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REVIEW ARTICLE

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Biosensors based on aptamer-conjugated gold nanoparticles: A review

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Abstract

Simply synthetized gold nanoparticles have been highly used in medicine and biotechnology as a result of their biocompatibility, conductivity, and being easily functionalized with biomolecules such as aptamer. Aptamer-conjugated gold nanoparticle structures synergically possess characteristics of both aptamer and gold nanoparticles including high binding affinity, high biocompatibility, enhanced target selectivity, and long circulatory half-life. Aptamer-conjugated gold nanoparticles have extensively gained considerable attention for designing of biosensing systems due to their interesting optical and electrochemical features. Moreover, biosensors based on aptamer-gold nanoparticles are easy to use, with fast response, and inexpensive which make them ideal in individualized medicine, disease markers detection, food safety, and so forth. Moreover, due to high selectivity and biocompatibility of aptamer-gold nanoparticles, these biosensing platforms are ideal tools for targeted drug delivery systems. The application of this nanostructure as diagnostic and therapeutic tool has been developed for detection of cancer in the early stage by detecting cancer biomarkers, pathogens, proteins, toxins, antibiotics, adenosine triphosphate, and other small molecules. This review obviously demonstrates that this nanostructure effectively is applicable in the field of biomedicine and possesses potential of commercialization aims.

KEYWORDS
aptamer, biosensor, gold nanoparticles

1 | INTRODUCTION

Aptamers are short single-stranded DNA or RNA, which have the specificity for its own target and binds to it with high affinity. The targets could be either simple inorganic molecules, or simple or complex proteins, or even the whole cell could be the target. Aptamers are neither immunogenic nor toxic and they could be generated much easier than the antibodies. These properties make aptamers ideal/promising alternatives for diagnostic and therapeutic applications.[1] Aptamer generation is done through a procedure called SELEX (Systematic Evolution of Ligands EXponential enrichment) in which the desired binder aptamer is generated and evolved from a random pool of oligonucleotides in several rounds and steps.[2,3] Aptamer-based biosensors with their special

features make them superior over other biological receptors, like antibodies, namely, (a) signal amplification by PCR, RT-PCR, and rolling circle amplification, microarray platforms for quantitative target analysis; (b) flexible structures in presence or absence of the target; (c) well-defined 3D aptamer-target structure; (d) aptamer formation through easy modulation by complementary DNA, which leads to new methods for signal generation like sandwich-type assay; (e) easy modification and labeling with dyes or functional groups; and (f) cognate generation of dual aptamers, which has led to sandwich-type sensing platform application.[4–13] By benefiting from aptamers hybridization properties and strong plasmonic effect of gold nanoparticles, Shu and colleagues designed a highly sensitive photoelectrochemical biosensor based on defect-engineered TiO_2 nanobars, which improved the visible light photoelectric response. It was indicated that the improved PEC sensitivity of the biosensor is positively related to the amount of the target aptamers, which could be used for the quantification of the target aptamer concentration.[14] Another photoelectrochemical-based biosensor with spatial-resolved PEC (SR-PEC) target detection strategy was proposed by Qiu and colleagues, which used carcinoembryonic antigen (CEA)-specific aptamers and capture DNA on two individual photoelectrodes for signal amplification in a "signal-on" and "signal-off" dual signal readouts manner.[15] A photothermal immunoassay biosensing strategy was introduced by Li and colleagues, employing plasmonic $Cu_{2-x}Se$ NCs loaded liposomes with aflatoxin B_1 aptamers assembled on the liposomes. The detection of the given analyte is based on aptamer–target–antibody complex formation that results in temperature increase under NIR irradiation. The increased temperature is in relation with the content of the target.[16]

Gold nanoparticles (AuNPs) have been applied in a wide and diverse range of biomedicines including diagnosis and therapy due to their unique chemical and physical properties; like surface plasmon resonance, redox behavior, conductivity, high surface-to-volume ratio, low toxicity, great biocompatibility etc. Additionally, AuNPs present a wide range of colors related to their size in aqueous solutions and show absorption peaks in a wavelength range of 500–550 nm.[17,18] Bioconjugates of AuNPs such as oligonucleotides, antibodies, and proteins have gained attention as alternative diagnostic platforms.[18] AuNP-based biosensors have been applied for a range of clinical diagnosis methods. For example, platforms for immunoassays in which AuNP–antibody bioconjugates have resulted in signal enhancement for ELISA assays,[19] or AuNP–ssDNA bioconjugates that have developed probes for specific DNA (or RNA) detection like single-nucleotide polymorphism (SNP) and mutations.[20]

Highlights

- Aptamer-conjugated gold nanoparticles have been highly used in biotechnology.
- Biosensors based on these nanoparticles are potent diagnostic and therapeutic tools.

Biosensors are analytical devices, basically containing an element that specifically recognizes the analyte, a transducer that converts the target–sensor interaction into measurable physical signals, and a unit that processes and interprets the signals into comprehensible results.[21,22] Biosensors could be categorized by their sensing strategy and these are optical, electrochemical, and piezoelectric. Sensing in optical, electrochemical, and piezoelectric biosensors are based on optical properties, electrical properties, and volume alteration, respectively.[23,24]

Aptamer-conjugated gold nanoparticles (Apt–AuNPs) have attracted attentions of researchers as they can serve as biosensors for detection of a variety of biological compounds. Apt–AuNPs provide optical sensing platforms including colorimetric sensing, fluorometric sensing, and electrochemical sensing.[25–27] This novel and high-tech generation of biosensors could be widely used in biomedicine due to high binding affinity, high biocompatibility, enhanced target selectivity, and long circulatory half-life. Noteworthy, aptamer-conjugated gold nanoparticles have applications other than solid biosensing. In general, Apt–AuNPs can be used as diagnostic and therapeutic tools. Due to development of application of this bioconjugate in recent years, here we review the studies designed for biosensing systems using Apt–AuNPs.

2 | CANCER DETECTION

Cancer is the leading premature death and disability cause worldwide. According to WHO reports in 2012, cancer is the fifth cause of death worldwide with 8.2 million deaths, which is expected to reach 13 million in 2030. Conventional diagnostic tests and exams that are employed widely are imaging, endoscopy procedures, biopsy, and cytology tests. However, there are emerging diagnostic tools such as biosensors for cancer biomarkers detection, such as ELISA-based sensing platforms[28,29] and electrochemical paper-based biosensors for cytokines and tumor markers detection,[30] paper electrode-based immunoassay for carcinoembryonic antigen (CEA),[31] rolling circle amplification coupled enzymatic biocatalytic precipitation photoelectrochemical-based immunoassay

TABLE 1 Summarized data of studies on detection of cancer biomarkers with aptamer-conjugated gold nanoparticles

Target	Cancer	Biosensing method	LOD	Linear range	Reference
MUC 1	Breast cancer	Electrochemical	2.2 nM	8.8–353.3 nM	37
		Optical sensing	5.3 ng/ml	5.3–200 ng/ml	38
PDGF		Electrochemical	0.52 nM	0.52–1.52 nM	36
PSA	Prostate cancer	Electrochemical	1 pg/ml	0.01–100 ng/ml	41
Androgen receptors		Electrochemical	0.5 ng/ml	0–110 ng/ml	42
CTCs	Human Caucasian Burkitt's lymphoma	Electrochemical	4 cells/ml	*	43
	Acute lymphoblastic leukemia		3 cells/mL	*	
	Non-small cell lung cancer	Electrochemical	*	*	44
	Human acute lymphoblastic leukemia	Electrochemical	*	*	48

TABLE 2 Summarized data of studies on further applications of aptamer-conjugated gold nanoparticles in the field of cancer diagnosis and therapy

Cancer	Target	Application	Reference
Breast cancer	MUC 1	Imaging Photothermal therapy Drug delivery	45,49
Prostate cancer	PSMA	CT imaging Drug delivery	46
Lung cancer	DDR2 cells	Peptide delivery tool	47

for prostate-specific antigen (PSA),[32] non-enzymatic, light activated, branched polyethylenimine (BPEI)-based photoelectrochemical immunoassay for α-fetoprotein (AFP),[33] hybridization chain reaction (HCR) coupled CoOOH nanosheets-coated g-C3N4/CuInS2 nanohybrids photoelectrochemical-based biosensors for carcinoembryonic antigen (CEA),[34] and so forth. Apt–AuNPs have been studied not only as diagnostic (Table 1) tools for early cancer detection, but also as carriers (Table 2) for therapeutic agents for cancer therapy.[22,35]

As mentioned earlier, there have been studies where Apt–AuNPs were employed as diagnostic tools for tumor markers detection. In a study conducted by Hasanzadeh et al., a DNA-aptamer with high specificity toward platelet-derived growth factor (PDGF) was designed and immobilized on AuNPs surfaces, supported with α-cyclodexterin, with different morphology. These aptasensors exhibited different electrochemical activities toward PDGF redox, regarding the shape and size of the AuNP. The aptasensors were employed for PDGF detection with square wave voltammetry (SWV) and cyclic voltammetry (CV) techniques under optimized condition and exhibited a linear range of 0.52–1.52 nM and limit of detection 0.52 nM. Furthermore, a cubic aptasensor exhibited excellent results for MCF-7 cells determination; with a linear range of 328–593 cells/ml and a limit of quantification of 328 cells/ml.[36] In another experiment done by Hu et al., a hairpin oligonucleotide aptamer, with a 25-base loop complementary to MUC1, was generated with biotin at 3′ end and then had immobilized S-bond on the AuNP surface. Horseradish peroxidase (HRP) was also immobilized on the particle surface. These all together generated a dual-labeled aptasensor particle. An electrode consisting of multiwalled carbon nanotubes (MWCNTs) and glassy carbon electrode (GCE) with streptavidin immobilized on, was also generated. In the presence of MUC1, the aptamer unfolds and the biotin becomes accessible to the streptavidin, thus generating signals. The modified electrodes in working solutions of H_2O_2 and o-phenylenediamine (OPD) lead to MUC1 detection via electrochemical reduction signal of DAP. This method exhibited a linear range of 8.8–353.3 nM and a limit of detection of 2.2 nM.[37] MUC1 detection was also studied in another experiment conducted by Wang et al.; this group developed an optical sensing technique by benefiting from salt tolerance and inner filter effect of AuNPs. By mixing carbon quantum dots (CDs) and AuNPs, the blue fluorescence of CDs is reduced. By exposing Apt–AuNPs to MUC1, aptamers bind to MUC1 and are released from AuNPs surface, thus AuNPs will aggregate by adding NaCl to the solution, which results in recovery of blue fluorescence. This method exhibited a limit of detection of 5.3 ng/ml and a linear range of 5.3–200 ng/ml.[38] In another study by Shan et al., a biosensor was generated based on quartz crystal microbalance (QCM) for human acute lymphoblastic leukemia cells selection. In this study, aptamers were immobilized on the QCM

surface resulting in capturing leukemia cells by aptamers and employing aminophenylboronic acid (APBA) conjugated AuNPs catalyzed silver enhancement, which results in signal amplification. This experiment exhibited a linear range of 2×10^3 to 1×10^5 cells/ml and limit of detection of 1160 cells/ml.[39] An aptamer-based nanomotor was fabricated by Azmoudeh and colleagues in order isolate HL-60 cells (human promyelocyte leukemia cells) from serum samples. In this new approach, a nanosheet Au/Ni/MnO_2-PEI electrode was fabricated and characterized using SEM and EDX. In the next step, HL-60 thiol-terminated oligonucleotide aptamers were added to the nanosheet, thus resulting in self-assembly of Apt/AuNPs on the surface. Fabricated Apt-nanomotors were transferred into human serum samples containing HL-60 cells. By adding the complementary aptamer, captured HL-60 cells (HL-60/Apt) were released into the solution. The concentration of separated cells was determined using fabricated aptamerKH1C12/Au_{nano}-PEDOT/GC electrode and EIS technique. The limit of detection for this approach was reported to be 250 cells/ml and the linear range was 2.5×10^1 to 5×10^5 cells/ml.[40] Kavosi et al. introduced a novel sensing method for prostate-specific antigen (PSA) detection. High level of PSA in blood is a sign of prostate cancer, which is conventionally determined by immunoassay techniques. However, in this novel approach, detection and determination of PSA is based on an aptasensor that relies on FRET phenomenon. In order to apply this method, they had anti-PSA antibody immobilized on cadmium telluride quantum dots (QDs) as donor and gold nanoparticles (AuNPs)-polyamidoamine (PAMAM)-aptamer as receptor in this system. In the presence of PSA, fluorescence intensity of QDs decreases due to formation of a sandwich complex between aptamer-PSA-antibody. The results showed a limit of detection of 1 pg/ml and a linear range of 0.01–100 ng/ml.[41] Crulhas et al. studied and experimented (tested) a new approach for prostate cancer prognosis based on androgen receptors released by prostate cells. The objective of the study was to develop an Apt–AuNP biosensing platform with a sensitivity and accuracy toward androgen receptor. Therefore, a methylene blue tagged aptamer-AuNP-modified graphene oxide (GO) platform was fabricated. Methylene blue acts as redox agent to reduce GO. In presence of androgen receptors, the immobilized aptamer on AuNPs surface changes configuration, thus resulting in reduction of electron transfer and electrochemical detection using SWV. The biosensor was reported to have a limit of detection of 0.5 ng/ml and a linear range of 0–110 ng/ml.[42] Circulating tumor cells (CTCs) are cancer cells separating from their primary or metastatic tumor sites and entering the blood stream via leaky junctions of blood vessels. Isolation and determination of CTCs from blood stream can provide insightful information about the disease stage and status. There have been numerous studies on capturing CTCs. In a recent study by Dou et al., they developed an electrochemical aptamer-based biosensing system, which is capable of detecting CTCs in human whole blood. Their sensing system consists of a magnetic graphene nanosheet modified with aptamer functionalized gold nanoparticles (AuNPs-Fe_3O_4-GS) as capture probe for CTCs and an aptamer-electroactive species-loaded gold nanoparticle (Apt–AuNPs-Thi/Fc-SH) serving as signal amplification probe. By adding these two components to blood samples, probes bind to targeted cells and then are isolated from sample with a magnet. Captured cells–probe complexes are then transferred onto a sensor electrode and SWV performed. The intensity of the wavelength indicated the concentration of CTCs. The limit of detection of this method for studied Ramos and CCRF-CEM is reported to be 4 and 3 cells/ml, respectively.[43] In the field of CTCs, Nguyen et al. designed microfluidic device based on aptamer conjugated self-assembled AuNPs monolayer in order to detect the CTC cell line of non-small cell lung cancer; A549 human lung adenocarcinoma cells with an electrochemical approach, using EIS (Figure 1).[44]Apt–AuNPs have also been studied as delivery tool for drug delivery in therapy and imaging. In a study conducted by Huang et al., MUC1 binding aptamers were generated and conjugated with AuNPs, and then these conjugates were immobilized on GO surface through hydrophobic interactions. This platform was coupled with laser desorption/ionization mass spectrometry (LDI-MS) and was employed for tumor imaging.[45] A multifunctional Apt–AuNP was developed by Kim et al. in which a prostate-specific membrane antigen (PSMA) binding RNA aptamer-AuNP was established as a molecular CT imaging system and showed four-fold greater CT intensity. Besides, Apt–AuNPs loaded with doxorubicin showed promising results in targeted cancer therapy.[46] In another study conducted by Kim et al., they developed a peptide delivery system in which Apt–AuNPs were loaded with peptides containing hexahistidine or glutation-S transferase tagged TM-JM1/2 domain of discoidin domain receptor 2 (DDR2). It was shown that cell proliferation was decreased in DDR2-positive lung cancer cells due to DDR2 inhibition by TM-JM1/2.[47] Kim et al. developed a highly specific labeling system for labeling and detection of a specific cell type. In this method, a DNA aptamer-AuNP was generated for selective and specific detection of human acute lymphoblastic leukemia cells. The Apt–AuNPs interactions with their target cells was confirmed by backscattered electron (BE) imaging of field emission scanning electron microscopy (FE-SEM) by counting AuNP numbers attached to cells.[48] According to another study done by Yang et al., Apt–AuNPs could also be employed as photothermal cancer therapy agents. In this study

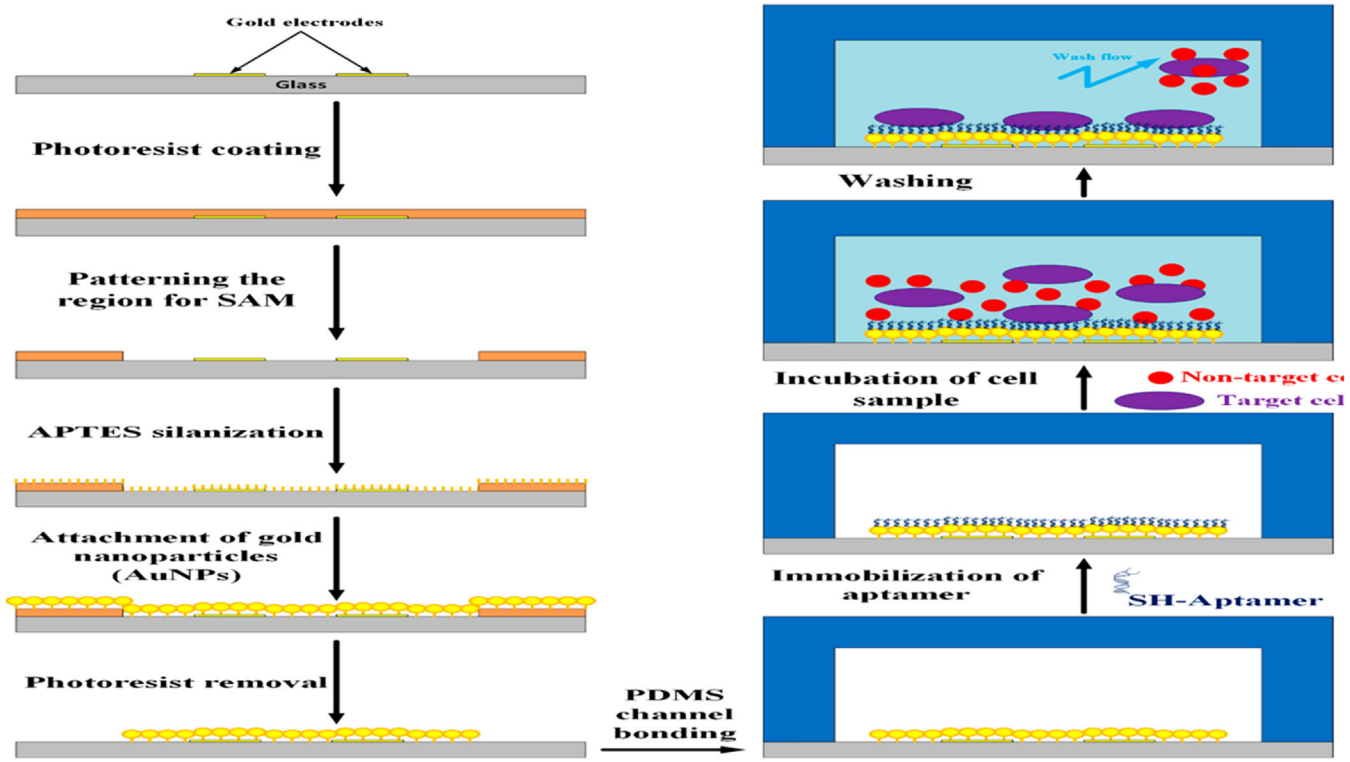

FIGURE 1 Schematic illustration of the electrochemical-based biosensor developed CTC detection and isolation (reprinted from,[44] fig. 2, published and licensed by MDPI, according to Creative Common CC BY license; http://creativecommons.org/licenses/by-nc/3.0/)

MUC1-binding Apt–AuNPs were hybridized with GO, went under near-infrared (NIR) light illumination and caused a transient overexpression of HSP70 due to the light-to-heat phenomenon, leading to irreversible damages to cancer cells.[49] In another study by Shiao et al., a multidrug delivery platform was developed using Apt–AuNPs loaded with doxorubicin and $TMPyP_4$ and employed to cancer cells. By exposure of the treated cells to a 632 nm light, cancer cells faced damage due to reactive oxygen triggered by $TMPyP_4$ and doxorubicin reaction.[50]

Apt-AuNP-based biosensors provide a rapid, functional, non-invasive and less time-consuming platform for cancer biomarker detection. Furthermore, they seemed to be promising delivery tools for both therapeutic and imaging agents, as they possess high affinity toward their targets with minimum random and nonspecific bonds to other analytes.

3 | PATHOGEN DETECTION

Infectious diseases with the potential of causing pandemic breakout are a global concern. Hence, there is a need for methods and technologies for detection, identification, and quantification of the infectious organisms; mainly pathogen bacteria. Conventional methods for pathogen detection are PCR, cell culture, and colony counting and ELISA, which are time-consuming and complex. In addition, these methods are employed together in order to get much accurate results. Therefore, establishing strategies with less complexity, time-saving with high throughput are favorable. Food industry, water and environment quality control, and clinical diagnosis are main areas benefiting from novel strategies for pathogen detection and identification at the source. Biosensors have attracted attention for their rapid, easy, and precise function. Among all, Apt-AuNP-based biosensors (Table 3) are quite desirable due to their distinct and unique features discussed before.[51,52]

One approach of Apt–AuNPs application is pathogen detection. In a study conducted by Oh et al., they developed a nonlabeled and portable device for detecting *Salmonella typhimurium* in pork meat samples. Aptamers were conjugated on a 20 nm AuNP monolayer, forming a LSRP sensing chip with a limit of detection of 1.0×10^4 cfu/ml.[53] Zhang et al. developed an aptasensor for prion protein detection, whereby the resonance light scattering (RLS) is enhanced by the aid of AuNPs in the presence of prion protein with the linear range of 0.2–50 nmol/L and a limit of detection of 0.07 nmol/L.[54] Other aptasensor for *S. typhimurium* was developed by Wu et al.; this method is called gold nanoparticle-based enzyme-linked antibody-aptamer sandwich (nano-ELAAS) method. The pathogen *S. typhimurium* is captured by its specific aptamer-AuNP, and then binds to its detector antibody. With the aid

TABLE 3 Summarized data of pathogen-detection studies with aptamer-conjugated gold nanoparticles

Microorganism	Biosensing method	LOD	Reference
Vibrio vulnificus	Delivering therapeutic agent	*	61
Salmonella typhimurium	Colorimetric	1.0 × 104 cfu/ml	53,55,62
	LSRP	1×10^3 cfu/ml	
	Electrochemical	16 cfu/ml	
	Delivering therapeutic agent	*	
Prion protein	RLS	0.07 nmol/L	54
Leishmania	Colorimetric	*	63
Listeria monocytogenes	Colorimetric	10 cfu/ml	59
Escherichia coli	Aptamer amplification	10 *E. coli* in 1 ml of sample	9
Bovine viral diarrhea virus type 1 (BVDV type 1)	Aptamer–aptamer sandwich type sensing	800 copies/ml	11
Zika virus	Colorimetric	1.0 × 105 PFU	60

of horseradish peroxidase and reporter antibodies, a colorimetric signal is generated and amplified. The linear range and limit of detection for this method are reported to be 1×10^3 to 1×10^8 cfu/ml and 1×10^3 cfu/ml, respectively.[55] Ge et al. developed another detection strategy for *S. typhimurium* that is based on an electrochemical aptasensor. This aptasensor is a two-step detection tool. The first step relies on target *S. typhimurium* binding to its aptamer leading to releasing primer binding part that further enters RCA reactions to produce long DNA molecules with tandem repeats. In the second step, RCA products can hybridize with biotinylated detection probes thus resulting in signal amplification. This new strategy was shown to be highly sensitive with a limit of detection of 16 cfu/ml and a linear range of 20–2×10^8 cfu/ml.[56] He et al. developed a highly sensitive method to detect microcystins. Microcystin is a lethal toxin secreted from blooming cyanobacteria that is an oncogene and also leads to severe liver damage and among all microcystins, microcystin-LR is the most important one due to its environmental analysis and human health. In this nobel method, MC-LR-specific aptamer and its complementary DNA were immobilized on AuNPs with 5 and 20 nm in diameter, respectively. In the absence of MC-LR, aptamer and its complementary DNA form a coupled structure but when MC-LR is present, it leads to complementary DNA/AuNP release. Next, the MC-LR/Apt/AuNPs are obtained by centrifugation and further passing through a nanopore for detection. The limit of detection for this method was reported to be 0.1 nM and linear range of 0.1–20 nM.[57] A highly sensitive method for detection of *E. coli* was introduced by Lee et al. in this method, *E. coli* are captured by antibody-conjugated magnetic beads and target binding RNA aptamers bind to *E. coli* in a sandwich manner. In the end by using RT-PCR, preheat-released aptamers can be amplified. This method leads to a highly sensitive detection that could detect 10 *E. coli* in 1 ml of sample.[9] Another detection strategy for *E. coli* was developed by Zhu et al.: this colorimetric strategy is also capable of typing *E. coli* strain due to highly specific aptamers for two different *E. coli* strains.[58] Park et al. developed a sandwich-type sensing platform, using a pair of aptamer with a high affinity toward bovine viral diarrhea virus type1 (BVDV type1). One of the aptamers conjugated with gold nanoparticles was obtained in aptamer–aptamer sandwich-type sensing format, with the limit of detection of 800 copies/ml.[11] Liu et al. designed a colorimetric assay for *Listeria monocytogenes* detection, which uses AuNPs as a reporting system. AuNPs aggregate and show color shift in presence of OPD. Aptamer-magnetic nanoparticle and IgY-coated nanosilver clusters were adopted as capture probes and recognition units that bind to the bacterial cell in a sandwich manner. After a magnetic separation step, nanosilver cluster oxidize OPD leading to AuNPs deaggregation, which results in red color development. This detection strategy has a limit of detection of 10 cfu/ml and a linear range of 10–106 cfu/ml.[59] Bosak and colleagues developed a colorimetric assay for Zika virus detection as well as Zika virus vector, *Aedes aegypti* and *Aedes albopictus*, salivary protein. Aptamer-modified AuNPs bind to the virus envelope proteins or mosquito salivary protein D7 resulting in blue color development. This strategy exhibited a limit of detection of 10 ng of the salivary protein and 1.0 × 10^5 PFU live Zika virus.[60]

Apt–AuNPs application is not just for pathogen detection in food or other possible sources of contamination but also delivering therapeutic agents in order to eliminating pathogens. An Apt–AuNP loaded with an antimicrobial peptide, like HPA3PHis, was developed in the study by Lee et al. for targeting *Vibrio vulnificus* in infected mice. The results exhibited that mice treated with Apt–AuNP-HPA3PHis showed 100% survival, while untreated infected mice died within 40 h of infection. Also Apt–AuNP-HPA3PHis was studied on infected HeLa cells and the result showed an intracellular *V. vulnificus* reduction

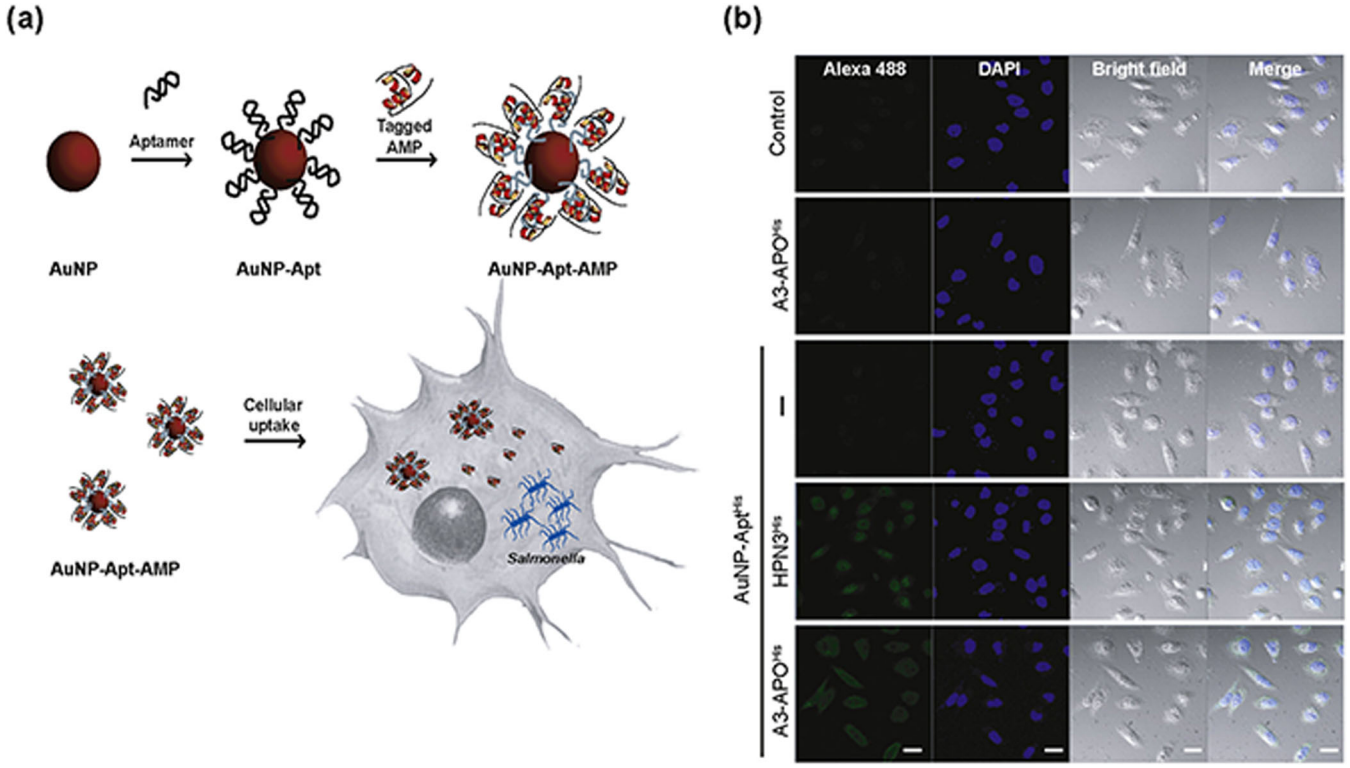

FIGURE 2 Schematic illustration of Apt–AuNP delivery system of antimicrobial peptides (AMPs) against *Salmonella typhimurium* developed by loading His-tagged AMPs onto Apt–AuNPs, which were delivered into *S. typhimurium*-infected HeLa cells (reprinted from,[62] Copyright 2016, with permission from Elsevier)

up to 90%, which extended cell viability.[61] Other study in which an antimicrobial peptide was delivered with assistance of an Apt–AuNP (Figure 2) was conducted by Yeom et al.: in this study an Apt–AuNP was loaded with A3-APOHis and was studied on mice infected with *S. typhimurium* and infected HeLa cells with the same bacteria. Results showed 100% survival of the infected mice and increased cell viability of the infected cells after being treated with Apt–AuNP-A3APOHis.[62]

4 | PROTEIN DETECTION

Proteins have crucial role in many areas from forensic investigations to early onset diagnosis. Thus, developing functional platforms for ultrasensitive and specific detection of targeted proteins, especially in low amounts and low abundance, is demanded. There have been some developments in establishing new strategies, like immune-PCR, immune-RCA and barcode assay, metal framework-based biosensors like colorimetric immunoassay biosensor using thymolphthalein-modified metal-polydopamine (MPDA@TP),[63] electrochemical biosensor using porous UIO-66-NH2,[64] photoelectrochemical biosensor using ZIF-8-assisted NaYF4:Yb,Tm@ZnO,[65] and photothermal-thermoelectric immunoassay biosensor using glucose oxidase-assisted 3,3′,5,5′-tetrametylbenzidine (TMB) oxidization;[66] but limitations still remain. Apt–AuNPs can come very handy in this field as they can detect low amounts of the analyte with a great specificity and they are user friendly (Table 4).

Wei et al. developed a colorimetric-based strategy for thrombin detection with unmodified Apt–AuNPs. They used an aptamer that could fold and form a duplex structure known as G-quadruplex/duplex. This aptamer cannot bind to AuNPs surface and protect the particles from aggregation and red-to-blue color shift due to high salt concentration, while the unfolded structure can bind to the AuNPs. In a solution containing this aptamer, there is an equilibrium between the folded and unfolded structures. By adding thrombin, aptamer folding is induced into the mentioned structure, thus leaving the AuNPs unprotected toward salt. After adding salt to this mixture AuNPs aggregate and the color change is visible for naked eye. The linear range was obtained at 0–167 nM and the limit of detection was reported to be 0.83 nM for this strategy.[67] Pandana et al. designed aptasensor for thrombin detection with thrombin-binding aptamers, 15-mer Bock and 29-mer Tasset. In this colorimetric assay, Bock aptamer-conjugated AuNP exhibited a reduction in

TABLE 4 Summarized data of protein-detection studies with aptamer-conjugated gold nanoparticles

Protein	Biosensing method	LOD	Linear range	Reference
Lysozyme	Electrochemiluminescence (ECL)	1.0×10^{-13} mol/L	1.0×10^{-13} to 1.0×10^{-8} mol/L	[78]
	Colorimetric	15 μl	1×10 to 2^{-1} μg/ml and 1×10^{-4} to 1×10^{3} μg/ml	[79]
Human α-thrombin	Resonance light scattering (RLS)	0.72 nM	*	[70]
	ECL	1 pM	1 pM to 10 nM	[74]
	Fluorescence turn-on technique	89 pM	*	[76]
	Colorimetric	100 nM	*	[69]
	Colorimetric	5 pM	5 pM to 2 nM 1–100 nM	[73]
	Chemiluminescence (CL)	2.6×10^{-14} m	6.3×10^{-14} to 6.3×10^{-11} m	[72]
	Colorimetric	0.83 nM	0–167 nM	[68]
	MALDI-TOF-MS	0.085 ng/μl	0.1–10 ng/μL	[75]
	Inductively coupled plasma mass spectroscopy (ICP-MS)	0.5 fmol	0.05–1 nM	[71]
d-Vasopressin	Electrochemical	0.72 nM	5 ng/ml to 56.5 mg/ml	[81]
Arginine vasopressin	Colorimetric	*	125–225 nM	[82]
Lactate dehydrogenase	Optical sensing	281 $\pm$ 11 pM	*	[80]
Human cardiac troponin 1	Optical	0.3 fM	0.4–2500 fM	[85]
Recombinant human erythropoietin-α	Optical Fluorescence assay	0.92 nM	0–500 nM	[83]
Immunoglobulin E (IgE)	Colorimetric	1.89×10^{-13} M	10 nM to 1 pM	[84]
Prion protein	RLS	0.07 nmol/L	0.2–50 nmol/L	[54]

plasmon resonance peak. On the other hand, Tasset aptamer-conjugated AuNP did not cause a spectral change despite its high affinity. The limit of detection for this aptasensor was reported as 100 nM.[68] Chenxiao et al. generated two aptamers that bind to different sites of the human α-thrombin in a sandwich manner and with aptamers self-assembly, a network is formed that enhances the resonance light scattering. The limit of detection for this strategy is reported to be 0.72 nM.[69] Zhao et al. developed another aptasensor for thrombin detection. In this study, Apt29 was conjugated with AuNPs (Apt29-AuNP) and the second thrombin binding aptamer, Apt15, was conjugated with streptavidin-coated magnetic beads. These aptamers bind to the targeted thrombin and result in signal amplification and separation of the target by AuNPs and magnetic beads, respectively. Ultrasensitive detection was applied by the means of inductivity coupled plasma mass spectrometry (ICP-MS). The limit of detection was reported to be 0.5 fmol. The sensitivity and specificity of this aptasensor was noteworthy that other serum proteins showed no interference.[70] Qi et al. developed an aptasensor being label-free and chemiluminescent. By the time the aptasensor binds to thrombin, in the presence of 0.5 M NaCl, AuNPs aggregation is induced and the catalytic activity of AuNPs on luminol-H_2O_2 chemiluminescence is enhanced. Limit of detection for this strategy was reported to be as low as 26 fM and the sensitivity of presented strategy was four times better than AuNP-based colorimetric ones.[71] Peng et al. designed a colorimetric assay for thrombin detection, using Apt–AuNP aptasensors. In this method, thrombin acts as a bridge as it has two binding sites for aptamers. Therefore, when Apt–AuNPs bind to target thrombin, the suspension color changes from wine-red to blue-purple due to distance-dependent optical properties of AuNPs. This color change can be monitored by naked eye or UV-Vis spectrometer. Limit of detection is 5 pM.[72] Duan et al. developed another strategy for thrombin detection and quantification. This strategy was based on TBR-labeled cysteamine-assisted ECL barcode assay, in which two aptamers were generated with high affinity toward thrombin and they bind to it in a sandwich manner. Later, these sandwich complexes are captured by micromagnetic particles and are quantified by electrochemiluminescence (ECL) signals.[73] In a study done by Xiong et al., a strategy for thrombin detection was developed based on magnetic graphene/AuNP composites conjugated with aptamers. In this strategy, thrombin is enriched and detected rapidly by MALDI-TOF-MS in biological samples. This strategy showed a linear relation ranging from 0.1 to 10 ng/μl

and the enriched thrombin attributed to the sensitive output of MALDI-TOF mass spectrometry signal, 0.085 ng/μl (2.36 nM), thrombin could be detected.[74] Li et al. developed a cost-effective aptasensor for precise and specific detection of thrombin. They opted for two thrombin-binding aptamers, Apt15 (15-mer Bock) and Apt29 (29-mer Tasset). Next, they developed Apt–AuNPs which was conjugated with fluorophore-labeled Apt29 with an AuNP by the aid of a poly-A tail. Apt15 was conjugated to magnetic beads for capturing and separation. Through a divide-and-conquer strategy, quenched fluorophores are activated by destroying poly-A tail interaction with AuNP. Moreover, poly-A DNA strands detach from AuNP surface by iodide and thiosulfate anions. This sandwich-type fluorescence turn-on aptasensor exhibited a limit of detection of 89 pM for thrombin.[75] An electrochemical-based aptasensor for thrombin protein as a model was developed by Wang et al. that relied on electrochemical–chemical–chemical (ECC) redox cycling and enzyme signal enhancement strategy. Two DNA aptamers were used, one (TBA1) immobilized on WSe_2/AuNP electrode and the second (TBA2) immobilized on biotinylated signal probe "carrier" AuNP. In the presence of thrombin protein, the protein is captured by TBA1 and AuNP/TBA2 in a sandwich manner. Next, by adding streptavidin-conjugated alkaline phosphatase, signal enhancement occurred by streptavidin-biotin reactions. Furthermore, ECC redox cycle that leads to further signal enhancement is triggered by ascorbic acid 2-phosphate hydrolization by alkaline phosphatase, which produces ascorbic acid. Multiple signal amplification, WSe_2 nanosheets' great conductivity, and high affinity thrombin aptamers resulted in highly sensitive detection of thrombin protein with the linear range of 0–1 ng/ml with limit of detection 190 fg/ml.[76]

Research groups also developed aptasensors for enzyme detection, like aptasensors designed specifically to detect lysozyme. Bai et al. designed a biosensor that could detect lysozyme with different concentrations in solutions with a high specificity and selectivity, and an ultrasensitive ECL signal was obtained. In this work, they presented an original biosensor coupled with an aptamer and [Ru(bpy)2(dcbpy) NHS] was prepared. In the next step, the biosensor was characterized with atomic force microscopy (AFM) and electrochemical impedance spectroscopy (EIS), and the results proved that the aptasensor was generated successfully. This strategy exhibited a limit of detection of 1.0×10^{13} mol/L and a decrease in ECL signal, with concentrations over 1.0×10^{-13} to 1.0×10^{-8} mol/L.[77] In another study conducted by Wang et al., an aptasensor was generated using polydimethylsiloxane (PDMS)–AuNP composite films. These composites were administered as platforms for immobilizing aptamers that inhibited silver reduction. By the time the aptasensor is exposed to analyte, the silver reduction is increased due to the catalytic efficiency of AuNPs. This sensitive colorimetric strategy was tested for lysozyme detection, quantitative and semiquantitative measurements with imaging software and naked eye, respectively, were carried out in a range of 1×10^2 to 1 μg/ml with a volume of reagent of 15 μl or less.[78] The other platform for an enzyme detection was developed by Jain et al. for detection of plasmodium falciparum lactate dehydrogenase (PfLDH). In this study, a single-stranded DNA aptamer (P38) targeting PfLDH was designed with a 40-mer random region flanked by primer binding sites on both sides. AuNPs with 16 nm in diameter were used as optical probes. These AuNP probes aggregation were mediated by cationic surfactant. Benzalkonium chloride (BCK) proved to be the most efficient cationic surfactant among others tested and characterized by their hydrocarbon tail. BCK-base aptasensor exhibited a limit of detection of 281 ± 11 pM.[79]

A novel aptasensor was developed to detect enantiomers of vasopressin. This novel electrochemical aptasensor benefits from graphene–mesoporous silica–AuNP hybrid as the electrochemical sensing platform that enhances the limit of detection for this substance by aptamer enrichment. In this study, Du et al. generated two aptamer fragments from a primary aptamer sequence, which distinguishes d-vasopressin, namely P1 and P2. P1 fragment is modified with thiol and immobilized on the graphene–mesoporous silica–AuNP hybrid, as capture probe. P2 fragment was used as detection probe that in the presence of d-vasopressin could unite with P1 fragment and form a three-way structure. When SH-P1/d-vasopressin/P2 is formed, a decrease in cyclic voltammetry (CV) response is shown. The more this complex covers the platform, the slower the apparent electron transfer will be, consistent with the partially blocked electrode theoretics. A limit of detection of 0.72 nM and a linear range of 5 ng/ml to 56.5 mg/ml was obtained for this strategy.[80] Ren et al. developed an aptasensor for distinguishing d-arginine vasopressin (d-AVP) from its l-enantiomer. In this study citrate-capped AuNPs were generated as colorimetric indicators. In the presence of d-AVP, these oligopeptides bind to their specific aptamers and cause the AuNPs disperse. But aptamers cannot recognize and bind to l-AVP, leading to AuNPs aggregation due to the interactions between guanidinium groups of the AVP and carboxylate groups of citrates. With increasing of l-AVP concentration, a new peak was observed at 620 nm, while pure AuNPs showed a plasmon resonance peak at 520 nm that indicates the interaction of the AuNP's plasma mode with the dipole–dipole interactions, which suggests l-AVP is acting as a cross-linking agent for AuNPs and make them aggregate. This strategy showed a limit of detection of 50 nM and a linear range

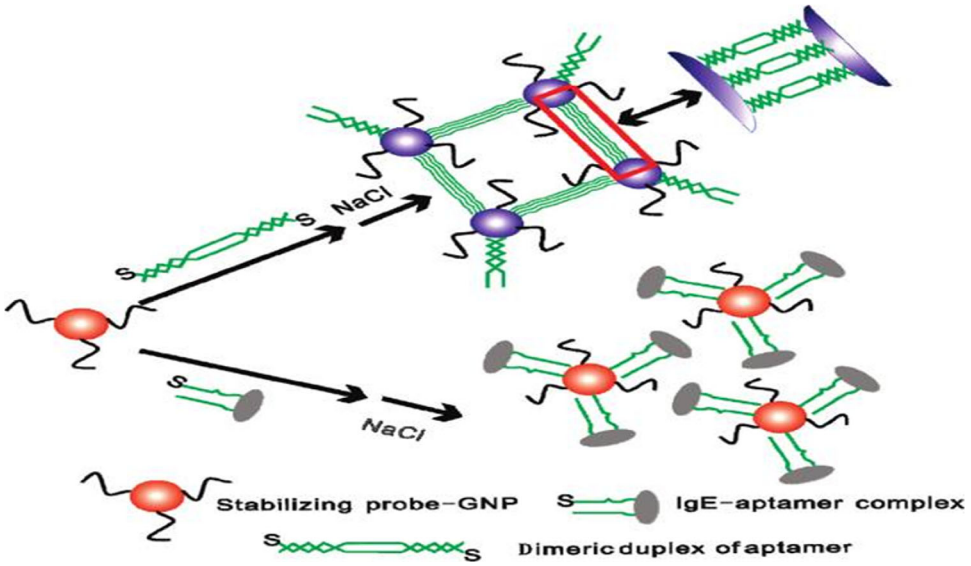

FIGURE 3 Schematic illustration of the colorimetric biosensing strategy developed for IgE as a model for protein detection (reprinted with permission from,[83] Copyright 2010, American Chemical Society)

of 125–225 nM for l-AVP. Also the visible color change was observed for l-AVP concentrations over 150 nm.[81] In another study, a fluorescent aptamer-conjugated AuNP probe was generated by Sun et al. to detect recombinant human erythropoietin-α (rHuEPO-α). They generated an anti-rHuEPO-α aptamer labeled with carboxymethylfluorescein (FAM) that was hybridized with complementary sequences on the AuNPs' surface. AuNPs act as a quencher for the FAM tag. Once these aptasensors are exposed to their target, they are released from the particle and generate a fluorescence signal. Limit of detection for this method was reported to be 0.92 nM, with a linear range of 0–500 nM.[82] Based on a unique aptamer-functionalized AuNPs aggregation behavior, a colorimetric strategy was developed by Wu et al. to detect immunoglobulin E (IgE) as a model (Figure 3). In this strategy, AuNPs were modified with aptamer probes with sticky ends. Salt addition leads to sticky ends pairing and AuNPs aggregation while in the presence of the analyte, a hairpin structure is formed and inhibits the AuNPs aggregation. The limit of detection of 1.89×10^{13} M and a linear range of 10 nM to 1 pM was reported for this novel strategy.[83] Rezaei et al. developed an aptasensor based on AuNP-quantum dot hybrid that can detect human cardiac troponin 1 (cTn1) in saliva. In this study, when the analyte binds to its aptamer, a fluorescent enhancement of the plexcitonic hybrid system is observed. This strategy exhibited a limit of detection of 0.3 fM and a response range of 0.4-2500 fM.[84] Interleukin-2 receptor α is a bread indicator of clinical disease activity in many inflammatory diseases. Jeon et al. developed a colorimetric assay for this protein's detection. The aptasensor is based on a highly specific DNA aptamer that is adsorbed on the surface of AuNPs. AuNPs mimic peroxidase activity thus in the presence of ortho-phenylenediamine and adsorbed DNA aptamers, which attracts more positively charged ortho-phenylenediamine to AuNP due to their negatively charged backbone, deeper brown color is developed due to enhanced oxidization of ortho-phenylenediamine. In the presence of interleukin-2 receptor α protein, the aptamer binds to the target and leaves the AuNP, which results in less color development. This aptasensor exhibited great performance with a limit of detection of 1 nM and a linear rage of 1–100 nM.[85] Bacterial and viral protein (toxins, antigens, etc.) detection is a mean to detect the infection and contamination in patients as well as food, water, animal products, and so forth. Fatin et al. developed a highly sensitive colorimetric aptasensor, based on split aptamer strategy for HIV-1 Tat protein. Two split RNA aptamers are used, the first strand is adsorbed to the surface of AuNPs, which prevents AuNP aggregation in presence of NaCl, while the second RNA aptamer strand is free and added to the solution later on. In the presence of Tat protein, the AuNP-adsorbed aptamer is freed and subsequently binds to arginine-rich region of Tat protein and forms a functional RNA duplex with the second RNA strand. Formation of this complex and presence of NaCl leads to AuNP aggregation and color shift from blue to red, which is visible with naked eye.[86]

An electrochemical-based aptasensor was developed by Li and colleagues for mycobacterium tuberculosis MPT64 antigen detection. In this method, two specific aptamers were used for both probe and electrode fabrication. The probe consists of aptamers, horseradish peroxidase, poly(vinyl pyrrolidone), AuNPs, and UiO-66. Elec-

TABLE 5 Summarized data of detection of other agents with aptamer-conjugated gold nanoparticles

Target	Biosensing method	Reference
ATP and adenosine	Colorimetric, silver enhancement, electrochemical	79,93–99
Antibiotics	Colorimetric, surface plasmon resonance, electrochemical	91,92
Cortisol	Colorimetric	108
Serotonin	Colorimetric	106
Riboflavin	Colorimetric	105
Theophylline	Colorimetric	104
Cocaine	Colorimetric	109
Tyrosinamide	Colorimetric	107
Arsenite	Colorimetric	110
Hg^{2+} in presence of Pb^{2+}	Colorimetric	111

trode is basically gold electrode modified with the same two specific aptamers. In presence of MPT64 antigen, aptamer-target sandwich complexes form and the signal is generated and then measured by differential pulse voltammetry (DPV). The limit of detection of this method was as low as 10 fg/ml and a linear range of 0.02–1000 pg/ml.[87]

Besides all developed strategies for fast and sensitive detection of the proteins using Apt–AuNPs, this system can also be used as a delivery system for delivering recombinant proteins into mammalian cells safely. In a study conducted by Ryou et al., they prepared a recombinant protein with His tag and an AuNP with His aptamers. By binding of the aptamer to its target, the system can be efficiently delivered to the target cell. This strategy was observed to be efficient in vivo too. An inhibition of tumor growth was observed in mice with xenograft tumors when BIM-loaded Apt–AuNPs were injected locally. Furthermore, when EGF and BIM-loaded Apt–AuNPs were injected intravenously into mice with a xenograft tumor derived from EGF receptor overexpressing cancer cells, a targeted delivery of the BIM to the tumor was observed. This system showed no cytotoxicity in vitro or in vivo.[88]

5 | OTHER AGENTS

5.1 | Antibiotics

Derbyshire et al. developed a colorimetric detection method using 2'-fluoro-pyrimidine derivatives of RNA stabilized on AuNPs, which on exposure to the aminoglycosides, induces AuNP aggregation (Table 5). In this strategy, they generated and isolated broad affinity aptamers by performing toggle SELEX by alternating between two structurally related aminoglycosides in sequential rounds. This method could detect aminoglycosides in a range of 1–100 nM.[89] Pang et al. developed another colorimetric detection strategy. They generated two aptamers for kanamycin and ampicillin, respectively. They used SERS as it gives information about the AuNPs surface coverage and aptamers conformational changes at a molecular level. The results showed that AuNPs have a great affinity to bind to ampicillin rather than its aptamer, so this gives rise to lack of AuNPs aggregation. On the other hand, data gathered from SERS signals showed that kanamycin-induced AuNPs aggregation leads to color change as well as aptamer conformational changes. Data showed that kanamycin has a greater affinity to its aptamer rather than the AuNP.[90] The other colorimetric method using Apt–AuNPs was developed by Song et al. In this method an aptamer was developed that had a great affinity toward kanamycin and its derivatives. This newly developed Apt–AuNP could detect kanamycin with a concentration as low as 25 nM.[91]

5.2 | ATP and adenosine

Liu et al. developed a colorimetric sensing method wherein in the absence of adenosine, as the analyte, Apt–AuNPs are aggregated and exhibit a purple color. The mechanism of this sensing method is that AuNPs are functionalized with two aptamers that link together with a linker sequence in the absence of the target by the exposure of the Apt–AuNPs to its target, Apt–AuNPs disperse and show red color.[92] Another colorimetric AuNP-based method too was developed by Liu et al. for adenosine detection. In this method, in a strong ionic solution and in the absence of the target molecule, aptamers bind to the AuNP surface by electrostatic forces, thus AuNPs disassemble and exhibit a red-colored solution. In the same ionic condition, by the target molecules presence, aptamers bind to their targets, leading to AuNPs aggregation and the solution color shifts to blue.[93] Another method was developed to detect adenosine in urine samples by Liu et al. In this method, adenosine-binding aptamers were immobilized

on AuNPs as well as protected DNA. Other AuNPs also were generated having complementary DNA sequences for aptamers, as well as protected DNA. In the absence of the target, this complementary DNA binds to aptamer, leading to aggregation of AuNPs. When the target adenosine is present, aptamers bind to them, AuNPs disassemble, resulting in color shift from blue to red.[94] Zhang et al. could develop another sensing method based on silver enhancement. In this method, adenosine binding thiol-modified aptamers were immobilized on AuNPs. Besides, other AuNPs were generated with DNA sequences complementary to adenosine binding aptamer. When the target is added, aptamer binds to its target and by adding salt (NaCl), the solution color changes. Then 1 μl of the sample was placed on an amine-modified slide glass. Then the spots were treated with silver enhancer for 10 min so that the visual difference is enhanced. Only 1 pmol of the target was enough for aptasensor to detect adenosine with naked eye.[95] An electrochemical sensing platform for adenosine detection was introduced by Yang et al. In this method, they generated an Au electrode consisting of immobilized thiol capture probes and MCH. They also designed streptavidin-coated magnetic beads coated with biotin adenosine-binding aptamer/thiol signal probe complex. By adding the target adenosine, aptamers bind to their targets and the thiol signal probes are released. Then this probe forms duplex with capture probes on the electrode via DNA hybridization. In the next step, AuNPs are added and bind to DNA strands by Au–S bond. These AuNPs adsorb thionine and lead to adenosine detection as low as 0.05 nM.[96]

An AuNP-based ATBR colorimetric strategy was developed by Wang et al. for ATP assay. In this strategy, ATP binding aptamers were hybridized to a complementary sequence to form a rigid duplex. In the absence of the target molecule, this rigid duplex is unable to stabilize AuNPs and inhibit AuNPs aggregation by adding salt. But once these are exposed to the target, the aptamer binds to the target leading to liberating the ssDNA complementary sequence. This random coil-like ssDNA stabilizes AuNPs so that they would not aggregate by salt addition.[97] Another colorimetric method for ATP assay was developed by Zhao et al., in which they generated an aptasensor using Apt–AuNPs that is hybridized with a complementary sequence. In the presence of ATP, aptamers are liberated from their complementary sequence and bind to their targets. By adding salt to this solution, red-to-blue color shift is observed due to AuNPs aggregation.[98] Sang and colleagues also developed another colorimetric detection method with a limit of detection of 1.7 nM. Poly(diallyldimethylammonium chloride) (PDDA) interacts electrostatistically with AuNPs, thus inducing AuNP aggregation. ATP-specific hairpin shape aptamers are attached to AuNPs. In the presence of ATP, the hairpin structure unfolds and releases ssDNA ends, which interacts with PDDA that leads to AuNPs dispersion and a color shift from blue to red.[99] Gao and colleagues developed a colorimetric sensing platform for ATP detection using target-triggered hybridization chain reaction (HCR). In this system, two ATP-specific hairpin DNA aptamers interact with AuNPs via their single-stranded sticky ends and prevent AuNPs aggregation after adding salt in the absence of the target. However, by introducing the target, the aptamer is opened and exposes a new sticky end for the second complementary aptamer for hybridization. This results in AuNPs uncovering this aggregation and color shift by adding salt.[100] Zhou et al. developed a method for ATP detection via SERS. In this method, they used two ATP-binding aptamers, one is attached to AuNPs and the other is attached to AuNP decorated GO nanostructures. When the nanostructures are exposed to ATP, aptamers bind to their target in a sandwich manner resulting in SERS signal enhancement. This method exhibited a limit of detection of 0.85 pM and a range of 10 pM to 10 nM ATP concentration.[101] Moreover, with this line of thought Mohammadinejad et al. designed a system for detection of ATP in MCF-7 cell using formation of MUC 1 Apt–AuNPs/ATP Apt-QDs.[102] As shown in Figure 4 after internalization of complex into MCF-7 cells by diagnosis of MUC 1 receptors by MUC 1 aptamer, ATP Apt-QDs can detect the ATP leading to release of ATP Apt-quantum dots from AuNPs and recovery of fluorescence intensity of quantum dots.

5.3 | Random small molecules

In a study conducted by Chavez et al., they developed a colorimetric sensing system based on aptamers and plasmonic response of the AuNPs. In this system, two kinds of AuNP/oligonucleotides were generated and these oligonucleotides had complementary sequences toward theophylline binding aptamer. This aptamer acts as a linker, thus AuNPs aggregate due to DNA hybridization. By the time theophylline is added, aptamer is liberated and binds to the target molecule, resulting in blue-to-red color shift.[103] Again, another colorimetric sensing method was developed by Chavez et al. for detecting riboflavin in vitro. The main goal of this study was to investigate how aptamer modifications affect Apt–AuNP stability and aggregation kinetic in addition of the target molecule. By adding different sequences to the aptamer tail and comparing the responses, they concluded that observed effects are independent of the added tail's sequence and aptamer modification can improve Apt–AuNP stability and sensing response.[104] Chavez et al. developed the other colorimetric

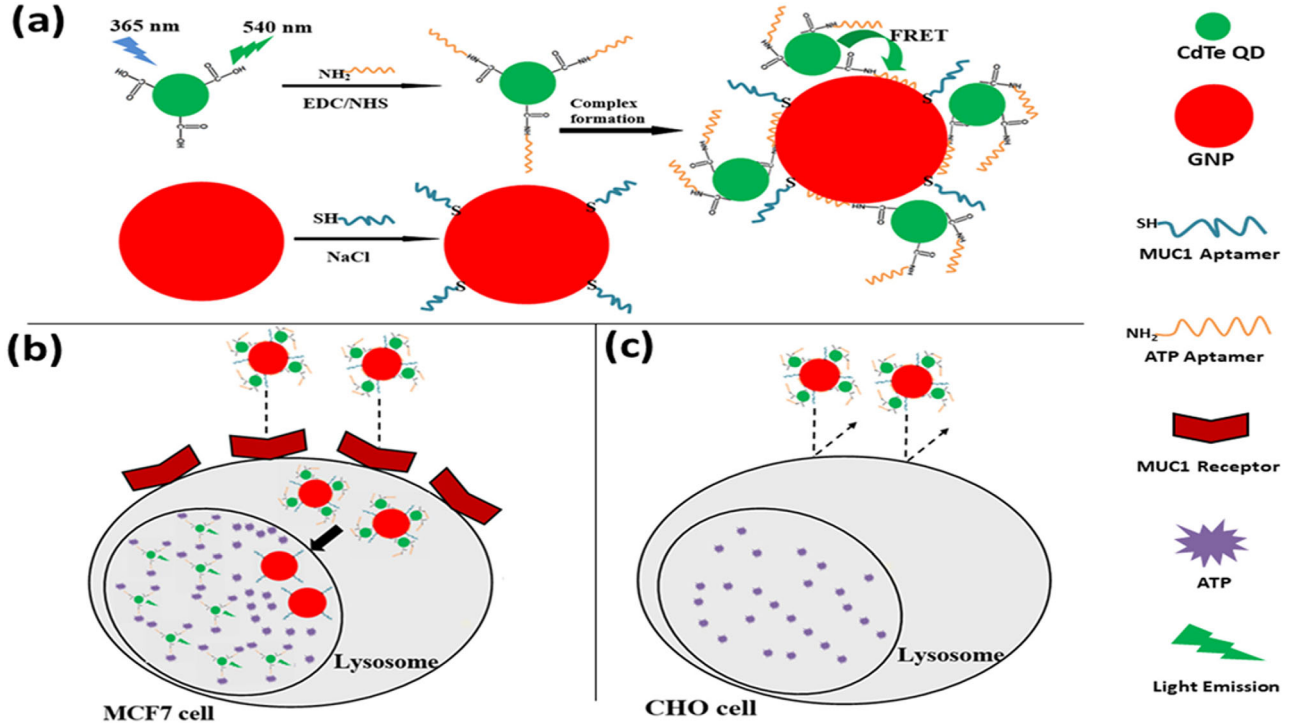

FIGURE 4 Schematic illustration of detection of ATP in MCF-7 cells using MUC 1 Apt–AuNPs/ATP Apt-QDs (reprinted from,[102] Copyright 2019, with permission from Elsevier)

sensing strategy where the output could be coupled with smartphones and tablets for on-the-spot analysis. This strategy was designed to detect serotonin in small samples in a short time. In this method, aptamer-conjugated AuNPs were exposed to serotonin, aptamers went under conformational changes that could enhance Apt–AuNPs stability against high concentrations of salt. This leads to blue-to-red color shift.[105] Guieu et al. designed a strategy where unmodified AuNPs were applied as colorimetric reporters for enzymatic cleavage-based aptamer assay. In this strategy, free tyrosinamid aptamers are targets of being cleaved by PDE 1 enzyme. This results in short-fragment formations that protect AuNPs from aggregation in high salt concentrations. On the other hand, by binding aptamer to its target, due to conformational changes, it cannot be cleaved by the enzyme. Thus AuNPs aggregate in high salt concentrations.[106] Martin et al. developed a colorimetric assay for cortisol detection. In this work, in the absence of target, cortisol binding aptamers bind to AuNPs, thus they do not aggregate by adding salt. But in the presence of the target, they liberate and bind to the target and undergo conformational changes. This results in AuNPs aggregation when salts are added. The other aim of this study was to establish a strategy to generate aptamers specifically for the desired target that can enhance the aptasensor's sensitivity.[107] Smith et al. designed a colorimetric assay to detect cocaine that is coupled to an android-based color analysis application to be used in field. They reported that the AuNP conjugated cocaine aptamer, liberate and bind to the target and the AuNPs aggregate when salt is added. In contrast, the aptamer did not bind to the EME and the solution color remained red after salt addition. The same results were observed upon examining with free aptamer.[108] A simple arsenite colorimetric detection method was developed by Mutsunaga and colleagues. In this strategy, AuNPs are covered with arsenite-specific aptamers in the absence of arsenite. Thus the solution color is red even in high concentrations of salt. After the addition of arsenite, aptamers detach from the surface of AuNPs and bind to their target. Hence, AuNPs aggregate and the solution color shifts to blue by adding salt. This method exhibited a limit of detection of 2.1 μM and a linear range of 1.0–10 μM.[109]

6 | CRITICAL NOTE

AuNPs offer many advantages like simple synthesis, great biocompatibility, low toxicity, and being functionalized with biomolecules over other nanomaterials. As for aptamers, great affinity and selectivity toward their target are the two most important characteristics.[17] Apt–AuNP bioconjugates exhibit unique and outstanding characteristics by benefiting from each technology properties such as increased target selectivity, enhanced target-binding affinity, rapid transport kinetics, and long circulatory half-life,

which make Apt-AuNPs promising tools for bioanalytical and biomedical applications. While Apt–AuNPs have shown promise in their application as platforms for bioanalysis and delivery systems, they are mostly still in the experimental stage, challenges still remain ahead. Hence, to fully realize the potential of the Apt–AuNP platform, in order to translate the scientific data into clinical applications of Apt–AuNP biosensing and delivery systems, it is important to develop novel aptamers toward clinically relevant targets and novel bioconjugating systems of Apt–nanomaterials for signal transduction.[110] Despite seemingly low toxicity and great biocompatibility of the nanomaterials as drug carriers, their long-term health effects, such as toxicity, inflammation, immunoreaction or oncogenesis, must be studied, both in vitro and in vivo. Apt–AuNPs will eventually become a practical tool to meet currently existing bioanalytical and biomedical obstacles; however, to reach that point, there are challenges remaining to overcome for their widespread applications.

7 | CONCLUSION AND OUTLOOK

Benefiting from accumulative effects of unique properties of gold nanoparticles and superior properties of aptamer; Apt–AuNPs have gained huge attention to develop new biosensing platforms. Apt–AuNPs are easily generated and possess high affinity toward their targets. Moreover, Apt–AuNPs have shown high efficacy and selectivity toward their targets in low concentrations. The promising results of studies have made this technology favorable to be applied commercially. Apt–AuNP biosensors can be widely applied in personalized medicine for early diagnosis and monitoring diseases like cancer, viral and bacterial infections, and so forth. Moreover, they can be applied in food and environment safety assessment by tracing and detecting even the slightest amounts of food pathogens and environmental pollutants. However, there are still some obstacles in their commercialization and introduction in the clinical trials. However, further studies and investigations are needed to approve their safety in the long-term.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Samin Nooranian performed data collection and analysis, reviewed the literature, and contributed to drafting the manuscript. Arash Mohammadinejad performed data analysis, editing, contributed to interpreting the data, and assisted in drafting the manuscript. Taraneh Mohajeri and Ghazaleh Aleyaghoob contributed to drafting the manuscript. Reza Kazemi Oskuee conceptualized, designed, supervised, and coordinated the study, and was responsible for the integrity of the data and the accuracy of its analysis and assisted in the final write-up. All the authors read the final manuscript and approved it.

DATA AVAILABILITY STATEMENT

Data are derived from public domain resources.

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