-	100 nM
Apt-Au NPs & DNAzyme	Pb2+	Colorimetric	10 min	0.4 µM
Apt-Au NPs & DNAzyme	Pb2+	Colorimetric	5 min	0.1 µM
Apt-Au NPs & DNAzyme	Pb2+	Colorimetric	6 min	120 nM
gold nanorod–nanoparticle (AuNR–AuNP)	Thrombin	SERS LSPR (NPPR)	-	887 pM 20 nM

in a bath containing para-benzoquinone, chitosan, glucose oxidase, and ionic liquid to complete the preparation of enzyme electrode. The response time of this amperometric biosensor for glucose was less than 5 seconds. Compared with smooth gold electrode modification (without the use of gold nanoparticles), sensitivity was increased 2.5 times, and the detection limit was improved 20 times.[72] Given the breadth and variety of strategies for using nano-aptasensors, the classification and grouping of these nano-tools is essential in spite of their complexity.[47]

Classification of Nano-Aptasensors

Like other bio-sensing groups, nano-aptasensors are divided into different types based on detection methods and strategies. According to the reporting method, they can be divided into colorimetric, fluorescence, mass spectrometry sensors, etc.

Colorimetric nano-aptasensors: The use of nano-aptasensors in colorimetric-based strategies involves a wide range of methods. In a simple example, variations in environmental colors due to the presence or absence of an analyte and the subsequent accumulation or diffusion of nanoparticles were considered as signals. Using this method, adenosine triphosphate was detected with a detection limit of 0.3 to 20 µm during several minutes.[60] With another method, researchers labeled aptamers using quantum dots. Considering the presence or absence of the target molecule, they measured the color variation caused by the quantum dots and reported it as an indicator of the presence of the target molecule. For example, Liu et al were able to detect cocaine to a final limit of 10 to 20 µM.[59]

Wang et al presented a more sensitive and precise method for detecting small molecules by stabilizing single-stranded DNA aptamers on gold plates in SPR. In this method, the aptamer structural changes caused by the binding of the target agent led to the binding of the complementary strands of DNA labeled with gold nanoparticles, which in turn amplified the SPR signal. The detection limit of this method was estimated to range from 1 micromole to one nanomole.[61] Gold nanomaterials are often used in colorimetric nano-aptasensors, so aptamar's thiol derivatives covalently bind so

aptamers derivatives immobilised on nanosurface covalently (au-s). These derivatives are more expensive than the non-manipulated types. To overcome this problem, Wang et al used genetic nano manipulated aptamers to develop an nano detection method that can detect adenosine tri-phosphate (2 µL) at at 37°C during a period of less than 1 hour a detection limit of 2 µmol, with a naked eye.[70] Chen et al increased the adenosine detection limit by up to 10 nM using a similar method.[69] In a colorimetric nano-aptasensor sample, they detected a protein target with a detection limit of up to 0.83 nM using non-manipulated gold nanoparticles (73). Wang et alused the same technique to increase the thrombin detection limit to 9 nm.[74] Jana et al also achieved similar results using the same method.[75] Xu et al detected thrombin with a detection limit of 2.5 nanomolar using nano-aptasensors based on dry-reagent strip gold nanoparticles. The author stated that thrombin was detected in human plasma up to a dilution rate of 0.6 pmol.[76]

Fluorescence nano-aptasensors: Fluorescent nanomaterials, including gold nanoparticles, silver crystals, and quantum dots, have a lot of potential for sensing applications. Fluorescent nanomaterials, especially quantum dots, have many advantages over traditional fluorescent materials, including optical stability, chemical stability, limited emissions, and extensive excitation.[77]

Researchers can use various luminescence methods, including chemiluminescence, transient energy luminescence, and delayed luminescence. Each of these scientific fields can have an impact on the promotion of nano-aptasensors. Emission and quenching act as on and off switches and make the sensor externally controllable. Song et al provided a sample of a fluorescent nano-aptasensor that was capable of detecting the amp up to 0.1 µM.[78]

Mass spectrometry-based nano-aptasensors: Nanomaterials are used in mass spectrometry to detect various agents. Fe_3O_4, gold, TiO_2 nanoparticles, etc. are more noticeable with this method. Gold nanoparticles (13 nm particle size) together with an aptamer were used to detect adenosine triphosphate and made it possible to detect this substance to about 3-48 µm.[79] Nano-aptasensors can also be classified based on the type of transducer, such as the field-effect transistor aptasensor.

Feld-effect transistor aptasensor: Field-effect transistor (FET) aptasensor are a series of transistors which control the current by an electric field. Given that only one carrier (free electron or electron cavity) is involved in the electrical current in these transistors, they can be considered as unipolar transistors that are placed against bipolar transistors. FETs are sensitive to chemical changes in which the analyte-active coating interaction results in a change in the intensity of the source current. The analyte-active coating interaction is similar to the potentiometric ion-selective sensors in terms of its chemical property. Over the past decade, researchers have offered nano-aptasensors using aptamers and field-effect transistors which were capable of precisely detecting and measuring analytes such as immunoglobulin E or pathogenic bacteria, in small dimensions, small sample sizes, and with high sensitivity. This sensing method can be very efficient.[71,80]

Classification of Nano-Aptasensors Based on Type of Transducer

Physical or chemical changes resulting from the aptamer-analyte attachment or detachment should be converted by a transducer to a transmittable signal. By converting signals based on different strategies, this section of sensor attempts to establish a quantitative relationship between the amount of analyte presence and the comprehensible signal for the processor of the nano-aptabiosensor.[81]

Electrochemical nano-aptasensors: In addition to being highly sensitive to and compatible with modern nanostructure and miniatorized system, electrochemical nano-aptasensors are more coherent than other similar ones. Some of these electrochemical nano-aptasensors are electrochemical impedance spectroscopy (EIS), potentiometric, ion selective electrode (ISE), electrochemiluminescence (ECL), closing velocity (CV), and differential pulse voltammetry (DPV) nano-aptasensors.[15,16,34,82,83]

Capacitance measurement electrochemical nano-aptasensor: Changes are made in the capacitance of a capacitor in the signal transducer section of this type of nano-aptasensor. In fact, the basis for the formation of these sensors is the convergence and accumulation of basic and applied sciences in the fields of chemistry, biology, and physics that finally come to serve nano-biotechnology. The basis of this type of biosensor is the change in dielectric properties of an electrode surface. Previous research has shown that such kind of biosensor can be used to detect the analyte-element binding stabilized on the surface of an electrode.[84] The binding of an analyte to a bio-element stabilized in a capacitor can directly change the capacitor capacity without the need for labeling.[85] In their study, Rashidiani et al detected nanomolar dilutions of botulinum neurotoxin type A light chain in an aptamer binding in a capacitive cell using an LCR meter (Figure 4). Another disadvantage associated with aptasensors is related to their nature. That is, the application of these materials requires a high level of skill, while most diagnostic laboratories do not have professional scientific cadres, and the use of these sensors in home detection tools makes the problem more complicated.[59] Using this type of sensor in research and applied fields is a step toward the widespread use of this technology.

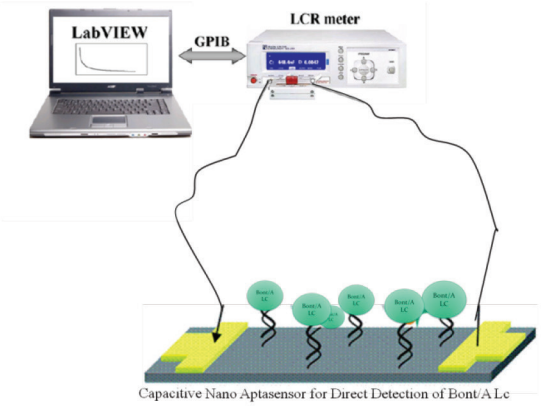

Figure 4. The Nano-Aptasensor Designed in This Research.

Conclusions

New approaches to the production of biosensors, in addition to the sharp reduction in detection limits, detection process times, test costs, and the need for user experience and skill, have increased the sensitivity, biocompatibility, and user friendliness of biosensors and the shelf life of materials and reagents.[15,16] Some of the primary biosensors were the size of a workroom, but recently, a mass spectrometer with the size of a suitcase and biosensors measuring a few cubic centimeters in size have surprised many consumers.[18] It should be explicitly stated that their advantages give nano-aptasensors the potential to be used in analyzing devices (biosensors, disease diagnosis, rapid detection of pesticides and risk factors), research areas (chemical and biochemical analysis, and the discovery and measurement of new drugs), and industrial areas (food industry, defense and security fields, and reagents).[27] This has made it a tempting market opportunity. Nano-sensors are inherently smaller (albeit not always) and more sensitive than other sensors, and in combination with aptamers, their sensitivity and specificity are significantly enhanced. In conclusion, because nano-aptasensors reduce the purchasing and operating costs, their use as arrays and masses can be cost-effective and can also be used extensively in parts. The military and national security sector also needs very sensitive sensors that can be used widely to monitor threats. In the medical field, there is also a need for highly sensitive sensors such as lab-on-a-chip (LOC) devices that can detect the smallest symptoms of a disease. Under optimal conditions, nano-aptasensors should have a high binding affinity to the target (low detection limit), high specificity (low interference), wide dynamic range, fast response time, and a high shelf-life. The results of tests on aptasensors in detecting various analytes (protein, peptide, small molecules, metal ions, and whole cells, etc) indicate high repeatability, excellent accuracy, and ease of use. The dissociation constant (KD) of aptamer-target has been reported as ranging from micromole to picomole,[47] but have not yet been fully commercialized in clinical and laboratory detection fields. One reason for the absence of aptamer-based detection devices may be the sensitivity of the conditions for their application and their lack of user-friendliness for commercialization and entry into the market.[59] However, the use of simple techniques such as capacitor capacity measurement in aptamer-based sensors can be an effective step in the enhancement of the user-friendliness of this type of sensor. Indicators that make this type of apta-biosensor superior include high sensitivity and low detection limit, short testing times, higher detection speed, the application of lower analyte volumes, lower price, miniaturization potential, and mass production.[83]

Authors' Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors declare they have no conflicts of interest.

References

1. Lindstrom M, Korkeala H. Laboratory diagnostics of botulism. Clin Microbiol Rev. 2006;19(2):298-314. doi:10.1128/CMR.19.2.298-314.2006.
2. Song K-M, Lee S, Ban C. Aptamers and their biological applications. Sensors. 2012;12(1):612-631. doi:10.3390/s120100612.
3. Capek P, Dickerson TJ. Sensing the deadliest toxin: technologies for botulinum neurotoxin detection. Toxins (Basel). 2010;2(1):24-53. doi:10.3390/toxins2020024.
4. Campolongo MJ, Tan SJ, Xu J, Luo D. DNA nanomedicine: Engineering DNA as a polymer for therapeutic and diagnostic applications. Adv Drug Deliv Rev. 2010;62(6):606-616. doi:10.1016/j.addr.2010.03.004.
5. Jayasena SD. Aptamers: an emerging class of molecules that rival antibodies in diagnostics. Clin Chem. 1999;45(9):1628-1650.
6. Ferreira CSM, Missailidis S. Aptamer-based therapeutics and their potential in radiopharmaceutical design. Braz Arch Biol Technol. 2007;50:63-76. doi:10.1590/S1516-89132007000600008.
7. Preclinical and phase 1A clinical evaluation of an anti-VEGF pegylated aptamer (EYE001) for the treatment of exudative age-related macular degeneration. Retina. 2002;22(2):143-152. doi:10.1097/00006982-200204000-00002.
8. Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: phase II study results. Ophthalmology. 2003;110(5):979-986. doi:10.1016/s0161-6420(03)00085-x.
9. Lim YC, Kouzani AZ, Duan W. Aptasensors design considerations. Computational intelligence and intelligent systems. Berlin, Heidelberg: Springer; 2009:118-127. doi:10.1007/978-3-642-04962-0.
10. Finney DJ. The median lethal dose and its estimation. Arch Toxicol. 1985;56(4):215-218.doi:10.1007/bf00295156.
11. Pearce LB, Borodic GE, First ER, MacCallum RD. Measurement of botulinum toxin activity: evaluation of the lethality assay. Toxicol Appl Pharmacol. 1994;128(1):69-77. doi:10.1006/taap.1994.1181.
12. Doellgast GJ, Triscott MX, Beard GA, et al. Sensitive enzyme-linked immunosorbent assay for detection of Clostridium botulinum neurotoxins A, B, and E using signal amplification via enzyme-linked coagulation assay. J Clin Microbiol. 1993;31(9):2402-2409.
13. Wictome M, Newton K, Jameson K, et al. Development of an in vitro bioassay for Clostridium botulinum type B neurotoxin in foods that is more sensitive than the mouse bioassay. Appl Environ Microbiol. 1999;65(9):3787-3792.
14. Dhaked RK, Singh MK, Singh P, Gupta P. Botulinum toxin: bioweapon & magic drug. Indian J Med Res. 2010;132:489-503.
15. Wang X, Zhou J, Yun W, et al. Detection of thrombin using electrogenerated chemiluminescence based on Ru(bpy)3(2+)-doped silica nanoparticle aptasensor via target protein-induced strand displacement. Anal Chim Acta. 2007;598(2):242-248. doi:10.1016/j.aca.2007.07.050.
16. Ikebukuro K, Kiyohara C, Sode K. Novel electrochemical sensor system for protein using the aptamers in sandwich manner. Biosens Bioelectron. 2005;20(10):2168-2172. doi:10.1016/j.bios.2004.09.002.
17. Wu J, Fu Z, Yan F, Ju H. Biomedical and clinical applications of immunoassays and immunosensors for tumor markers. TrAC Trends in Analytical Chemistry. 2007;26(7):679-688. doi:10.1016/j.trac.2007.05.007.
18. Kissinger PT. Biosensors-a perspective. Biosens Bioelectron. 2005;20(12):2512-2516. doi:10.1016/j.bios.2004.10.004.
19. Schiavo G, Santucci A, Dasgupta BR, et al. Botulinum neurotoxins serotypes A and E cleave SNAP-25 at distinct COOH-terminal peptide bonds. FEBS Lett. 1993;335(1):99-103. doi:10.1016/0014-5793(93)80448-4.
20. Gan N, Wang LY, Xu WM, Li TH, Jiang QL. Electrochemical immuno-biosensor for the rapid determination of Nuclear Matrix Protein 22 (NMP22) antigen in urine samples by Co (III) phthlocyanine/Fe3O4/Au collide coimmobilized electrode. Chin J Anal Chem. 2007;35(11):1553-1558. doi:10.1016/S1872-2040(07)60093-0.
21. Zhang L, Yuan R, Huang X, Chai Y, Cao S. Potentiometric

immunosensor based on antiserum of Japanese B encephalitis immobilized in nano-Au/polymerized o-phenylenediamine film. Electrochem commun. 2004;6(12):1222-1226. doi:10.1016/j.elecom.2004.09.020.
22. Erickson D, Mandal S, Yang AHJ, Cordovez B. Nanobiosensors: optofluidic, electrical and mechanical approaches to biomolecular detection at the nanoscale. Microfluid Nanofluidics. 2008;4(1):33-52. doi:10.1007/s10404-007-0198-8.
23. Zhang L, Liu Y, Chen T. A mediatorless and label-free amperometric immunosensor for detection of h-IgG. Int J Biol Macromol. 2008;43(2):165-169. doi:10.1016/j.ijbiomac.2008.04.010.
24. Ellington AD, Szostak JW. In vitro selection of RNA molecules that bind specific ligands. Nature. 1990;346(6287):818-822. doi:10.1038/346818a0.
25. Tuerk C, Gold L. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. Science. 1990;249(4968):505-510. doi:10.1126/science.2200121.
26. Oliphant AR, Brandl CJ, Struhl K. Defining the sequence specificity of DNA-binding proteins by selecting binding sites from random-sequence oligonucleotides: analysis of yeast GCN4 protein. Mol Cell Biol. 1989;9(7):2944-2949. doi:10.1128/MCB.9.7.2944.
27. Song KM, Lee S, Ban C. Aptamers and their biological applications. Sensors(Basel). 2012;12(1):612-631. doi:10.3390/s120100612.
28. Mascini M. Aptamers and their applications. Anal Bioanal Chem. 2008;390(4):987-988. doi:10.1007/s00216-007-1769-y.
29. Birch JR, Racher AJ. Antibody production. Adv Drug Deliv Rev. 2006;58(5-6):671-685. doi:10.1016/j.addr.2005.12.006.
30. Keefe AD, Pai S, Ellington A. Aptamers as therapeutics. Nat Rev Drug Discov. 2010;9(7):537-550. doi:10.1038/nrd3141.
31. Mairal T, Ozalp VC, Lozano Sanchez P, Mir M, Katakis I, O'Sullivan CK. Aptamers: molecular tools for analytical applications. Anal Bioanal Chem. 2008;390(4):989-1007. doi:10.1007/s00216-007-1346-4.
32. Song S, Wang L, Li J, Fan C, Zhao J. Aptamer-based biosensors. TrAC Trends in Analytical Chemistry. 2008;27(2):108-117. doi:10.1016/j.trac.2007.12.004.
33. Nimjee SM, Rusconi CP, Sullenger BA. Aptamers: an emerging class of therapeutics. Annu Rev Med. 2005;56:555-583. doi:10.1146/annurev.med.56.062904.144915.
34. Numnuam A, Chumbimuni-Torres KY, Xiang Y, et al. Aptamer-based potentiometric measurements of proteins using ion-selective microelectrodes. Anal Chem. 2008;80(3):707-712. doi:10.1021/ac701910r.
35. Zhu Y, Chandra P, Song KM, Ban C, Shim YB. Label-free detection of kanamycin based on the aptamer-functionalized conducting polymer/gold nanocomposite. Biosens Bioelectron. 2012;36(1):29-34. doi:10.1016/j.bios.2012.03.034.
36. Sett A, Das S, Sharma P, Bora U. Aptasensors in Health, Environment and Food Safety Monitoring. Open Journal of Applied Biosensor. 2012;1(2):9-19. doi:10.4236/ojab.2012.12002.
37. Gronewold TM, Glass S, Quandt E, Famulok M. Monitoring complex formation in the blood-coagulation cascade using aptamer-coated SAW sensors. Biosens Bioelectron. 2005;20(10):2044-2052. doi:10.1016/j.bios.2004.09.007.
38. Schlensog MD, Gronewold TMA, Tewes M, Famulok M, Quandt E. A Love-wave biosensor using nucleic acids as ligands. Sens Actuators B Chem. 2004;101(3):308-315. doi:10.1016/j.snb.2004.03.015.
39. Kramer M. Nano–Cantilever Biosensor Design and Analysis. 2006.
40. Stojanovic MN, de Prada P, Landry DW. Aptamer-Based Folding Fluorescent Sensor for Cocaine. J Am Chem Soc. 2001;123(21):4928-4931. doi:10.1021/ja0038171.
41. Nutiu R, Li Y. Structure-switching signaling aptamers. J Am Chem Soc. 2003;125(16):4771-4778. doi:10.1021/ja028962o.
42. Yu Y, Cao Q, Zhou M, Cui H. A novel homogeneous label-free aptasensor for 2,4,6-trinitrotoluene detection based on an assembly strategy of electrochemiluminescent graphene oxide with gold nanoparticles and aptamer. Biosens Bioelectron. 2013;43:137-142. doi:10.1016/j.bios.2012.12.018.
43. Xu S, Zhang X, Liu W, Sun Y, Zhang H. Reusable light-emitting-diode induced chemiluminescence aptasensor for highly sensitive and selective detection of riboflavin. Biosens Bioelectron. 2013;43:160-164. doi:10.1016/j.bios.2012.12.012.
44. Cella LN, Sanchez P, Zhong W, Myung NV, Chen W, Mulchandani A. Nano aptasensor for protective antigen toxin of anthrax. Anal Chem. 2010;82(5):2042-2047. doi:10.1021/ac902791q.
45. Zhu N, Gao H, Xu Q, Lin Y, Su L, Mao L. Sensitive impedimetric DNA biosensor with poly(amidoamine) dendrimer covalently attached onto carbon nanotube electronic transducers as the tether for surface confinement of probe DNA. Biosens Bioelectron. 2010;25(6):1498-1503. doi:10.1016/j.bios.2009.11.006.
46. Yoon J, Choi N, Ko J, Kim K, Lee S, Choo J. Highly sensitive detection of thrombin using SERS-based magnetic aptasensors. Biosens Bioelectron. 2013;47:62-67. doi:10.1016/j.bios.2013.03.003.
47. Chiu TC, Huang CC. Aptamer-functionalized nano-biosensors. Sensors (Basel). 2009;9(12):10356-10388. doi:10.3390/s91210356.
48. Burda C, Chen X, Narayanan R, El-Sayed MA. Chemistry and properties of nanocrystals of different shapes. Chem Rev. 2005;105(4):1025-1102. doi:10.1021/cr030063a.
49. Huang YF, Huang KM, Chang HT. Synthesis and characterization of Au core-Au-Ag shell nanoparticles from gold seeds: impacts of glycine concentration and pH. J Colloid Interface Sci. 2006;301(1):145-154. doi:10.1016/j.jcis.2006.04.079.
50. Wang H, Yang R, Yang L, Tan W. Nucleic acid conjugated nanomaterials for enhanced molecular recognition. ACS Nano. 2009;3(9):2451-2460. doi:10.1021/nn9006303.
51. Liu J, Cao Z, Lu Y. Functional nucleic acid sensors. Chem Rev. 2009;109(5):1948-1998. doi:10.1021/cr030183i.
52. Lee JS, Ulmann PA, Han MS, Mirkin CA. A DNA-gold nanoparticle-based colorimetric competition assay for the detection of cysteine. Nano Lett. 2008;8(2):529-533. doi:10.1021/nl0727563.
53. Carrillo-Carrion C, Simonet BM, Valcarcel M. Determination of TNT explosive based on its selectively interaction with creatinine-capped CdSe/ZnS quantum dots. Anal Chim Acta. 2013;792:93-100. doi:10.1016/j.aca.2013.07.004.
54. Bogomolova A, Aldissi M. Real-time aptamer quantum dot fluorescent flow sensor. Biosens Bioelectron. 2011;26(10):4099-4103. doi:10.1016/j.bios.2011.04.001.
55. Zhou Z, Du Y, Dong S. DNA-Ag nanoclusters as fluorescence probe for turn-on aptamer sensor of small molecules. Biosens Bioelectron. 2011;28(1):33-37. doi:10.1016/j.bios.2011.06.028.
56. Yang H, Ji J, Liu Y, Kong J, Liu B. An aptamer-based biosensor for sensitive thrombin detection. Electrochem commun. 2009;11(1):38-40. doi:10.1016/j.elecom.2008.10.024.
57. Warner MG, Grate JW, Tyler A, et al. Quantum dot immunoassays in renewable surface column and 96-well plate formats for the fluorescence detection of botulinum neurotoxin using high-affinity antibodies. Biosens Bioelectron. 2009;25(1):179-184. doi:10.1016/j.bios.2009.06.031.
58. Liu J, Lee JH, Lu Y. Quantum dot encoding of aptamer-linked nanostructures for one-pot simultaneous detection of multiple analytes. Anal Chem. 2007;79(11):4120-4125. doi:10.1021/ac070055k.
59. Liu J, Mazumdar D, Lu Y. A simple and sensitive "dipstick" test in serum based on lateral flow separation of aptamer-linked nanostructures. Angew Chem Int Ed Engl. 2006;45(47):7955-7959. doi:10.1002/anie.200603106.
60. Liu J, Lu Y. Fast colorimetric sensing of adenosine and cocaine based on a general sensor design involving aptamers and nanoparticles. Angew Chem Int Ed Engl. 2005;45(1):90-94. doi:10.1002/anie.200502589.
61. Wang J, Zhou HS. Aptamer-based Au nanoparticles-enhanced surface plasmon resonance detection of small molecules. Anal Chem. 2008;80(18):7174-7178. doi:10.1021/ac801281c.
62. Zhao W, Chiuman W, Lam JC, et al. DNA aptamer folding on gold nanoparticles: from colloid chemistry to biosensors. J Am Chem

Soc. 2008;130(11):3610-3618. doi:10.1021/ja710241b.
63. Zhang J, Wang L, Pan D, et al. Visual cocaine detection with gold nanoparticles and rationally engineered aptamer structures. Small. 2008;4(8):1196-1200. doi:10.1002/smll.200800057.
64. Li X, Qi H, Shen L, Gao Q, Zhang C. Electrochemical aptasensor for the determination of cocaine incorporating gold nanoparticles modification. Electroanalysis. 2008;20(13):1475-1482. doi:10.1002/elan.200704193.
65. Zhang CY, Johnson LW. Single quantum-dot-based aptameric nanosensor for cocaine. Anal Chem. 2009;81(8):3051-3055. doi:10.1021/ac802737b.
66. Zhao W, Chiuman W, Brook MA, Li Y. Simple and rapid colorimetric biosensors based on DNA aptamer and noncrosslinking gold nanoparticle aggregation. Chembiochem. 2007;8(7):727-731. doi:10.1002/cbic.200700014.
67. Zhang S, Xia J, Li X. Electrochemical biosensor for detection of adenosine based on structure-switching aptamer and amplification with reporter probe DNA modified Au nanoparticles. Anal Chem. 2008;80(22):8382-8388. doi:10.1021/ac800857p.
68. Freeman R, Li Y, Tel-Vered R, Sharon E, Elbaz J, Willner I. Self-assembly of supramolecular aptamer structures for optical or electrochemical sensing. Analyst. 2009;134(4):653-656. doi:10.1039/b822836c.
69. Chen SJ, Huang YF, Huang CC, Lee KH, Lin ZH, Chang HT. Colorimetric determination of urinary adenosine using aptamer-modified gold nanoparticles. Biosens Bioelectron. 2008;23(11):1749-1753. doi:10.1016/j.bios.2008.02.008.
70. Wang J, Wang L, Liu X, et al. A Gold Nanoparticle-Based Aptamer Target Binding Readout for ATP Assay. Adv Mater. 2007;19(22):3943-3946. doi:10.1002/adma.200602256.
71. Maehashi K, Katsura T, Kerman K, Takamura Y, Matsumoto K, Tamiya E. Label-free protein biosensor based on aptamer-modified carbon nanotube field-effect transistors. Anal Chem. 2007;79(2):782-787. doi:10.1021/ac060830g.
72. Zeng X, Li X, Xing L, et al. Electrodeposition of chitosan-ionic liquid-glucose oxidase biocomposite onto nano-gold electrode for amperometric glucose sensing. Biosens Bioelectron. 2009;24(9):2898-2903. doi:10.1016/j.bios.2009.02.027.
73. Wei H, Li B, Li J, Wang E, Dong S. Simple and sensitive aptamer-based colorimetric sensing of protein using unmodified gold nanoparticle probes. Chem Commun (Camb). 2007(36):3735-3737. doi:10.1039/b707642h.
74. Wang Y, Li D, Ren W, Liu Z, Dong S, Wang E. Ultrasensitive colorimetric detection of protein by aptamer-Au nanoparticles conjugates based on a dot-blot assay. Chem Commun (Camb). 2008(22):2520-2522. doi:10.1039/b801055b.
75. Jana NR, Ying JY. Synthesis of functionalized Au nanoparticles for protein detection. Adv Mater. 2008;20(3):430-434. doi:10.1002/adma.200701348.
76. Xu H, Mao X, Zeng Q, Wang S, Kawde AN, Liu G. Aptamer-functionalized gold nanoparticles as probes in a dry-reagent strip biosensor for protein analysis. Anal Chem. 2009;81(2):669-675. doi:10.1021/ac8020592.
77. Michalet X, Pinaud FF, Bentolila LA, et al. Quantum dots for live cells, in vivo imaging, and diagnostics. Science. 2005;307(5709):538-544. doi:10.1126/science.1104274.
78. Song Y, Zhao C, Ren J, Qu X. Rapid and ultra-sensitive detection of AMP using a fluorescent and magnetic nano-silica sandwich complex. Chem Commun (Camb). 2009(15):1975-1977. doi:10.1039/b818415a.
79. Huang YF, Chang HT. Analysis of adenosine triphosphate and glutathione through gold nanoparticles assisted laser desorption/ionization mass spectrometry. Anal Chem. 2007;79(13):4852-4859. doi:10.1021/ac070023x.
80. Lee HS, Kim KS, Kim CJ, Hahn SK, Jo MH. Electrical detection of VEGFs for cancer diagnoses using anti-vascular endotherial growth factor aptamer-modified Si nanowire FETs. Biosens Bioelectron. 2009;24(6):1801-1805. doi:10.1016/j.bios.2008.08.036.
81. Tombelli S, Minunni M, Mascini M. Analytical applications of aptamers. Biosens Bioelectron. 2005;20(12):2424-2434. doi:10.1016/j.bios.2004.11.006.
82. Cho EJ, Lee JW, Ellington AD. Applications of aptamers as sensors. Annu Rev Anal Chem (Palo Alto Calif). 2009;2:241-264. doi:10.1146/annurev.anchem.1.031207.112851.
83. Feng K, Sun C, Kang Y, et al. Label-free electrochemical detection of nanomolar adenosine based on target-induced aptamer displacement. Electrochem commun. 2008;10(4):531-535. doi:10.1016/j.elecom.2008.01.024.
84. Chuang YH, Chang YT, Liu KL, Chang HY, Yew TR. Electrical impedimetric biosensors for liver function detection. Biosens Bioelectron. 2011;28(1):368-372. doi:10.1016/j.bios.2011.07.049.
85. Newman A, Hunter K, Stanbro W. The capacitive affinity sensor: a new biosensor. Bordeaux, France: Proceedings of the Second International Meeting on Chemical Sensors; 1986.