Published in final edited form as:

Curr Anal Chem. 2022 ; 18(6): 705–722. doi:10.2174/1573411017666210804105750.

Recent advances of using personal glucose meter as a biosensor readout for non-glucose targets

Songbai Zhang[1,2,*], **Shuang Li**[1], **Rixin Yan**[1], **Zhiyun Zhou**[1], **Yuting Wu**[2], **Yi Lu**[2,*]

[1]Hunan Provincial Key Laboratory of Water Treatment Functional Materials, Hunan Province Engineering Research Center of Electroplating Wastewater Reuse Technology, Hunan Province Cooperative Innovation Center for The Construction & Development of Dongting Lake Ecological Economic Zone, College of Chemistry and Materials Engineering, Hunan University of Arts and Science, Changde 415000, P. R. China

[2]Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States

Abstract

Background: Personal glucose meter (PGM) has become the most successful biosensor in past decades due to its advantages of small size, convenient operation, and low cost. To take advantage of many years of research and development of PGMs, new signal transduction methods has been developed to expand the PGM from simple monitoring blood glucose to detection of numerous non-glucose targets.

Objectives: This review summarizes recent advance of PGM-based biosensors for non-glucose targets including signal transduction, signal amplification and target molecule recognition and analysis. Current challenges and future directions are also discussed.

Conclusion: PGM can be used as biosensor readout to detect various non-glucose targets from metal ion, small molecule to protein and even living organisms such as bacteria and other pathogens by using different signal transduction elements such as invertase and amylase, and different signal amplification methods such as nanomaterials, nucleic acid reaction, liposome encapsulation, hydrogel trapping, DNAzyme amplification and biotin-streptavidin reaction.

Keywords

Personal glucose meter; non-glucose target; point of care; biosensor; signal transduction; signal amplification; target recognition

[*]Address correspondence to these author at the Department of Chemistry, College of Chemistry and Materials Engineering, Hunan University of Arts and Science, 415000, Changde, China; Tel/Fax: +86-736-7186115; zsb0119@163.com; and at the Department of Chemistry, University of Illinois at Urbana-Champaign, 61801-3364, Urbana, IL United states; Tel/Fax: 217-333-2619, 217-244-3186; yi-lu@illnois.edu.

CONFLICT OF INTEREST

Yi Lu is a co-founder of GlucoSentient, Inc..

1. INTRODUCTION

With the development of global economy and the improvement of people's living standards, the aging population continues to grow, and people with diabetes in the world is also increasing rapidly. According to the latest Diabetes Atlas (9th Edition, 2019) released by the International Diabetes Federation, 463 million adults are suffering from diabetes in the world in 2019 (equivalent to one for every 11 people). It is estimated that the number of people with diabetes will reach 578.4 million by 2030 and 702.01 million by 2045 [1]. Diabetes is a group of metabolic diseases characterized by hyperglycemia, which is caused by the deficiency of insulin secretion or the impairment of its biological function, or both. Chronic hyperglycemia can lead to chronic damage and dysfunction of various tissues, especially eyes, kidneys, heart, blood vessels and nerves. Research shows that timely and accurate blood glucose monitoring can help people with diabetes to adjust the dosage of insulin according to the changes of blood glucose level, improve their daily life and eating habits, further effectively control the blood glucose level, prevent the occurrence of extremely high blood glucose and extremely low blood glucose, and reduce the incidence of complications [2,3].

Because of the importance of glucose monitoring, enormous efforts have been devoted to developing personal glucose meter (PGMs), also called blood glucose meter. At present, there are about 10 billion times of glucose detection in the world every year, and the majority of the biosensors produced in the world are used for glucose detection. Among them, PGM accounts for about 80% of the diabetes detection device market [4,5]. Since the first practical PGM was developed in 1968, PGM has gone through five stages of development [5], with the first electrochemical PGM in 1986 as a major advancement. Compared with colorimetric technology, electrochemical PGM has the advantages of smaller volume, more convenient use, shorter reaction time and so on, gradually replacing colorimetric method to become the mainstream of blood glucose meter market. According to statistics, the market share of electrochemical PGM in the United States is more than 70%, while it is 100% in Japan. The general working principle of PGM is that glucose in blood interacts with enzymes such as glucose oxidase or glucose dehydrogenase to trigger a redox reaction and resulting electrochemical event can be measured by an electrode [6-9].

While PGM has enjoyed tremendous success, it can normally detect only a single target of glucose, even though there are needs to detect many other non-glucose targets, including HbA1c, insulin and many other biomarkers for diseases associated with complications from diabetes and those even without the diabetes. To meet the needs, many biosensing devices, including those interfaced with smartphones, have been developed, but it takes time and costly to develop a new biosensing device from laboratory to market. As a result, few, if any, biosensing device can match the portability, cost effectiveness and familiarity to millions of users of PGMs.

Instead of developing a new competing biosensing device, in 2011, Lu Group used sucrose invertase as a signal transduction element and successfully applied the PGM to detect several non-glucose targets, making a novel contribution to the applications of PGM [10]. This work demonstrates that people can use the approved medical technology PGM to

detect non-glucose targets, which will greatly reduce the cost, time and risk of new products to the market. Inspired by this original work, many researchers have developed a series of biosensors to detect non-glucose targets with PGMs as readout devices, which greatly enriched the application of PGMs in clinical diagnosis, food safety, environmental monitoring and other fields, opening a new avenue for the point-of-care test (POCT) of various targets [5,11-14]. In this review, we summarize progresses that have been made in recent years in applying PGMs for the analysis of non-glucose targets from the aspects of signal transduction, signal amplification, target molecule recognition and analysis. We also discuss the existing challenges and future development trend in this area.

2. SIGNAL TRANSDUCTOIN

Although studies have shown that some of the PGMs can also be used to detect NAD(P)H (nicotinamide adenine dinucleotide (phosphate) hydrogen) due to the redox interact or involvement of NAD(P)H in the enzymatic reaction for the detection [15,16], most PGM-based biosensors for non-glucose targets reported in the literature are based on the detection of glucose. Therefore, in the aspect of signal transduction, researchers mainly consider how to transform target-recognition events into glucose detection. In addition to invertase, researchers also use other enzymes to convert their respective substrates, such as starch, maltose, or lactose into glucose (Figure 1). An alternative method is to encapsulate glucose directly in liposomes or porous materials, and then release the glucose upon selective binding of the target.

2.1. Sucrose converted to glucose by invertase

Invertase is a common enzyme, which exists in yeast, bacteria and plants. It can catalyze hydrolysis of sucrose to produce glucose and fructose. Lu Group is the first to use invertase as a signal transduction element to detect non-glucose targets with a blood glucose meter [10]. They used sulfoccinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC) to conjugate amino groups on the surface of invertase with a sulfhydryl modification at the end of DNA aptamers or DNAzymes. In this way, they constructed biosensors that can detect small organic molecules such as cocaine, adenosine, protein macromolecule such as interferon gamma (IFN-γ) and metal ion uranium (UO_2^{2+}), respectively. As shown in Figure 2, they immobilized the biotin-modified nucleic acid strand to the avidin modified magnetic beads through biotin-avidin affinity reaction, and then formed a sandwich structure with aptamer probe and invertase signal probe. When there is a target molecule in the sample, the aptamer probe can specifically recognize and bind cocaine, adenosine or IFN-γ molecules, leading to the displacement and release of invertase signal probe. After magnetic separation, the invertase signal probe reacts with sucrose to catalyze the hydrolysis of sucrose to produce glucose, so as to establish biosensors with a PGM as signal readout devices for these non-glucose targets. To detect UO_2^{2+}, a uranyl-specific 39E DNAzyme and the corresponding substrate strand are used as recognition elements. When the sample contains UO_2^{2+}, the DNAzyme catalyzes the hydrolysis and cleavage of the substrate strand, which releases invertase-labeled substrate strand fragment and finally produce the detection signal of glucose.

Inspired by this pioneering work, researchers have developed a series of different biosensors for detecting non-glucose targets by using invertase as signal transduction element [15-60]. In most of these sensors, invertase is labeled on the nucleic acid strand as a signal probe. For example, Xiang and Lu immobilized the capture probe on the magnetic beads, and then formed a sandwich structure with the target DNA and invertase-labeled nucleic acid probe. With this design, a biosensor for the detection of hepatitis B virus (HBV) DNA fragment was established, with a detection limit of 40pm [17]. Xiang and Lu also immobilized the antibody on the magnetic beads, labeled the ochratoxin A (OTA) aptamer probe with invertase, and formed a sandwich structure with the target molecule OTA to realize the competitive detection of small molecule of OTA toxin, with the detection limit of 6.8 ng/mL [18]. In addition, Ma et al. immobilized the aptamer probe of platelet-derived growth factor-BB (PDGF-BB) on magnetic beads, and then formed a sandwich reaction structure with the target molecule PDGF-BB and sucrose invertase labeled aptamer probe. The sensitive analysis of PDGF-BB was realized with a PGM as the signal readout device, and the detection limit was 2.9 fM [58]. Moreover, Wang et al. immobilized the antibody of cardiac biomarker myoglobin on the microplate, and then formed a sandwich structure with the target molecule myoglobin and the invertase labeled myoglobin aptamer probe, which realized the quantitative detection of myoglobin with a detection limit of 50 pM [62]. Furthermore, Zhou et al. used invertase-labeled alkynyl functionalized DNA as a signal probe and realized the quantitative analysis of Cu^{2+} by click chemistry. Using a GM as a signal readout device, the detection limit was 3.4 nM [19]. Also, Gu et al. immobilized biotinylated DNA on magnetic beads, hybridized with aptamer probe and invertase-labeled signal probe of melamine, and realized the sensitive detection of melamine in milk by PGM (Figure 3A). The detection limit of melamine in 80% whole milk without any pretreatment can reach 67.5 ppb, which meets the analysis requirements of melamine in milk [22]. Additionally, Xu et al. used nucleic acid probes that can recognize mercury ions, by taking advantage of biotinylated T-base contained capture probe and invertase modified T-base contained signal probe, to recognize and detect mercury ions through T-Hg^{2+}-T complex, and the linear detection range can reach 3 orders of magnitude [23]. Meanwhile, Deng et al. immobilized biotinylated nucleic acid probe on magnetic beads and hybridized with invertase modified signal probe. With M.SssI CpG methyltransferase, the 5'-CCGG-3' fragment in the hybridized double strand was methylated, and then cleaved by Hpa II restriction endonuclease, resulting in release of invertase labeled fragment. The activity of M.SssI DNA methyltransferase was analyzed by PGM [30].

Invertase can also be labeled with biotin to realize signal transduction through biotin-avidin reaction. For example, Xiang and Lu immobilized prostate-specific antigen (PSA) antibody the magnetic beads and reacted with the target molecule PSA and biotinylated PSA antibody to for sandwich structure, and then reacted with avidin and invertase labeled biotin to achieve the sensitive detection of tumor marker PSA [18]. Su et al. immobilized the biotin-labeled invertase and biotin-labeled DNA on the avidin modified magnetic beads and achieved the amplified detection of Cu^{2+} by click chemistry, with the detection limit of 10 nM [51]. Yang et al. used Zr^{4+} functionalized magnetic beads to selectively capture protein kinase-induced biotin-phosphopeptide, and then realized the detection of protein kinase through the sandwich reaction between avidin and invertase labeled biotin, achieving

a detection limit of 0.0001 U/μL [24] (Figure 3B). Biotinylated antibody and biotinylated invertase were immobilized on avidin-modified gold nanoparticles as signal transduction elements. Using lateral flow test strip, competitive reaction occurred when the sample contained small molecule 8-OHdG, while sandwich reaction occurred when the sample contained large molecule PSA, and then sucrose solution was added to the detection line and control line, respectively. The biotinylated invertase immobilized on gold nanoparticles catalyze the hydrolysis of sucrose to glucose, which can be detected by PGM. The sensitive analysis of small molecule 8-OHdG and large molecule PSA could be realized with detection limits of 0.23 ng/mL and 1.26 ng/mL, respectively [54].

Furthermore, invertase can be labeled on the antibody as a signal transduction element. Joo et al. immobilized monoclonal antibody on magnetic beads, and then formed sandwich structure with target molecule Salmonella bacteria and its invertase-labeled polyclonal antibody, which can realize the quantitative and sensitive analysis of Salmonella with the detection limit of 10 cfu/mL [40]. Zhu et al. immobilized alpha-fetoprotein antibody (anti-AFP) on the surface of screen-printed gold electrode (SPGE), and then formed sandwich structure with AFP and invertase-labeled anti-AFP. Quantitative analysis of AFP was realized by using PGM as signal readout device with the detection limit of 0.18 ng/mL [60] (Figure 3 C).

It was also reported that invertase was modified on β-cyclodextrin polymer, and β-cyclodextrin/invertase polymer bioconjugate was used as a signal probe to form a sandwich structure with target chloramphenicol and the polydopamine molecularly imprinted membrane immobilized on the magnetic beads. The PGM was used as a signal readout to realize the analysis of chloramphenicol in food with the detection limit of 0.16 ng/mL [20].

In addition, invertase can be modified on nanomaterials as a signal transduction element. Xu et al. mixed invertase with gold nanoparticles, then modified the nucleic acid strand on gold nanoparticles as a signal probe, which could hybridize with the aptamer probe of dopamine immobilized in the microplate (Figure 3D). To detect dopamine, an aptamer probe selectively recognized dopamine, the signal probe was replaced, and the sensitive analysis of dopamine was realized by the invertase-modified on the gold nanoparticles with the detection limit of 30 nM [25]. Similarly, Zhang et al. modified the nucleic acid strand and invertase on gold nanoparticles to obtain signal probes. The substrate strand was immobilized on the microplate and hybridized with the DNAzyme strand. Upon addition of the cofactor Pb^{2+}, the substrate strand was hydrolyzed and cleaved, and the residue of the substrate strand on the microplate hybridized with the signal probe to realize the sensitive analysis of Pb^{2+} with the detection limit of 1.0 pM [27]. Moreover, Huang et al. modified invertase and *E. coli* O157:H7 antibody on magnetic nanoparticles as labeling probe and immobilized another antibody of *E. coli* O157: H7 on nitrocellulose membrane as detection line. The pathogenic bacteria *E. coli* O157: H7 in the sample was fixed on the detection line by sandwich reaction, while the unreacted magnetic nanoparticles labeled probe flowed to the absorption pad and reacted with the sucrose stored in the absorption pad. The generated glucose was quantitatively analyzed by PGM. The detection limit of *E. coli* O157: H7 was 6.2×10^4 cfu/mL [42].

2.2. Amylose converted to glucose by amylase

Other glucose-producing enzymes can also be used to build biosensors based on PGM. Among them, amylase is one of the most studied. It can hydrolyze amylose to produce glucose, which can be used as a signal transduction element to construct PGM-based biosensor [63-71]. Yang Group first reported the use of amylase to hydrolyze amylose trapped in hydrogels to detect non-glucose target (Figure 4A). They grafted two short DNA sequences (strand A and strand B) onto linear polyacrylamide polymers to form polymer strands A and B (PS-A and PS-B). The strand A and strand B hybridizes with aptamers to form a sandwich complex, thereby cross-linking PS-A and PS-B to form gels, which contain glucoamylase. Without the target, the glucoamylase was captured in the gel steadily and separated from the amylose in the gel solution. When the target molecules are introduced, aptamer specifically and preferentially bind with target molecules to form target-aptamer complexes, resulting in the collapse of hydrogel and release of glucoamylase, which catalyzes the hydrolysis of amylose to produce large amounts of glucose for PGM quantitative readout. The detection limit was as low as 3.8 μM [63]. Li Group used similar principle to construct hydrogel for microRNA (miRNA) detection. When the target miRNA was added, the activity of MNAzyme was restored, inducing the cleavage of the substrate strand and resulting in the collapse of hydrogel and the release of amylase. Then the amylose was generated to produce glucose, which was used to detect the miRNA-21 with the detection limit of 0.325 fmol [69]. Furthermore, Gao et al. trapped amyloglucosidase in the hydrogel formed by DNA tetrahedron. The tetrahedral edge contained methylation sites of Dam methyltransferase. After methylation, the site was cleaved by *Dpn* I restriction endonuclease, resulting in collapse of hydrogel and release of amyloglucosidase, which catalyzed the hydrolysis of starch to produce glucose. The sensitive analysis of Dam methyltransferase was achieved by PGM, and the detection limit was as low as 0.001 U/mL [71].

In addition to amylase encapsulated in hydrogels, amylase can be encapsulated in the liposome as a signal transduction element. For example, Yang Group encapsulated amylase amyloglucosidase in liposome, modified thrombin aptamer probe on liposome, and formed sandwich structure with thrombin target and another aptamer immobilized on magnetic bead. Upon addition of surfactant, the liposome was ruptured and amyloglucosidase were released, which catalyzed amylose to produce glucose and realized macromolecular protein detection of thrombin and C-reactive protein (CRP) with detection limit of 1.8 nM and 0.3 nM, respectively [66]. Zhang et al. modified the nucleic acid strand on the glucoamylase-encapsulated liposome and hybridized with the nucleic acid strand immobilized on the magnetic bead to form double strands complex (Figure 4B). The hybrid complex contained the active site of Dam methyltransferase, which was cut by *Dpn* I restriction endonuclease after methylation. The magnetic separation supernatant was added with surfactant and the released glucoamylase catalyzed substrate amylose to generate glucose. The sensitive analysis of methyltransferase Dam was realized, and the detection limit was 0.002 U/L [68].

Moreover, glucoamylase can also be modified on nanomaterials as a signal transduction element. Fu et al. modified the glucoamylase and antibody on gold nanoparticles to form a sandwich structure with neuron-specific enolase and antibody immobilized in the microplate

(Figure 4C). Glucoamylase catalyzed amylopectin to produce glucose. Finally, the sensitive analysis of neuron specific enolase was realized by PGM with the detection limit of 0.05 ng/mL [64].

2.3. Other forms of signal transduction

Besides most commonly used invertase and amylase, other glucose-producing enzymes have been reported to construct PGM-based biosensors. For example, Lu group labeled glycated hemoglobin (HbA1c) antibody with alkaline phosphatase (ALP) to form a sandwich structure with the target protein HbA1c and another antibody immobilized on the magnetic bead. With this structure, HbA1c was detected with a PGM by using the ALP to catalyze Glucose-1-phosphate to produce glucose. The detection limit of HbA1c was 3mg/L [72]. We also used ALP to detect galactose-1-phosphate uridine transferase activity, which can be used for galactosemia detection in real clinical samples [73]. Similarly, Abardía-Serrano et al. used ALP modified signal probe to hybridize with PCA3 (nuclear acid prostate cancer antigen 3) and capture probe immobilized on magnetic beads to catalyze glucose-1-phosphate to produce glucose. The sensitive analysis of PCA3 was realized by PGM, and the target DNA as low as 5 pM could be detected [74].

In addition to glucose production, some glucose consuming reactions can also be used to construct PGM-based biosensors [75-80]. For example, Luo et al. used antibody functionalized magnetic nanoparticles to capture and enrich Salmonella, formed sandwich structure with antibody on glucose oxidase modified silica nanoparticles. Upon addition of a certain amount of glucose, glucose oxidase catalyzed glucose to produce gluconic acid, and the amount of glucose concentration reduction was linearly correlated with the concentration of Salmonella with a detection limit of 72 CFU/mL [76]. Fang et al. also used PGM to evaluate the biological toxicity of environmental pollutants. The microorganism in water can consume glucose, and the environmental pollutants in water can reduce the consumption of glucose after the microorganism apoptosis. The change of glucose concentration can be used to evaluate the biological toxicity of environmental pollutants in water [77].

There is also a more direct way of signal transduction, i.e., glucose is directly encapsulated in some materials (such as liposomes, porous materials) and can be released upon binding of targets. Lin group reported a novel sensing strategy, in which glucose was encapsulated in liposomes, and the antibody was modified on liposomes. The antibody modified on magnetic beads and the target protein phospho-p53^{15} (protein 53 phosphorylated on Serine 15) were sandwiched, and then surfactant Triton X-100 destroyed the liposome to release the encapsulated glucose, which can be detected by PGM. The detection limit of phospho-p53^{15} protein was 50 pg/mL [81]. The group also trapped the liposomes coated with glucose on the conjugate pad of lateral flow strip, and adsorbed the magnetic beads modified with antibodies on the detection area with magnets. When the sample contained the target protein phospho-p53^{15}, the antibody on the liposome, the target protein and the antibody on the magnetic bead formed a sandwich structure, so that the liposome was enriched in the detection area, and then the surfactant Triton X-100 was added to destroy the liposome and release glucose. Finally, phospho-p53^{15} protein can be detected by PGM with the detection limit of 50 pg/mL [82]. Tang et al. encapsulated glucose in liposomes, modified biotin

on liposomes, and immobilized the antibody of model analyte AFB1 on the microplate. Through the sandwich reaction with the target AFB1 and biotin labeled antibody, as well as the sandwich reaction of antibody-biotin/avidin/biotin labeled liposomes, the sensitive analysis of small molecule toxin AFB1 was realized, and the detection limit was as low as 0.6 pg/mL [83]. Liang et al encapsulated glucose in porous silica nanomaterials with positive charge, sealed the pores with single nucleic acid strand with negative charge. Hg^{2+} in the sample induce the formation of T-Hg^{2+}-T base pair with nucleic acid strand, which makes single nucleic acid strand break away from porous silica nanomaterials, releases encapsulated glucose and detects it with PGM, which can realize the quantitative analysis of Hg^{2+} with a detection limit of 0.1 nM [84].

In addition, a sensing strategy that can be measured with a PGM without using glucose has been reported recently. The Lu group found that the PGM also has a metrological response to nicotinamide coenzymes, such as NAD(P)H (nicotinamide adenine dinucleotide (phosphate) hydrogen) [15,16]. Since numerous enzymatic assays use NAD(P)H either as a cofactor or as a product of the enzymatic reactions, this discovery has expanded the targets of PGM-based biosensor for many non-glucose targets that cannot be recognized by antibodies, DNAzymes or aptamers. For example, using the sensing strategy based on this principle to detect L-lactate in serum and blood, the detection limit is 0.14 mM and 0.11 mM, respectively [85]. Li group constructed a biosensor for the detection of organophosphorus peptide (OP) by directly reducing ferrocyanide from mediator ferricyanide in PGM. The detection limit of paraoxon can reach 5 μg/L [86].

In general, there are two main approaches used for signal transduction in developing PGM-based biosensing strategies, namely enzymatic generation of glucose and nanocarrier encapsulation of glucose. For enzymatic generation of glucose, the enzyme turnover is the main factor affecting the analytical performance of the biosensor. It has been reported that the highest number of 3430 s^{-1} was found for invertase [12], that is why invertase is used as the signal transduction element in most reports. For nanocarrier encapsulation of glucose, the amount of encapsulated glucose is the main factor affecting the analytical performance of the sensor. Liposome has become the most commonly used nanocarrier because of its superior loading capacity and convenient unloading capacity.

3. SIGNAL AMPLIFICATION

The quantitative linear detection range of glucose for commercial PGM is only 0.6-33 mmol/L (10-600 mg/L), and the limit of detection (LOD) is often way above those required for many non-glucose targets. Therefore, it is necessary to employ signal amplification in the construction of PGM-based biosensors to reach the required LOD. Besides the enzymatic amplification of glucose-producing enzyme itself, the signal amplification methods commonly used in PGM-based biosensors to detect non-glucose targets include nanomaterials amplification, nucleic acid reaction amplification (such as RCA, HCR, CHA and ICSDP), DNAzyme amplification, liposome encapsulation amplification, hydrogel encapsulation amplification, and biotin-avidin reaction amplification.

3.1. Nanomaterials amplification

Nanomaterials commonly used in PGM-based biosensors include gold nanoparticles, magnetic nanoparticles, porous silica nanomaterials, and graphene [21,25,27,43,51,54,55,64,75,84,87,88]. For example, Fu et al. modified the antibody of glucoamylase and NSE (neuron-specific enolase) on the surface of gold nanoparticles with a diameter of 16 nm as signal amplification elements, and achieved quantitative analysis of NSE in microplate by sandwich reaction. Large amount of amylase modified on gold nanoparticles was used to achieve the amplified detection of NSE with the detection limit of 0.05 ng/mL [64]. In addition, Xu et al. modified DNA2 and a large number of invertase on gold nanoparticles as signal amplification elements, modified DNA1 in microplates, and hybridized DNA1 with DNA2 to form double strand complex. The dopamine in the sample reacts with aptamer probe DNA1 to replace the DNA2-gold nanoparticle-invertase, and then catalyzes the hydrolysis of sucrose to produce glucose. The amplified detection of dopamine can be realized by PGM [25]. Furthermore, Fang et al. reduced $HAuCl_4$ on PAMAM dendrimer with $NaBH_4$ to form gold nanoparticles and formed gold nanoparticles-PAMAM complex, and then modified gold nanoparticles with a large amount of invertase as signal amplification element to achieve the sensitive analysis of target nucleic acid with the detection limit as low as 0.26 pM [43]. In addition to the direct modification of invertase on the surface of gold nanoparticles, avidin can also be modified on the surface of gold nanoparticles, and then biotin labeled invertase can be modified on the surface of gold nanoparticles through biotin-avidin reaction to achieve signal amplification [54].

In addition to being used as sensing interface in PGM-based biosensors, magnetic nanoparticles can also be used as signal amplification elements. For example, Su et al. connected the biotin labeled invertase and biotin labeled nucleic acid strand to the avidin modified magnetic beads through biotin-avidin reaction, which realized signal amplification and sensitive analysis of Cu^{2+} [51]. Similarly, Hu et al. modified invertase onto magnetic beads as signal amplification elements to achieve the amplification and detection of PSA [21] (Figure 5A).

3.2. Nucleic acid reaction amplification

Accurate, sensitive and rapid detection of specific nucleic acid sequences is of major significance in drug development, clinical diagnosis and environmental science. When using PGM as signal readout device to construct a biosensor for the detection of nucleic acid samples, various nucleic acid reactions can be used as signal amplification elements to achieve highly sensitive analysis of target nucleic acid, such as exonuclease III (Exo III) auxiliary signal amplification [59], isothermal circular strand displacement polymerization (ICSDP) [26], hybridization chain reaction (HCR) [37], catalyzed hairpin assembly (CHA) [46], strand displacement amplification (SDA) [70], rolling circle amplification (RCA) [47,53], and the combination of several nucleic acid reaction amplification methods [36,45,89,90]. Moreover, due to the application of functional nucleic acids, these signal amplification methods based on nucleic acid reaction can be used not only for the highly sensitive analysis of nucleic acids, but also for the detection of other target molecules recognized by functional nucleic acids [91]. For example, Xu et al. hybridized a short DNA strand with a long DNA strand and left the protruding 3 'end of the long DNA strand which

Exo III could not digest. After adding the target DNA to hybridize with the double strands to obtain the blunt 3' end, Exo III can digest the long strand from the blunt 3 'end and releases the short strand, which is used to hybridize with the capture probe on the magnetic bead and the signal probe labeled with invertase to form a sandwich structure. Then, through the transduction of invertase, the target DNA can be amplified and detected by a personal glucose meter [59]. Xu et al. also used the isothermal circular strand displacement polymerization (ICSDP) signal amplification technology in the construction of PGM-based biosensor. They modified the hairpin probe on the magnetic bead, which can be opened upon hybridization with the target DNA. The invertase modified primer hybridize with the opened hairpin probe, and induced the ICSDP reaction in the presence of Klenow DNA polymerase to replace the target DNA strand and achieve the purpose of signal amplification [26]. Zhu et al. immobilized the antibody of vascular endothelial growth factor (VEGF) in the microplate, and then formed a sandwich structure with VEGF and its aptamer probe. Then, the aptamer probe was used to initiate the hybridization reaction of two invertase labeled nucleic acid strand. Thus, the highly sensitive analysis of VEGF was realized, and the detection limit was as low as 1.2 pg/mL [37]. Ge et al. immobilized the AFP antibody in the microplate, then formed a sandwich structure with the target protein AFP and the antibody labeled with gold nanoparticles, and then used the nucleic acid chain modified on gold nanoparticles as the primer for rolling circle amplification. The amplified long strand product hybridized with tens of thousands of invertase labeled signal probe to achieve signal amplification, which can realize the highly sensitive detection of AFP [47]. Sun et al. used the similar sensing strategy to developed an ultrasensitive PGM-based biosensor for PSA detection based on rolling circle amplification [53] (Figure 5B).

3.3. Liposome encapsulation amplification

Liposomes are promising candidates for signal amplification since it is easy to encapsulate molecules in their lumen and used as functional vesicles [81]. When using liposome encapsulation for signal amplification, glucose molecules can be directly encapsulated in liposome [81-83], and some glucose producing enzymes (such as glucoamylase) can be also encapsulated in liposome [66-68] as signal elements. For example, Xue et al. hybridized the miRNA with the padlock probe which can be cyclized in the presence of T4 RNA ligase 2. With the help of Phi 29 DNA polymerase, rolling circle amplification reaction occurred and the products were digested by Nb.BbvCI nickase to obtain a large number of trigger probes. The trigger probe reacted with cDNA modified on magnetic beads and pDNA modified on glucoamylase encapsulated liposomes. As a result, the target miRNA was analyzed with ultra-sensitivity by using multiple signal amplification of rolling circle amplification, nickase cleavage and liposome. The detection limit was as low as 0.1 fM [67]. Tang et al. developed a novel PGM-based immunosensing strategy for sensitive detection of AFB1 using surfactant-responsive cargo release from glucose-encapsulated liposome nanocarrier [83] (Figure 5C).

3.4. Hydrogel trapping amplification

DNA hydrogel, especially hydrogel formed entirely from DNA, is a widely hydrated three-dimensional DNA network formed by sequential directional self-assembly. These hydrogels have many advantages, such as large surface area, good biocompatibility, designed

mechanical properties and abundant functional sites. They can be used as functional materials for sensing, tissue engineering and drug release. In particular, their sensitive response to external trigger factors makes them favored by POCT device construction. For example, Yan et al. hybridized cocaine aptamer with two nucleic acid strands bond with linear polyacrylamide polymers to form DNA hydrogel, and trapped glucoamylase in the hydrogel to separate the amylose from the hydrogel. The target molecule cocaine specifically binds with the aptamer sequence, resulting in the collapse of the hydrogel and releasing of glucoamylase. The amylose was catalyzed to generate glucose, which can be read by PGM for amplified detection of cocaine [63].

3.5. DNAzyme amplification

As a kind of functional nucleic acid, DNAzyme can catalyze the cleavage of substrate strand with the help of metal ion cofactor, which can be used for metal ions detection. DNAzyme can also be used as a signal amplifier to construct PGM-based biosensors [29,38,44,50,56]. Lu group used 8-17 DNAzyme and 39E DNAzyme to construct biosensors for different non-targets based on personal glucose meter. In the presence of metal ions to be measured, DNAzyme catalyzes the hydrolysis and cleavage of the substrate strand, and the released substrate fragment was used as invasive DNA to replace the invertase labeled signal probe hybridized with biotinylated nucleic acid immobilized on magnetic beads, and catalyzes the hydrolysis of sucrose to produce glucose, which realizes the detection of Pb^{2+} and UO_2^{2+} [29]. Yang et al. hybridized aptamer probe of aflatoxin AFB1 with the substrate strand which was modified with thiol group and invertase in the two ends. When the target molecule was added, aptamer probe specifically binds with AFB1 and released from the substrate chain. Then the added DNAzyme strand can hybridize with the substrate strand and cleave the substrate strand in the presence of cofactors. The invertase labeled substrate fragment was released from the electrode and used to catalyze the hydrolysis of sucrose to produce glucose, thus realizing the quantitative analysis of AFB1 [44]. Recently, we hybridized the aptamer probe of OTA with the DNAzyme strand and immobilized it on magnetic beads together with the invertase modified substrate strand (Figure 5 D). After the target molecule of OTA in the sample specifically combines with the aptamer probe, the DNAzyme strand is replaced to react with the substrate strand on the magnetic bead, and the hydrolysis of the substrate strand is catalyzed by the cofactor. Theoretically, one molecule of OTA can trigger the hydrolysis of all the substrate strands on the magnetic bead, thus realizing the highly sensitive detection of OTA [92].

3.6. Biotin-avidin amplification

One molecule avidin can bind to four molecules of biotin, which can be used to amplify the signal through biotin-avidin reaction. Most of the signal amplification methods reported in the literature are based on modifying biotinylated invertase to the surface of avidin functionalized magnetic beads to achieve signal amplification [51,54]. However, there are also reports that biotin-avidin is directly used as signal amplification element [24,39,74]. For example, Yang et al. immobilized phosphorylated peptides on the surface of Zr^{4+} functionalized magnetic beads (ZrMBs), and connected biotinylated invertase to ZrMBs with avidin as a bridge to realize the amplification detection of protein kinase A [24].

From the above reports, most of the sensing strategies directly make use of the turnover of enzyme to achieve enzymatic amplification. In order to obtain higher detection sensitivity, researchers often combine an additional or even multiple amplification strategy to achieve lower detection limit and wider linear detection range. However, the more complex the amplification strategy is, the slower the detection speed may be. Therefore, how to achieve signal amplification without sacrificing detection speed remains a big challenge.

4. TARGET RECOGNITION AND ANALYSIS

In the process of constructing PGM-based biosensors for quantitative analysis of different target molecules, it is necessary to select different recognition elements to specifically recognize the target molecules of interest, and then combine with signal transduction elements and signal amplification elements to design sensing strategy, and finally use personal glucose meter to carry out quantitative analysis. According to the literature reports, current PGMs can analyze metal ions, small molecules, macromolecular proteins, nucleic acids and even cells and bacteria. Especially in recent years, the development of aptamers (obtained by SELEX technology in vitro, which can specifically recognize a variety of target molecules [56,92-104]) has greatly expanded the detection range of PGMs.

4.1. Metal ions recognition and analysis

Metal ions, especially Pb^{2+}, Cu^{2+}, and Hg^{2+} and other heavy metal ions are the main pollutants in the environment. After they enter the biological chain, they can interact with protein, enzyme, nucleic acid and other cellular components, change their functions, cause diseases, endanger the normal growth of human body, and destroy the ecological balance of the environment. Therefore, it is of significance to develop rapid analytical method for detection of heavy metal ions in the environment. The commonly used metal ion recognition elements include DNAzymes, aptamers and other nucleic acids with specific sequences. DNAzymes can catalyze cleavage of substrates when some metal ions are used as cofactors. For example, Xiang and Lu constructed a biosensor for the detection of Pb^{2+} and UO_2^{2+} using 8-17 DNAzyme and 39E DNAzyme, which specifically recognize Pb^{2+} and UO_2^{2+}, respectively [29]. In the presence of cofactors, DNAzyme catalyzes the hydrolysis and cleavage of the substrate strand, and the cleaved fragment of the substrate strand is used to displace the invertase labeled signal probe immobilized on the magnetic beads and realize the detection of heavy metal ions. Zhang et al. used 8-17 DNAzyme, which has specific response to Pb^{2+}, as the recognition element, and immobilized the biotinylated substrate chain on the microplate. In the presence of Pb^{2+}, DNAzyme catalyzed the hydrolysis and cleavage of the substrate strand. The remained biotinylated substrate fragment hybridized with the signal probe immobilized on invertase modified gold nanoparticles and achieve sensitive detection of Pb^{2+} using PGM as the readout device [27].

The recognition elements of Cu^{2+} mainly depends on the click chemistry reaction [51] between alkynyl-DNA and azido-DNA or the ligation DNAzyme [35] which specifically recognize Cu^{2+}. For example, Su et al. constructed a biosensor to detect Cu^{2+} by using click chemistry and personal glucose meter. The Cu^{2+} is reduced to Cu^{+} by sodium ascorbate, which catalyzes the click linking between the alkynyl-DNA immobilized on screen printed

carbon electrode and the azido-DNA attached to the invertase modified magnetic bead. The invertase catalyzed the hydrolysis of sucrose to generate glucose, which is detected by the PGM and realize amplified analysis of Cu^{2+} [51]. Ming et al. constructed a biosensor for detecting Cu^{2+} based on PGM and ligation DNAzyme releasing strategy. The DNAzyme catalyzed the ligation of nucleophilic attack of the phosphorus center of DNA1 by the hydroxyl group on DNA2 and forming a phosphodiester bond in the presence of Cu^{2+}. By introducing invertase labeled DNA and capture-DNA modified magnetic beads, the ligation product can hybridize with them and form invertase modified MBs. The invertase can catalyze the hydrolysis of sucrose to generate glucose and can be monitored by the PGM. The detection limit of Cu^{2+} is 1 nM [35].

The main recognition element for detecting Hg^{2+} is thymine (T)-containing oligonucleotide [23,36,84]. Liang et al. used wrapping DNA as bio-gate to encapsulate glucose in mesoporous silica nanoparticles (MSNs). A T-terminal assistant DNA hybridized with bio-gate DNA to form T–Hg^{2+}–T base pairing. Exo III can digest the wrapping DNA from the 3′-hydroxyl terminus of the duplex DNA, which further releases Hg^{2+} and continuous detachment of wrapping DNA from MSNs. As a result, the bio-gate is opened, allowing the pore-trapped glucose to diffuse out of MSNs and be detected by PGM [84]. Huang et al. employed thymine-thymine (T-T) mismatches DNA as specific recognition elements for selectively capturing Hg^{2+} to form hairpin structure, which triggered the operation of T-rich DNA machine and produce a large amount of product for signal amplification. The product hybridized with capture DNA and invertase labeled signal probe to form a sandwich hybridization structure. The invertase catalyzed sucrose into glucose, which can be monitored by PGM to realize quantification of Hg^{2+} concentration [36]. Table 1 summarizes the analytical performance of some representative reports using PGM for metal ion detection.

4.2. Small molecules recognition and analysis

Aptamer is usually used as recognition element for detection of small molecules with PGM-based biosensors [22,25,28,44,63]. For example, melamine detection in milk and other foods has attracted many attentions since the discovesry that melamine-adulterated food causes sever kidney. Lu group obtained a melamine aptamer by structure-switching selection method, and used the aptamer sequence to form a sandwich structure with invertase labeled signal probe biotinylated nucleic acid probe immobilized on magnetic beads. After the melamine molecule in the sample specifically combined with the aptamer, the invertase labeled signal probe was replaced and catalyze the sucrose to produce. High sensitivity detection of melamine in milk was realized by PGM [22]. Lu group also used the aptamer sequence of cocaine to construct a similar sandwich structure to obtain MB/DNA-INV conjugate, which was captured in the conjugate pad of lateral flow dipstick. When the sample flowed through the conjugate pad, the aptamer probe bond specifically with cocaine molecule, and the invertase labeled signal probe was replaced and flowed to the absorption pad to catalyze the hydrolysis of sucrose in the absorption pad to generate glucose, thus realizing the rapid detection of small molecule of cocaine [28]. There are also reports on the use of molecularly imprinted probe [20,88] or antibody [34,48,83] to recognize small molecules. Chen et al. developed a portable and antibody-free sandwich assay for

determination of chloramphenicol (CAP) in animal derived food by a PGM based on magnetic molecular imprinted probe (m-MIP) nanoparticles and a β-cyclodextrin/invertase functionalized signal tag [20]. Tang et al. used antibody as recognition element to form sandwich structure with small molecule target of AFB1, and glucose encapsulated liposome as signal amplification element to realize high sensitivity analysis of AFB1 [83]. Zhao et al. developed an immunosensor by using a primary antibody coated $ZnFe_2O_4$ nanoparticles to capture the target MC-LR. Invertase coated secondary antibody-conjugated graphene oxide-Au NPs can be immobilized for formatting the sandwich immuno-complexes, which allowed for enzymatic conversion of sucrose to glucose [55]. For example, Xiang and Lu immobilized OTA antibody on magnetic beads, and used invertase labeled aptamer as a signal probe to form a sandwich structure with OTA small molecule and OTA antibody, which realized the sensitive analysis of OTA small molecule with a detection limit of 6.8 ng/mL [18]. The analytical performance of some representative reports using PGM for small molecules detection are summarized in Table 2.

4.3. Protein recognition and analysis

The development of a rapid and highly sensitive protein detection technology is of great significance for diagnosing and treating diseases, and screening drugs. When developing biosensors based on PGMs to detect proteins, antibodies [47,53,54,60,64,72,81,82] or aptamers [33,37,38,58,66] or combinations of antibodies and aptamers [62] are usually used as the recognition element. For the detection of methyltransferase protein, nuclear acid with specific methylation site is used as the recognition element [30,39,68,71]. Sun et al. immobilized antibody Ab1 of PSA on the magnetic beads and antibody Ab2 on the gold nanoparticles to react with PSA to form sandwich structure. The nucleic acid strand modified on the gold nanoparticles was used as a primer to initiate the rolling circle amplification reaction, and then the invertase modified detection probe was hybridized with the amplification products to realize the amplified detection of PSA [53]. We hybridized the aptamer probe of interferon-γ (IFN-γ) with biotinylated DNA immobilized on magnetic beads and the invertase labeled signal probe to form a sandwich structure. After the target molecule specifically combined with the aptamer probe, the invertase modified signal probe was replaced, and then the sucrose was hydrolyzed to glucose. Finally, we measured glucose with a personal glucose meter to realize the quantitative analysis of IFN-γ [33]. Platelet derived growth factor BB (PDGF-BB), an important cytokine in serum, plays a vital role in regulating cell growth and division. Hong et al. synthesized ZnS nano crystal clusters and modified the aptamers of PDGF-BB on them, then formed a sandwich structure with the target protein of PDGF-BB and another aptamer immobilized on the surface of gold electrode. When Ag^+ was added to the sample, the Zn^{2+} in ZnS nano crystal clusters was replaced by Ag^+, and then 8-17 DNAzyme catalyzed the hydrolysis of the substrate strand under the help of Zn^{2+} cofactor. The substrate strand fragment labeled with invertase catalyzed the hydrolysis of sucrose to glucose, thus the sensitive analysis of PDGF-BB was realized by the PGM [38]. Wang Group immobilized antibody of cardiac biomarker myoglobin (anti-Myo) on polystyrene microplate to serve as recognition element. A biosensor for the detection of myoglobin was successfully constructed by using the invertase labeled aptamer probe to react with myoglobin to form a sandwich structure [62]. DNA methyltransferase (MTase) plays an important role in many biological processes and

has been recognized as a predictive cancer biomarker far before other signs of malignancy and a therapeutic target in cancer treatment. Yuan group immobilized the hybrid duplex of S1/S2 containing the active site of M.SssI methyltransferase and *Hpa* II restriction endonuclease on the gold electrode as the recognition element. Methylated dsDNA was formed after methylated by M.SssI methyltransferase, *Hpa* II endonuclease can specifically recognize this site and cleave the unmethylated double strand S1/S2, while the methylated dsDNA remains intact. Biotinylated S3 can be further hybridized with methylated dsDNA. Then, avidin and biotinylated invertase are added in turn to catalyze the hydrolysis of sucrose to glucose to realize the sensitive analysis of M.SssI methyltransferase [39]. Table 3 summarizes the analytical performance of some representative reports using PGM for protein analysis.

4.4. Nucleic acid recognition and analysis

DNA detection has attracted more attention because of its important role in etiology analysis, genetic disease diagnosis and forensic examination. Recent studies have shown that microRNA (miRNA, 18-25 nt small non-coding RNA, known to help regulate gene expression and maintain cell physiological processes) is associated with the occurrence and development of human cancer cells. The tumor specific fingerprints of miRNAs can provide important information for tumor occurrence, invasion and metastasis. Therefore, it is of great significance to develop biosensors for nucleic acid detection. When constructing PGM-based biosensors for detecting nucleic acids (including DNA and miRNA), nucleic acids are usually used as recognition elements [15,18,21,65,67,68,72,86]. Lu group used capture probe immobilized on magnetic beads and invertase labeled signal probe as the recognition element to recognize target DNA hepatitis B virus (HBV) DNA fragment to form a sandwich structure. Sucrose was hydrolyzed to glucose by invertase, and the sensitive detection of HBV DNA fragment was realized by a personal glucose meter [17]. Wang Group uses polystyrene plates to make a chip with one central channel and four branch channels. Capture-B, Capture-C and Capture-D that recognizes the target DNA of HBV-B, HBV-C and HBV-D, respectively, and a negative control Capture-R were immobilized in four branch channels, respectively. Samples were injected into central channel and flowed through four branch channels, the target DNA in the sample hybridized with different capture probes, then the invertase labeled signal probe was added to form a sandwich structure with the target DNA, and then the sucrose solution was added to react with the invertase in the channel. The generated glucose was detected by a personal glucose meter, and the target DNA of HBV-B, HBV-C and HBV-D could be analyzed simultaneously [61]. Using nucleic acid as recognition element, Shan et al. constructed a DNA biosensor by using loop based DNA competitive hybridization reaction and personal glucose meter. When the sample contains the target DNA, the target DNA replaces the invertase labeled signal probe labeled due to the competitive binding, and catalyzes the hydrolysis of sucrose to produce glucose. As a result, the sensing strategy for quantitative analysis of target DNA is constructed [52]. Zhang group has developed a DNA walking machine that can detect miRNA-21 with a personal glucose meter and a fluorescence meter. The hairpin probe H1 labeled with quenching group BHQ and fluorescent group FAM at both ends was immobilized on the magnetic bead. The target miRNA in the sample hybridized with hairpin probe H1. After opening the hairpin structure, the invertase labeled hairpin probe H2

hybridized with H1. As a result, the target miRNA was replaced and reacted with another molecule H1. The restore of FAM labeled on H1 and invertase labeled on H2 make the proposed sensor can be used to detect miRNA-21 by PGM and fluorescent meter with detection limit of 98 pM and 60 pM, respectively [46]. Using nucleic acid as recognition element, Huang et al. hybridized DNAzyme strand with locking strand and immobilized the duplex and invertase labeled substrate strand on magnetic beads. Upon hybridization of miRNA-21 with locking strand, the DNAzyme strand was released and hybridized with the substrate strand, and catalyzed the hydrolysis of the substrate strand in the presence of cofactor. The invertase labeled substrate fragment was released to catalyze the hydrolysis of sucrose to produce glucose, and the amplified detection of miRNA-21 was realized [56]. The analytical performance of some representative reports using PGM for nucleic acid detection are summarized in Table 4.

4.5. Cell and bacteria recognition and analysis

The detection, identification and quantification of pathogens are very important for clinical diagnosis, environmental monitoring and food safety. PGMs can also be used as readout to detect pathogenic bacteria, such as *Salmonella* [40,75], *E. coli* O157:H7 [41,42,76], *Staphylococcus aureus* [32] and other pathogenic bacteria using antibody or aptamer as recognition elements. For example, Luo et al. used antibodies as recognition elements to immobilize on magnetic beads and glucose oxidase functionalized silica nanoparticles (SiNPs), respectively. The analyte *Salmonella* reacted with antibodies to form a sandwich structure. Glucose oxidase catalyzed the hydrolysis of glucose, and there was a linear relationship between the amount of glucose reduction detected by personal glucose meter and the content of *Salmonella* [75]. Huang et al. modified the magnetic beads with antibodies as recognition elements, and then reacted with *E. coli* O157:H7 and invertase labeled antibody to form a sandwich structure. The magnetic beads were adsorbed in the capillary with magnets. The sucrose flowed through the capillary and was hydrolyzed by invertase to produce glucose which was detected by personal glucose meter. The detection limit of *E. coli* O157:H7 was 79 CFU/mL [41]. Wan et al. constructed a biosensor for detection of *Staphylococcus aureus* based on personal glucose meter with aptamer as recognition element, and the detection limit was 1.0×10^5 CFU/mL [32]. There are also a few reports that the sensor can be constructed to detect cells based on personal glucose meter. Circulating tumor cells (CTCs) are malignant cells in peripheral blood stream or lymphatic system that are shed from tumor tissues, which play critical roles in the occurrence of cancer and metastases. Using SK-BR-3 breast cancer cell line CTC as model target and two different antibodies, anti-EpCAM and anti-human epidermal growth factor receptor 2 (HER2), as recognition elements, Yang et al. constructed a PGM-based biosensor for CTC detection. They fixed anti-EpCAM antibody on magnetic beads and anti-HER2 antibody on streptavidin coated polystyrenes microbeads. The target CTC cells reacted with two antibodies to form a sandwich structure, and then the invertase catalyze the hydrolysis of sucrose to generate glucose. Using a PGM as readout device, the detection limit of CTC cells was 7 cells [49]. Table 5 summarizes the analytical performance of some representative reports using PGM for cell and bacteria detection.

From the perspective of target recognition and analysis, many sensing strategies for different analytes have been developed, and the most commonly used target recognition elements are still antibodies and aptamers. It is still an important direction for researchers to develop new recognition elements and construct new analysis strategies for new targets. In addition, the development of multi-component sensing strategy is still a challenge for blood glucose meter as a readout.

CONCLUSIONS AND PERSPECTIVES

As a POCT device, personal glucose meter is widely used in clinical diagnosis and personal blood glucose monitoring of diabetic patients because of its convenient operation, low cost, good selectivity and no need of expensive instruments. In recent years, it has been reported that PGM can be used to detect various non-glucose targets, which greatly expands the application scope of PGM. Starting from the main components of biosensor, this review summarizes the signal transduction models, signal amplification methods and target recognition elements of PGM-based biosensors and provide examples of applying the sensors in detecting different non-glucose targets.

In the area of signal transduction, glucose producing enzymes, such as invertase, amylase and alkaline phosphatase, can be used to convert different sugar sources into glucose, or glucose can be directly encapsulated in liposomes and other materials and can be releases upon binding of the target. For signal amplification, nanomaterials, nucleic acid reactions, liposomes or hydrogel, DNAzyme, biotin-avidin reaction have been used. For target recognition and analysis, for the detection of metal ions, DNAzyme and aptamers with specific response to some metal ions are usually used as recognition elements. For some metal ions detection, special nucleic acids can also be used as recognition elements, such as click chemistry for Cu^{2+} detection and T-Hg^{2+}-T base pair for Hg^{2+} detection. Antibodies or aptamers are mainly used as recognition elements for the detection of small organic molecules such as mycotoxins and drug residues. For protein detection, antibodies, aptamers or the combination of the two are usually used as recognition elements. Nucleic acid modifying enzymes, such as methyltransferase, can also be used to detect nucleic acids containing methylation recognition sites. For the detection of nucleic acids such as target DNA or miRNA, nucleic acids with complementary sequences are usually used as recognition elements through nucleic acid hybridization. For the detection of cells or bacteria, antibodies are mainly used as recognition elements, and a few pathogenic bacteria (such as Staphylococcus aureus) have corresponding aptamers as recognition elements. By using these strategies, the PGM-based biosensors are widely used in clinical diagnosis, food safety and environmental detection.

Although much progress has been made in the construction of biosensors for detecting non-glucose targets based on PGMs, there are still challenges in each area of signal transduction, amplification and target recognition for practical applications and thus require further development in the future. (1) In the area of signal transduction, most of the biosensors based on PGMs use glucose-producing enzymes. New signal transduction methods with more robust enzymes and higher activities need to be developed to improve better analytical performance. (2) In signal amplification, the detection sensitivity of PGM itself is not high

enough. Therefore, various signal amplification methods are needed. To meet the need, the use of complex signal amplification methods has been reported, but implementation of these steps often reduces the detection speed. Therefore, it is necessary to develop new signal amplification methods, which can improve the detection sensitivity, realize the sensitive detection of low abundance analytes without the sacrifice of detection speed. (3) In target recognition, in addition to antibody, aptamer, DNAzyme, modified nucleic acid and other recognition elements with more functional groups can be developed to allow detecting new targets with higher affinity and selectivity. (4) In the aspect of target analysis, the first is to expand the application range of PGMs in different fields and different targets. The second is that most of the biosensors based on PGMs as readout can only detect one target analyte at a time. The development of biochip and other methods using PGMs as signal readout to realize multi-component analysis is also needed. (5) In the design of the PGM itself, we need to develop the software to make the detection results of non-glucose targets directly displayed on the meter, eliminating the manual conversion steps and enhancing the practicability of its detection of non-glucose targets.

ACKNOWLEDGEMENTS

We wish to thank Lu groups members and collaborators for contributions to work described in this review.

FUNDING

This study is financially supported by Research Foundation of Education Bureau of Hunan Province (Grant No.19B384), Open Project of State Key Laboratory of Chemo/biosensing and Chemometrics (Grant No. 2016010), China Postdoctoral Science Foundation (Grant No. 2015M582339), Changde Science and Technology Innovation Project (Grant No. 2019ZD25, 2020ZD29) and US National Institute of Health (GM141931 and MH110975).

REFERENCES

[1]. Leke AZ; Maboh NM; Maeya SE; Armstrong O; Ndumbe LD; Nyenti BP; Afumbom AD; Sone NB; Etiendem D; Nkwati ES Epidemiological Transition of Type 2 Diabetes Mellitus in Rural South West Cameroon. Open J. Endocr. Metab. Dis 2020, 10, 45–58. 10.4236/ojemd.2020.104006.

[2]. Vashist SK; Zheng D; Al-Rubeaan K; Luong JHT; Sheu FS Technology behind Commercial Devices for Blood Glucose Monitoring in Diabetes Management: A Review. Anal. Chim. Acta 2011, 703 (2), 124–136. 10.1016/j.aca.2011.07.024. [PubMed: 21889626]

[3]. Galant AL; Kaufman RC; Wilson JD Glucose: Detection and Analysis. Food Chem. 2015, 188, 149–160. 10.1016/j.foodchem.2015.04.071. [PubMed: 26041177]

[4]. Aggidis AGA; Newman JD; Aggidis GA Investigating Pipeline and State of the Art Blood Glucose Biosensors to Formulate next Steps. Biosens. Bioelectron 2015, 74, 243–262. 10.1016/j.bios.2015.05.071. [PubMed: 26143465]

[5]. Zhang L; Gu C; Ma H; Zhu L; Wen J; Xu H; Liu H; Li L Portable Glucose Meter : Trends in Techniques and Its Potential Application in Analysis. Anal. Bioanal. Chem 2019, 411, 21–36. 10.1007/s00216-018-1361-7. [PubMed: 30280228]

[6]. Newman JD; Turner APF Home Blood Glucose Biosensors: A Commercial Perspective. Biosens. Bioelectron 2005, 20 (12), 2435–2453. 10.1016/j.bios.2004.11.012. [PubMed: 15854818]

[7]. Wang J Electrochemical Glucose Biosensors. Chem. Rev 2008, 108, 814–825. 10.1109/ISDA.2007.4389694. [PubMed: 18154363]

[8]. Yoo EH; Lee SY Glucose Biosensors: An Overview of Use in Clinical Practice. Sensors 2010, 10 (5), 4558–4576. 10.3390/s100504558. [PubMed: 22399892]

[9]. Chen C; Xie Q; Yang D; Xiao H; Fu Y; Tan Y; Yao S Recent Advances in Electrochemical Glucose Biosensors: A Review. RSC Adv. 2013, 3 (14), 4473–4491. 10.1039/c2ra22351a.

[10]. Xiang Y; Lu Y Using Personal Glucose Meters and Functional DNA Sensors to Quantify a Variety of Analytical Targets. Nat. Chem 2011, 3 (9), 697–703. 10.1038/nchem.1092. [PubMed: 21860458]

[11]. Lan T; Zhang J; Lu Y Transforming the Blood Glucose Meter into a General Healthcare Meter for in Vitro Diagnostics in Mobile Health. Biotechnol. Adv 2016, 34 (3), 331–341. 10.1016/j.biotechadv.2016.03.002. [PubMed: 26946282]

[12]. Lisi F; Peterson JR; Gooding JJ The Application of Personal Glucose Meters as Universal Point-of-Care Diagnostic Tools. Biosens. Bioelectron 2020, 148, 111835. 10.1016/j.bios.2019.111835. [PubMed: 31707326]

[13]. Tu J; Torrente-rodríguez RM; Wang M; Gao W The Era of Digital Health : A Review of Portable and Wearable Affinity Biosensors. Adv. Funct. Mater 2020, 30, 1906713. 10.1002/adfm.201906713.

[14]. Zhang J; Lan T; Lu Y Translating in Vitro Diagnostics from Centralized Laboratories to Point-of-Care Locations Using Commercially-Available Handheld Meters. Trends Anal. Chem. J 2020, 124, 115782. 10.1016/j.trac.2019.115782.

[15]. Zhang J; Lu Y Biocomputing for Portable, Resettable, and Quantitative Point-of-Care Diagnostics: Making the Glucose Meter a Logic-Gate Responsive Device for Measuring Many Clinically Relevant Targets. Angew. Chem. Int. Ed 2018, 57, 9702–9706. 10.1002/anie.201804292.

[16]. Xu J; Qiao X; Zhang J; Cheng N; Sheng Q; Zheng J; Cao W; Yue T; Lu Y Point-of-Care Monitoring of Intracellular Glutathione and Serum Triglyceride Levels Using a Versatile Personal Glucose Meter. Anal. Methods 2019, 11, 1849–1856. 10.1039/C8AY02709A.

[17]. Xiang Y; Lu Y Using Commercially Available Personal Glucose Meters for Portable Quantification of DNA. Anal. Chem 2012, 84 (4), 1975–1980. 10.1021/ac203014s. [PubMed: 22235863]

[18]. Xiang Y; Lu Y Portable and Quantitative Detection of Protein Biomarkers and Small Molecular Toxins Using Antibodies and Ubiquitous Personal Glucose Meters. Anal. Chem 2012, 84 (9), 4174–4178. 10.1021/ac300517n. [PubMed: 22455548]

[19]. Zhou J; Xu K; Zhou P; Zheng O; Lin Z; Guo L; Qiu B; Chen G A Portable Chemical Sensor for Histidine Based on the Strategy of Click Chemistry. Biosens. Bioelectron 2014, 51, 386–390. 10.1016/j.bios.2013.08.015. [PubMed: 24007674]

[20]. Chen S; Gan N; Zhang H; Hu F; Li T; Cui H; Cao Y; Jiang Q A Portable and Antibody-Free Sandwich Assay for Determination of Chloramphenicol in Food Based on a Personal Glucose Meter. Anal. Bioanal. Chem 2015, 407 (9), 2499–2507. 10.1007/s00216-015-8478-8. [PubMed: 25644521]

[21]. Hun X; Xu Y; Luo X Peptide-Based Biosensor for the Prostate-Specific Antigen Using Magnetic Particle-Bound Invertase and a Personal Glucose Meter for Readout. Microchim. Acta 2015, 182 (9–10), 1669–1675. 10.1007/s00604-015-1483-y.

[22]. Gu C; Lan T; Shi H; Lu Y Portable Detection of Melamine in Milk Using a Personal Glucose Meter Based on an in Vitro Selected Structure-Switching Aptamer. Anal. Chem 2015, 87 (15), 7676–7682. 10.1021/acs.analchem.5b01085. [PubMed: 26200202]

[23]. Xue-tao X; Kai-yi L; Jia-ying Z Highly Sensitive and Portable Mercury(II) Ion Sensor Using Personal Glucose Meter. Anal. Methods 2015, 7 (1), 81–85. 10.1039/C4AY01502A.

[24]. Yang W; Lu X; Wang Y; Sun S; Liu C; Li Z Portable and Sensitive Detection of Protein Kinase Activity by Using Commercial Personal Glucose Meter. Sensors Actuators, B Chem. 2015, 210, 508–512. 10.1016/j.snb.2015.01.027.

[25]. Hun X; Xu Y; Xie G; Luo X Aptamer Biosensor for Highly Sensitive and Selective Detection of Dopamine Using Ubiquitous Personal Glucose Meters. Sensors Actuators, B Chem. 2015, 209, 596–601. 10.1016/j.snb.2014.11.135.

[26]. Xue-Tao X; Kai-Yi L; Jia-Ying Z Portable and Sensitive Quantitative Detection of DNA Based on Personal Glucose Meters and Isothermal Circular Strand-Displacement Polymerization Reaction. Biosens. Bioelectron 2015, 64, 671–675. 10.1016/j.bios.2014.09.094. [PubMed: 25441417]

[27]. Zhang J; Tang Y; Teng L; Lu M; Tang D Low-Cost and Highly Efficient DNA Biosensor for Heavy Metal Ion Using Specific DNAzyme-Modified Microplate and Portable Glucometer-Based Detection Mode. Biosens. Bioelectron 2015, 68, 232–238. 10.1016/j.bios.2015.01.001. [PubMed: 25576929]

[28]. Zhang J; Shen Z; Xiang Y; Lu Y Integration of Solution-Based Assays onto Lateral Flow Device for One-Step Quantitative Point-of-Care Diagnostics Using Personal Glucose Meter. ACS Sensors 2016, 1 (9), 1091–1096. 10.1021/acssensors.6b00270.

[29]. Xiang Y; Lu Y An Invasive DNA Approach toward a General Method for Portable Quantification of Metal Ions Using a Personal Glucose Meter. Chem. Commun 2013, 49 (6), 585–587. 10.1039/C2CC37156A.

[30]. Deng H; Peng SY; Gao Z Highly Sensitive Detection of M.SssI DNA Methyltransferase Activity Using a Personal Glucose Meter. Anal. Bioanal. Chem 2016, 408 (21), 5867–5872. 10.1007/s00216-016-9701-y. [PubMed: 27311957]

[31]. Wang W; Huang S; Li J; Rui K; Zhang JR; Zhu JJ Coupling a DNA-Based Machine with Glucometer Readouts for Amplified Detection of Telomerase Activity in Cancer Cells. Sci. Rep 2016, 6, 1–9. 10.1038/srep23504. [PubMed: 28442746]

[32]. Wan Y; Qi P; Zeng Y; Sun Y; Zhang D Invertase-Mediated System for Simple and Rapid Detection of Pathogen. Sensors Actuators B. Chem 2016, 233, 454–458. 10.1016/j.snb.2016.04.098.

[33]. Lan T; Xiang Y; Lu Y Detection of Protein Biomarker Using a Blood Glucose Meter. Methods Mol Biol. 2015, 1256, 99–109. 10.1007/978-1-4939-2172-0. [PubMed: 25626534]

[34]. Yue Q; Li C Biosensing of DNA Oxidative Damage : A Model of Using Glucose Meter for Non-Glucose Biomarker Detection. Int. J. Nanomedicine 2017, 12, 979–987. 10.2147/IJN.S125437. [PubMed: 28203077]

[35]. Ming J; Fan W; Jiang TF; Wang YH; Lv ZH Portable and Sensitive Detection of Copper(II) Ion Based on Personal Glucose Meters and a Ligation DNAzyme Releasing Strategy. Sensors Actuators, B Chem. 2017, 240, 1091–1098. 10.1016/j.snb.2016.09.091.

[36]. Huang S; Wang W; Cheng F; Yao H; Zhu JJ Highly Sensitive Detection of Mercury Ion Based on T-Rich DNA Machine Using Portable Glucose Meter. Sensors Actuators, B Chem. 2017, 242, 347–354. 10.1016/j.snb.2016.10.123.

[37]. Zhu X; Kou F; Xu H; Lin L; Yang G; Lin Z A Highly Sensitive Aptamer-Immunoassay for Vascular Endothelial Growth Factor Coupled with Portable Glucose Meter and Hybridization Chain Reaction. Sensors Actuators B. Chem 2017, 253, 660–665. 10.1016/j.snb.2017.06.174.

[38]. Hong L; Zhou F; Shi D; Zhang X; Wang G Portable Aptamer Biosensor of Platelet-Derived Growth Factor-BB Using a Personal Glucose Meter with Triply Amplified. Biosens. Bioelectron 2017, 95, 152–159. 10.1016/j.bios.2017.04.023. [PubMed: 28445812]

[39]. Chen Y; Yi H; Xiang Y; Yuan R Commercial Glucometer as Signal Transducer for Simple Evaluation of DNA Methyltransferase Activity and Inhibitors Screening. Anal. Chim. Acta 2018, 1001, 18–23. 10.1016/j.aca.2017.11.045. [PubMed: 29291802]

[40]. Joo J; Kwon D; Shin HH; Park K-H; Cha HJ; Jeon S A Facile and Sensitive Method for Detecting Pathogenic Bacteria Using Personal Glucose Meters. Sensors Actuators B Chem. 2013, 188, 1250–1254. 10.1016/j.snb.2013.08.027.

[41]. Huang F; Zhang H; Wang L; Lai W; Lin J A Sensitive Biosensor Using Double-Layer Capillary Based Immunomagnetic Separation and Invertase-Nanocluster Based Signal Amplification for Rapid Detection of Foodborne Pathogen. Biosens. Bioelectron 2018, 100, 583–590. [PubMed: 29032045]

[42]. Huang H; Zhao G; Dou W Portable and Quantitative Point-of-Care Monitoring of Escherichia Coli O157 : H7 Using a Personal Glucose Meter Based on Immunochromatographic Assay. Biosens. Bioelectron 2018, 107, 266–271. 10.1016/j.bios.2018.02.027. [PubMed: 29477883]

[43]. Fang J; Guo Y; Yang Y; Yu W; Tao Y; Dai T; Yuan C Portable and Sensitive Detection of DNA Based on Personal Glucose Meters and Nanogold-Functionalized PAMAM Dendrimer. Sensors Actuators B. Chem 2018, 272 (1), 118–126. 10.1016/j.snb.2018.05.086.

[44]. Yang X; Shi D; Zhu S; Wang B; Zhang X; Wang G Portable Aptasensor of Aflatoxin B1 in Bread Based on a Personal Glucose Meter and DNA Walking Machine. ACS Sensors 2018, 3, 1368–1375. 10.1021/acssensors.8b00304. [PubMed: 29943575]

[45]. Dong Q; Liu Q; Guo L; Li D; Shang X; Li B; Du Y A Signal-Flexible Gene Diagnostic Strategy Coupling Loop-Mediated Isothermal Amplification with Hybridization Chain Reaction. Anal. Chim. Acta 2019, 1079, 171–179. 10.1016/j.aca.2019.06.048. [PubMed: 31387708]

[46]. Wu T; Cao Y; Yang Y; Zhang X; Wang S; Xu L; Zhang X A Three-Dimensional DNA Walking Machine for the Ultrasensitive Dual-Modal Detection of MiRNA Using a Fluorometer and Personal Glucose Meter. Nanoscale 2019, 11, 11279–11284. 10.1039/c9nr03588e. [PubMed: 31165838]

[47]. Ge L; Li B; Xu H; Pu W; Kwok HF Backfilling Rolling Cycle Amplification with Enzyme-DNA Conjugates on Antibody for Portable Electrochemical Immunoassay with Glucometer Readout. Biosens. Bioelectron 2019, 132, 210–216. 10.1016/j.bios.2019.02.051. [PubMed: 30875633]

[48]. Qiu S; Yuan L; Wei Y; Zhang D; Chen Q; Lin Z DNA Template-Mediated Click Chemistry-Based Portable Signal-on Sensor for Ochratoxin A Detection. Food Chem. 2019, 297, 124929. 10.1016/j.foodchem.2019.05.203. [PubMed: 31253344]

[49]. Yang J; Huang X; Gan C; Yuan R; Xiang Y Highly Specific and Sensitive Point-of-Care Detection of Rare Circulating Tumor Cells in Whole Blood via a Dual Recognition Strategy. Biosens. Bioelectron 2019, 143, 111604. 10.1016/j.bios.2019.111604. [PubMed: 31466047]

[50]. Liu C; Zhang S; Li X; Xue Q; Jiang W Multi-Code Magnetic Beads Based on DNAzyme-Mediated Double-Cycling Amplification for a Point-of-Care Assay of Telomerase Activity. Analyst 2019, 144, 4241–4249. 10.1039/c9an00589g. [PubMed: 31210200]

[51]. Su J; Xu J; Chen Y; Xiang Y; Yuan R; Chai Y Sensitive Detection of Copper(II) by a Commercial Glucometer Using Click Chemistry. Biosens. Bioelectron 2013, 45 (1), 219–222. 10.1016/j.bios.2013.01.069. [PubMed: 23500367]

[52]. Shan Y; Zhang Y; Kang W; Wang B; Li J; Wu X; Wang S Quantitative and Selective DNA Detection with Portable Personal Glucose Meter Using Loop-Based DNA Competitive Hybridization Strategy. Sensors Actuators B. Chem 2019, 282, 197–203. 10.1016/j.snb.2018.11.062.

[53]. Sun F; Sun X; Jia Y; Hu Z; Xu S; Li L; Na N; Ouyang J Ultrasensitive Detection of Prostate Specific Antigen Using a Personal Glucose Meter Based on DNA-Mediated Immunoreaction. Analyst 2019, 144, 6019–6024. 10.1039/c9an01558b. [PubMed: 31538152]

[54]. Zhu X; Sarwar M; Zhu J; Zhang C; Kaushik A Using a Glucose Meter to Quantitatively Detect Disease Biomarkers through a Universal Nanozyme Integrated Lateral Fluidic Sensing Platform. Biosens. Bioelectron 2019, 126, 690–696. 10.1016/j.bios.2018.11.033. [PubMed: 30544082]

[55]. Zhao L; Teng L; Zhang J; Li H Point-of-Care Detection of Microcystin-LR with a Personal Glucose Meter in Drinking Water Source. Chinese Chem. Lett. J 2019, 30, 1035–1037. 10.1016/j.cclet.2019.01.001.

[56]. Huang X; Li J; Lu M; Zhang W; Xu Z; Yu B Point-of-Care Testing of MicroRNA Based on Personal Glucose Meter and Dual Signal Amplification to Evaluate Drug-Induced Kidney Injury. Anal. Chim. Acta 2020, 1112, 72–79. 10.1016/j.aca.2020.03.051. [PubMed: 32334684]

[57]. Huang X; Xu Z; Liu J-H; Yu B-Y; Tian J Dual Signal Amplification for MicroRNA-21 Detection Based on Duplex-Specific Nuclease and Invertase. RSC Adv. 2020, 10, 11257–11262. 10.1039/c9ra10657j. [PubMed: 35495318]

[58]. Ma X; Chen Z; Zhou J; Weng W; Zheng O; Lin Z; Guo L; Qiu B; Chen G Aptamer-Based Portable Biosensor for Platelet-Derived Growth Factor-BB (PDGF-BB) with Personal Glucose Meter Readout. Biosens. Bioelectron 2014, 55, 412–416. 10.1016/j.bios.2013.12.041. [PubMed: 24434497]

[59]. Xu X; Liang K; Zeng J Portable and Sensitive Quantitative Detection of DNA Using Personal Glucose Meters and Exonuclease III-Assisted Signal Amplification. Analyst 2014, 139 (19), 4982–4986. 10.1039/C4AN00905C. [PubMed: 25105176]

[60]. Zhu X; Zheng H; Xu H; Lin R; Han Y; Yang G; Lin Z; Guo L; Qiu B; Chen G A Reusable and Portable Immunosensor Using Personal Glucose Meter as Transducer. Anal. Methods 2014, 6 (14), 5264–5268. 10.1039/C4AY00490F.

[61]. Wang Q; Wang H; Yang X; Wang K; Liu F; Zhao Q; Liu P; Liu R Multiplex Detection of Nucleic Acids Using a Low Cost Microfluidic Chip and a Personal Glucose Meter at the Point-of-Care. Chem. Commun 2014, 50 (29), 3824–3826. 10.1039/C4CC00133H.

[62]. Wang Q; Liu F; Yang X; Wang K; Wang H; Deng X Sensitive Point-of-Care Monitoring of Cardiac Biomarker Myoglobin Using Aptamer and Ubiquitous Personal Glucose Meter. Biosens. Bioelectron 2014, 64, 161–164. 10.1016/j.bios.2014.08.079. [PubMed: 25216451]

[63]. Yan L; Zhu Z; Zou Y; Huang Y; Liu D; Jia S; Xu D; Wu M; Zhou Y; Zhou S; Yang CJ Target-Responsive "Sweet" Hydrogel with Glucometer Readout for Portable and Quantitative Detection of Non-Glucose Targets. J. Am. Chem. Soc 2013, 135 (10), 3748–3751. 10.1021/ja3114714. [PubMed: 23339662]

[64]. Fu X; Feng X; Xu K; Huang R A Portable and Quantitative Enzyme Immunoassay of Neuron-Specific Enolase with a Glucometer Readout. Anal. Methods 2014, 6 (7), 2233–2238. 10.1039/C3AY42075B.

[65]. Wang Q; Wang H; Yang X; Wang K; Liu R; Li Q; Ou J A Sensitive One-Step Method for Quantitative Detection of α-Amylase in Serum and Urine Using a Personal Glucose Meter. Analyst 2015, 140 (4), 1161–1165. 10.1039/C4AN02033B. [PubMed: 25516912]

[66]. Lin B; Liu D; Yan J; Qiao Z; Zhong Y; Yan J; Zhu Z; Ji T; Yang CJ Enzyme-Encapsulated Liposome-Linked Immunosorbent Assay Enabling Sensitive Personal Glucose Meter Readout for Portable Detection of Disease Biomarkers. ACS Appl. Mater. Interfaces 2016, 8 (11), 6890–6897. 10.1021/acsami.6b00777. [PubMed: 26918445]

[67]. Xue Q; Kong Y; Wang H; Jiang W Liposome-Encoded Magnetic Beads Initiated by Padlock Exponential Rolling Circle Amplification for Portable and Accurate Quantification of MicroRNAs. Chem. Commun 2017, 53 (78), 10772–10775. 10.1039/C7CC05686A.

[68]. Zhang Y; Xue Q; Liu J; Wang H Magnetic Bead-Liposome Hybrids Enable Sensitive and Portable Detection of DNA Methyltransferase Activity Using Personal Glucose Meter. Biosens. Bioelectron 2017, 87, 537–544. 10.1016/j.bios.2016.08.103. [PubMed: 27611472]

[69]. Si Y; Li L; Wang N; Zheng J; Yang R; Li J Oligonucleotide Cross-Linked Hydrogel for Recognition and Quantitation of MicroRNAs Based on a Portable Glucometer Readout. ACS Appl. Mater. Interfaces 2019, 11, 7792–7799. 10.1021/acsami.8b21727. [PubMed: 30714711]

[70]. Kong Y; Liu X; Liu C; Xue Q; Wang H A Dandelion-like Liposomes-Encoded Magnetic Bead Probe-Based Toehold-Mediated DNA Circuit for the Amplification Detection of MiRNA. Analyst 2019, 144, 4694–4701. 10.1039/c9an00887j. [PubMed: 31268436]

[71]. Gao X; Li X; Sun X; Zhang J; Zhao Y; Liu X; Li F DNA Tetrahedra-Cross-Linked Hydrogel Functionalized Paper for Onsite Analysis of DNA Methyltransferase Activity Using a Personal Glucose Meter. Anal. Chem 2020, 92 (6), 4592–4599. 10.1021/acs.analchem.0c00018. [PubMed: 32081006]

[72]. Xiang Y; Lan T; Lu Y Using the Widely Available Blood Glucose Meter to Monitor Insulin and HbA1c. J. Diabetes Sci. Technol 2014, 8 (4), 855–858. 10.1177/1932296814532875. [PubMed: 25562889]

[73]. Zhang J; Xiang Y; Novak DE; Hoganson GE; Zhu J; Lu Y Using a Personal Glucose Meter and Alkaline Phosphatase for Point-of-Care Quantification of Galactose-1-Phosphate Uridyltransferase in Clinical Galactosemia Diagnosis. Chem. - An Asian J 2015, 10 (10), 2221–2227. 10.1002/asia.201500642.

[74]. Abardía-Serrano C; Miranda-Castro R; De-los-Santos-Álvarez N; Lobo-Castañón MJ New Uses for the Personal Glucose Meter: Detection of Nucleic Acid Biomarkers for Prostate Cancer Screening. Sensors 2020, 20, 5514. 10.3390/s20195514. [PubMed: 32993106]

[75]. Luo Y; Dou W; Zhao G Rapid Electrochemical Quantification of Salmonella Pullorum and Salmonella Gallinarum Based on Glucose Oxidase and Antibody-Modified Silica Nanoparticles. Anal. Bioanal. Chem 2017, 409 (17), 4139–4147. 10.1007/s00216-017-0361-3. [PubMed: 28429065]

[76]. Chavali R; Kumar Gunda NS; Naicker S; Mitra SK Detection of Escherichia Coli in Potable Water Using Personal Glucose Meters. Anal. Methods 2014, 6 (16), 6223. 10.1039/C4AY01249F.

[77]. Fang D; Gao G; Yu Y; Shen J; Zhi J Adaptive Use of a Personal Glucose Meter (PGM) for Acute Biotoxicity Assessment Based on the Glucose Consumption of Microbes. Analyst 2016, 141 (10), 3004–3011. 10.1039/C5AN02478A. [PubMed: 27055358]

[78]. Ahn JK; Kim HY; Park KS; Park HG A Personal Glucose Meter for Label-Free and Washing-Free Biomolecular Detection. Anal. Chem 2018, 90, 11340–11343. 10.1021/acs.analchem.8b02014. [PubMed: 30152994]

[79]. Ahn JK; Kim HY; Lee CY; Park KS; Park HG Label-Free and Washing-Free Alkaline Phosphatase Assay Using a Personal Glucose Meter. J. Biol. Eng 2019, 13, 51. 10.1186/s13036-019-0182-3. [PubMed: 31178924]

[80]. Kim HY; Lee CY; Kim H; Park KS; Park HG Portable Glucose Meter-Utilized Label-Free and Washing-Free Telomerase Assay. Analyst 2020, 145, 5578–5583. 10.1039/d0an00655f. [PubMed: 32627768]

[81]. Zhao Y; Du D; Lin Y Glucose Encapsulating Liposome for Signal Amplification for Quantitative Detection of Biomarkers with Glucometer Readout. Biosens. Bioelectron 2015, 72, 348–354. 10.1016/j.bios.2015.05.028. [PubMed: 26005847]

[82]. Zhao Y; Chen X; Lin S; Du D; Lin Y Integrated Immunochromatographic Strip with Glucometer Readout for Rapid Quantification of Phosphorylated Proteins. Anal. Chim. Acta 2017, 964, 1–6. 10.1016/j.aca.2017.01.011. [PubMed: 28351626]

[83]. Tang J; Huang Y; Liu H; Zhang C; Tang D Novel Glucometer-Based Immunosensing Strategy Suitable for Complex Systems with Signal Amplification Using Surfactant-Responsive Cargo Release from Glucose-Encapsulated Liposome Nanocarriers. Biosens. Bioelectron 2016, 79, 508–514. 10.1016/j.bios.2015.12.097. [PubMed: 26748368]

[84]. Liang X; Wang L; Wang D; Zeng L; Fang Z Portable and Quantitative Monitoring of Mercury Ions Using DNA-Gated Mesoporous Silica Nanoparticles Using a Glucometer Readout. Chem. Commun 2016, 52, 2192–2194. 10.1039/C5CC08611F.

[85]. Zhang J; Xiang Y; Wang M; Basu A; Lu Y Dose-Dependent Response of Personal Glucose Meters to Nicotinamide Coenzymes: Applications to Point-of-Care Diagnostics of Many Non-Glucose Targets in a Single Step. Angew. Chemie - Int. Ed 2016, 55 (2), 732–736. 10.1002/anie.201507563.

[86]. Tang W; Yang J; Wang F; Wang J Thiocholine-Triggered Reaction in Personal Glucose Meters for Portable Quantitative Detection of Organophosphorus Pesticide. Anal. Chim. Acta 2019, 1060, 97–102. 10.1016/j.aca.2019.01.051. [PubMed: 30902336]

[87]. Deng K; Zhang Y; Tong X Sensitive Electrochemical Detection of MicroRNA-21 Based on Propylamine-Functionalized Mesoporous Silica with Glucometer Readout. Anal. Bioanal. Chem 2018, 410, 1863–1871. 10.1007/s00216-018-0859-3. [PubMed: 29353431]

[88]. Chen S; Zhang J; Gan N; Hu F; Li T; Cao Y; Pan D An On-Site Immunosensor for Ractopamine Based on a Personal Glucose Meter and Using Magnetic β-Cyclodextrin-Coated Nanoparticles for Enrichment, and an Invertase-Labeled Nanogold Probe for Signal Amplification. Microchim. Acta 2015, 182 (3–4), 815–822. 10.1007/s00604-014-1392-5.

[89]. Liu C; An Y; Zhang Y; Li X; Xue Q; Wang H Digital Quantitative Detection of Serum Circulating MiRNAs Using Dual-Enhanced Magnetobiosensors Based on Cascaded Nucleic Acid Circuits. Chem. Commun 2019, 55 (91), 13733–13736. 10.1039/c9cc07841j.

[90]. Jia Y; Sun F; Na N; Ouyang J Detection of P53 DNA Using Commercially Available Personal Glucose Meters Based on Rolling Circle Amplification Coupled with Nicking Enzyme Signal Amplification. Anal. Chim. Acta 2019, 1060, 64–70. 10.1016/j.aca.2019.01.061. [PubMed: 30902332]

[91]. Zeng L; Gong J; Rong P; Liu C; Chen J A Portable and Quantitative Biosensor for Cadmium Detection Using Glucometer as the Point-of-Use Device. Talanta 2019, 198, 412–416. 10.1016/j.talanta.2019.02.045. [PubMed: 30876580]

[92]. Zhang S; Luan Y; Xiong M; Zhang J; Lake R; Lu Y DNAzyme Amplified Aptasensing Platform for Ochratoxin A Detection Using a Personal Glucose Meter. ACS Appl. Mater. Interfaces 2021, 13 (8), 9472–9481. 10.1021/acsami.0c20417. [PubMed: 33550797]

[93]. Li B; Wei H; Dong S Sensitive Detection of Protein by an Aptamer-Based Label-Free Fluorescing Molecular Switch. Chem. Commun 2007, No. 1, 73–75. 10.1039/b612080f.

[94]. Du Y; Chen C; Yin J; Li B; Zhou M; Dong S; Wang E Solid-State Probe Based Electrochemical Aptasensor for Cocaine: A Potentially Convenient, Sensitive, Repeatable, and Integrated Sensing Platform for Drugs. Anal. Chem 2010, 82 (4), 1556–1563. 10.1021/ac902566u. [PubMed: 20095580]

[95]. Ahmad R; Jang H; Batule BS; Park HG Barcode DNA-Mediated Signal Amplifying Strategy for Ultrasensitive Biomolecular Detection on Matrix-Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) Mass Spectrometry. Anal. Chem 2017, 89 (17), 8966–8973. 10.1021/acs.analchem.7b01535. [PubMed: 28780857]

[96]. Tang Z; Shangguan D; Wang K; Shi H; Sefah K; Mallikratchy P; Chen HW; Li Y; Tan W Selection of Aptamers for Molecular Recognition and Characterization of Cancer Cells. Anal. Chem 2007, 79 (13), 4900–4907. 10.1021/ac070189y. [PubMed: 17530817]

[97]. Ma H; Liu J; Ali MM; Mahmood MAI; Labanieh L; Lu M; Iqbal SM; Zhang Q; Zhao W; Wan Y Nucleic Acid Aptamers in Cancer Research, Diagnosis and Therapy. Chem. Soc. Rev 2015, 44 (5), 1240–1256. 10.1039/c4cs00357h. [PubMed: 25561050]

[98]. Kim K; Jo E; Park J; Young G; Shin Y; Lee LP; Kim M Gold Nanocap-Supported Upconversion Nanoparticles for Fabrication of a Solid-Phase Aptasensor to Detect Ochratoxin A. Biosens. Bioelectron 2020, 150, 111885. 10.1016/j.bios.2019.111885. [PubMed: 31759762]

[99]. Wang L; Zhu J; Han L; Jin L; Zhu C; Wang E; Dong S Graphene-Based Aptamer Logic Gates and Their Application to Multiplex Detection. ACS Nano 2012, 6 (8), 6659–6666. 10.1021/nn300997f. [PubMed: 22823159]

[100]. Zhu J; Zhang L; Zhou Z; Dong S; Wang E Aptamer-Based Sensing Platform Using Three-Way DNA Junction-Driven Strand Displacement and Its Application in DNA Logic Circuit. Anal. Chem 2014, 86, 312–316. 10.1021/ac403235y. [PubMed: 24308699]

[101]. Zhu J; Zhang L; Zhou Z; Wang E Molecular Aptamer Beacon Tuned DNA Strand Displacement to Transform Small Molecules into DNA Logic Outputs. Chem. Commun 2014, 50, 3321–3323. 10.1039/c3cc49833f.

[102]. Li F; Zhang H; Wang Z; Newbigging AM; Reid MS; Li X-F; Le XC Aptamers Facilitating Amplified Detection of Biomolecules. Anal. Chem 2015, 87, 274–292. 10.1021/ac5037236. [PubMed: 25313902]

[103]. Li Y; Sun L; Zhao Q Aptamer-Structure Switch Coupled with Horseradish Peroxidase Labeling on a Microplate for the Sensitive Detection of Small Molecules. Anal. Chem 2019, 91, 2615–2619. 10.1021/acs.analchem.8b05606. [PubMed: 30675773]

[104]. Zheng F; Ke W; Shi L; Liu H; Zhao Y Plasmonic Au-Ag Janus Nanoparticle Engineered Ratiometric Surface-Enhanced Raman Scattering Aptasensor for Ochratoxin A Detection. Anal. Chem 2019, 91, 11812–11820. 10.1021/acs.analchem.9b02469. [PubMed: 31424931]

[105]. Dong L; Tan Q; Ye W; Liu D; Chen H; Hu H; Wen D; Liu Y; Cao Y; Kang J; Fan J; Guo W; Wu W Screening and Identifying a Novel SsDNA Aptamer against Alpha-Fetoprotein Using CE-SELEX. Sci. Rep 2015, 5, 15552. 10.1038/srep15552. [PubMed: 26497223]

[106]. Si Z; Xie B; Chen Z; Tang C; Li T; Yang M Electrochemical Aptasensor for the Cancer Biomarker CEA Based on Aptamer Induced Current Due to Formation of Molybdophosphate. Microchim. Acta 2017, 184 (9), 3215–3221. 10.1007/s00604-017-2338-5.

[107]. Tang Y; Li H; Li B Homogeneous and Universal Transduction of Various Nucleic Acids to an Off-Shelf Device Based on Programmable Toehold Switch Sensing. Chem. Commun 2020, 56, 2483–2486. 10.1039/c9cc09154h.

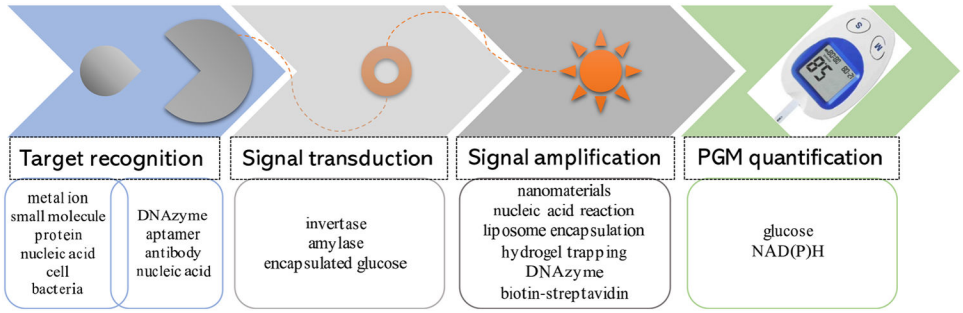

Figure 1.
Typical components and strategies of the PGM-based biosensor for non-glucose targets.

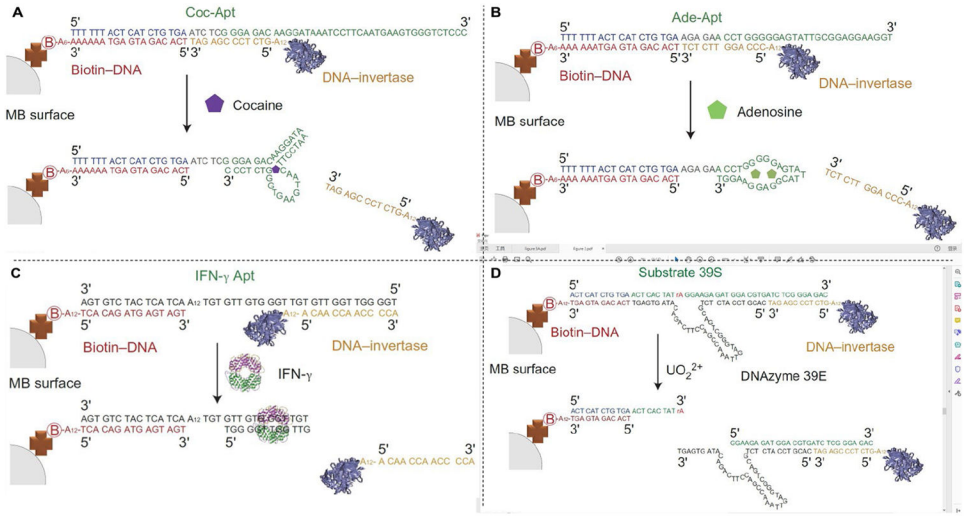

Figure 2.

The first PGM-based biosensor for non-glucose targets of (A) cocaine, (B) adenosine, (C) IFN-γ and (D) UO_2^{2+} by Lu Group using invertase as signal transduction element.

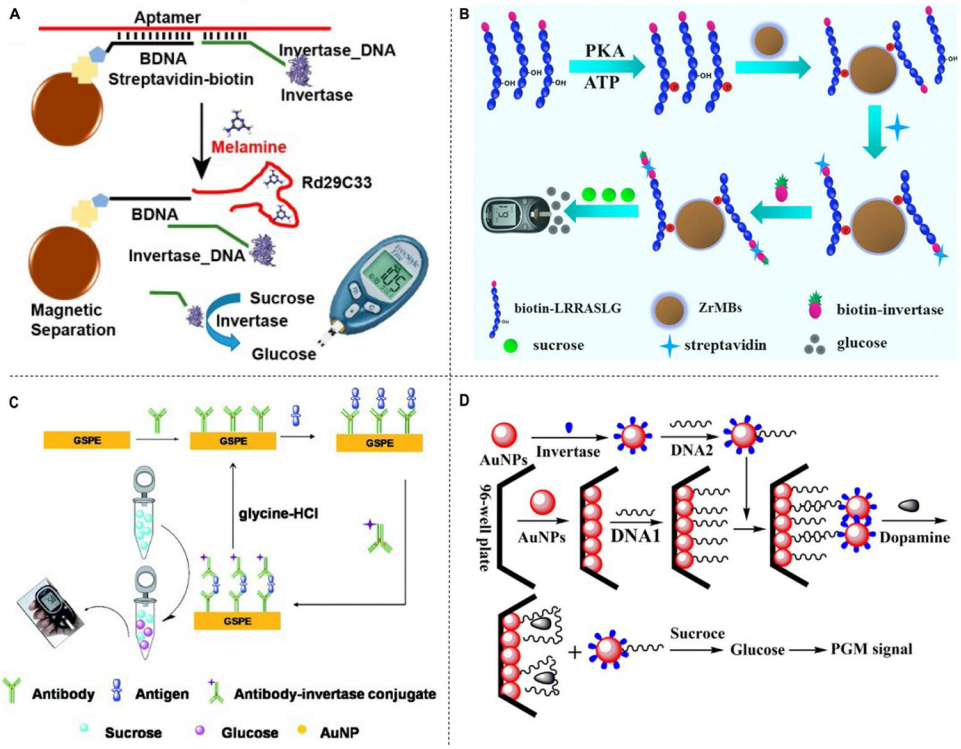

Figure 3.

PGM-based biosensors using transduction element of invertase modified on (A) DNA, (B) biotin, (C) antibody and (D) nanoparticles.

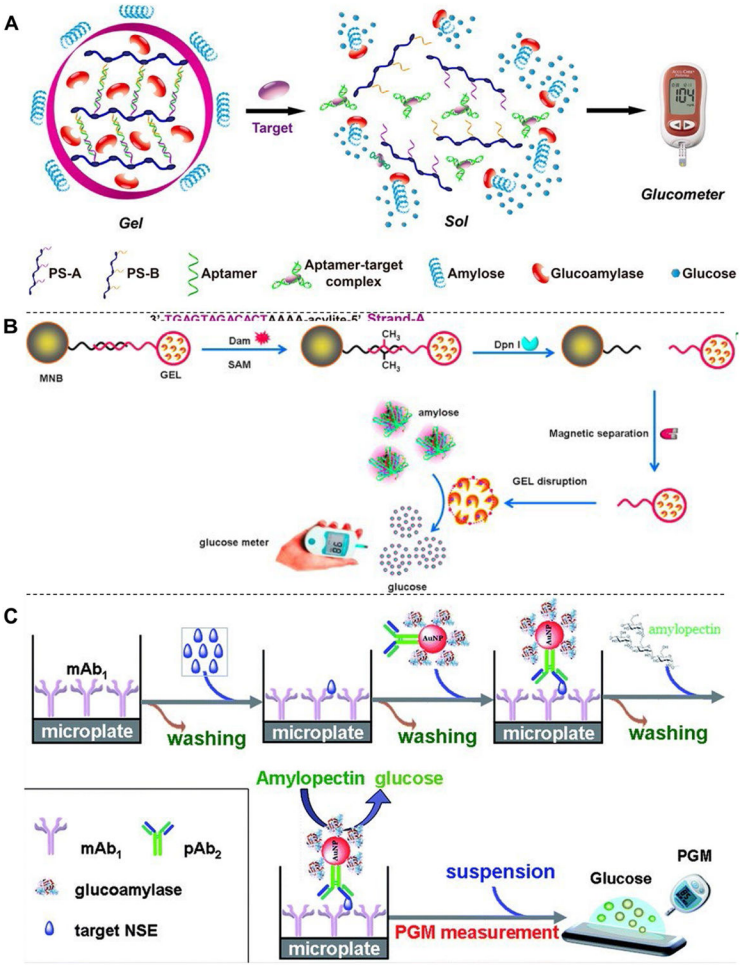

Figure 4.

PGM-based biosensors using amylase as transduction element. (A) Amylase trapped in hydrogel. (B) Amylase encapsulated in liposome. (C) Amylase immobilized on nanoparticles.

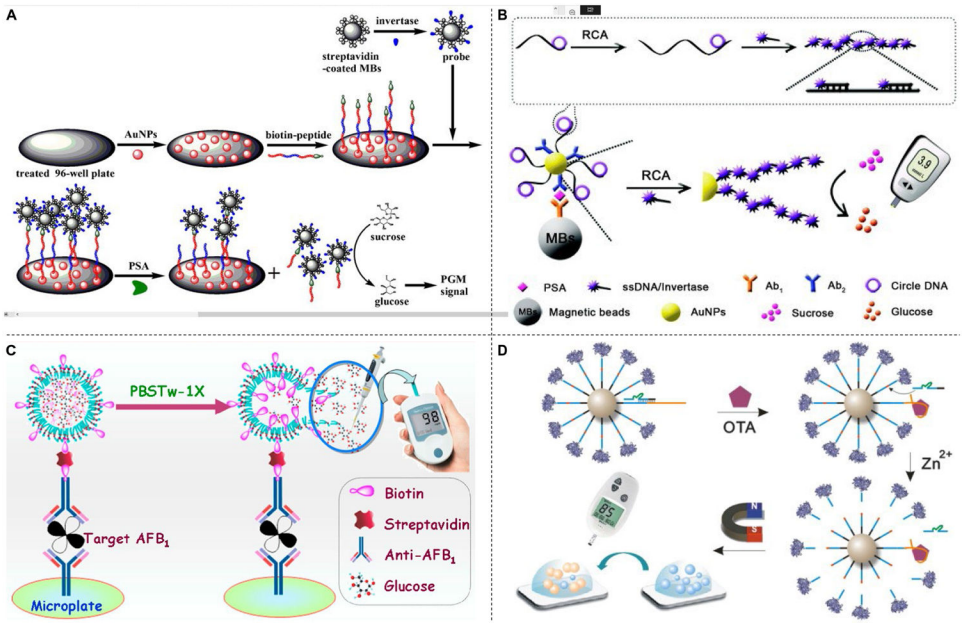

Figure 5.

Typical signal amplification methods used in PGM-based biosensors. (A) Nanomaterials amplification. (B) Nucleic acid reaction amplification. (C) Liposome encapsulation amplification. (D) DNAzyme amplification.

Table 1.

Analytical performance of some representative PGM sensors for metal ion detection.

Target	Recognition element	Signal transduction	Signal amplification	Detection limit	References
Hg^{2+}	T-Hg^{2+}-T	invertase	enzymatic	N.A.	[21]
Pb^{2+}	DNAzyme	invertase	AuNPs	1.0 pM	[27]
Pb^{2+}	DNAzyme	invertase	enzymatic	16 nM	[29]
Cu^{2+}	ligation DNAzyme	invertase	enzymatic	1 nM	[35]
Hg^{2+}	T-Hg^{2+}-T	invertase	nicking enzyme	10^{-17} M	[36]
Cu^{2+}	click chemistry reaction	invertase	magnetic bead	10 nM	[51]
Hg^{2+}	T-Hg^{2+}-T	encapsulated glucose	Exo III and mesoporous silica nanoparticles	0.1 nM	[84]

Abbreviations: T-Hg^{2+}-T = thymine-Hg^{2+}-thymine; N.A. = Not applicable; AuNPs = gold nanoparticles; Exo = exonuclease.

Table 2.

Analytical performance of some representative PGM sensors for small molecules.

Target	Recognition element	Signal transduction	Signal amplification	Detection limit	References
chloramphenicol	molecularly imprinted probe	invertase	AuNPs	0.16 ng/mL	[20]
melamine	aptamer	invertase	enzymatic	0.33 μM	[22]
dopamine	aptamer	invertase	AuNPs	0.03 μM	[25]
cocaine	aptamer	invertase	enzymatic	7.7 μM	[28]
AFB1	aptamer	invertase	DNAzyme	10 pM	[44]
OTA	aptamer	invertase	enzymatic	72 pg/mL	[48]
MC-LR	antibody	invertase	GO-Au NPs	0.1 ng/mL	[55]
AFB1	antibody	encapsulated glucose	liposome encapsulation	0.6 pg/mL	[83]
RAC	antibody	invertase	AuNPs	0.34 μg/kg	[88]
cocaine	aptamer	amylase	hydrogel trapping	3.8 μM	[63]
OTA	aptamer	invertase	DNAzyme	0.88 pg/mL	[92]
8-OHdG	antibody	invertase	enzymatic	1.73 ng/mL	[34]
OTA	antibody and aptamer	invertase	enzymatic	6.8 ng/mL	[18]

Abbreviations: AuNPs = gold nanoparticles; AFB1 = aflatoxin B1; OTA = ochratoxin A; MC-LR = microcystin-LR; GO = graphene oxide; RAC = ractopamine; 8-OHdG = 8-hydroxy-2’-deoxyguanosine.

Table 3.

Analytical performance of some representative PGM sensors for protein analysis.

Target	Recognition element	Signal transduction	Signal amplification	Detection limit	References
M.SssI MTase	nucleic acid	invertase	enzymatic	0.37 U/mL	[30]
VEGF	antibody and aptamer	invertase	HCR	1.2 pg/mL	[37]
PDGF-BB	aptamer	invertase	DNAzyme	0.11 fM	[38]
M.SssI MTase	nucleic acid	invertase	biotin-streptavidin	0.3 U/mL	[39]
AFP	antibody	invertase	RCA	0.087 ng/mL	[47]
PSA	antibody	invertase	AuNPs and RCA	0.1 pg/mL	[53]
PSA	antibody	invertase	AuNPs	1.26 ng/mL	[54]
AFP	antibody	invertase	enzymatic	0.18 ng/mL	[60]
myoglobin	aptamer	invertase	enzymatic	50 pM	[62]
NSE	antibody	invertase	AuNPs	0.05 ng/mL	[64]
Dam MTase	nucleic acid	amylase	liposome encapsulation	0.002 U/mL	[68]
Dam MTase	nucleic acid	amyloglucosidase	hydrogel trapping	0.001 U/mL	[71]
HbA1c	antibody	ALP	enzymatic	3 mg/L	[72]
phospho-p53^{15}	antibody	encapsulated glucose	liposome encapsulation	50 pg/mL	[81]
PDGF-BB	aptamer	invertase	enzymatic	2.9 fM	[58]

Abbreviations: MTase = methyltransferase; VEGF = vascular endothelia growth factor; HCR = hybridization chain reaction; PDGF-BB = platelet-derived growth factor BB; AFP = alpha-fetoprotein; PSA = prostate specific antigen; AuNPs = gold nanoparticles; NSE = neuron-specific enolase; HbA1c = glycated hemoglobin; ALP = alkaline phosphatase; phospho-p53^{15} = protein 53 phosphorylated on Serine 15.

Table 4.

Analytical performance of some representative PGM sensors for nucleic acid.

Target	Recognition element	Signal transduction	Signal amplification	Detection limit	References
HBV DNA	nucleic acid	invertase	enzymatic	40 pM	[17]
miRNA-21	nucleic acid	invertase	DNA walking machine	60 pM	[46]
specific DNA	nucleic acid	invertase	enzymatic	100 pM	[52]
specific DNA	nucleic acid	invertase	Exo III	50 pM	[59]
HBV DNA	nucleic acid	invertase	enzymatic	10 pM	[61]
miRNA-21	nucleic acid	amylase	RCA and liposome encapsulation	0.1 fM	[67]
miRNA-21	nucleic acid	amylase	hydrogel trapping	0.325 fmol	[69]
miRNA-21	nucleic acid	amylase	TCSDR and liposome encapsulation	0.7 fM	[70]
PCA3	nucleic acid	ALP	biotin-avidin	5 pM	[74]
miRNA-21	nucleic acid	encapsulated glucose	mesoporous silica nanoparticle	19 pM	[87]

Abbreviations: HBV = hepatitis B virus; Exo = exonuclease; AuNPs = gold nanoparticles; miRNA = microRNA; TCSDR = toehold-mediated circular strand displacement reaction; PCA3 = prostate cancer antigen 3; ALP = alkaline phosphatase.

Table 5.

Analytical performance of some representative PGM sensors for cell and bacteria detection.

Target	Recognition element	Signal transduction	Signal amplification	Detection limit	References
S. aureus	aptamer	invertase	enzymatic	1.0×10^5 CFU/mL	[32]
salmonella	antibody	invertase	enzymatic	10 CFU/mL	[40]
E. coli O157:H7	antibody	invertase	invertase-nanocluster	79 CFU/mL	[41]
E. coli O157:H7	antibody	invertase	magnetic nanoparticle	6.2×10^4 CFU/mL	[42]
CTCs	antibody	invertase	polystyrene microsphere	7 cells	[49]
salmonella	antibody	glucose oxidase	silica nanoparticle	72 CFU/mL	[75]

Abbreviations: *S. aureus* = *Staphylococcus aureus*; *E. coli* = *Escherichia coli*; CTCs = circulating tumor cells.