Trends in Analytical Chemistry 173 (2024) 117654

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

journal homepage: www.elsevier.com/locate/trac

Colorimetric biosensing assays based on gold nanoparticles functionalized/combined with non-antibody recognition elements

Hu Chen [a,1,**], Songtao Cai [a,1], Jianxin Luo [a], Xiaohu Liu [b,c], Lijuan Ou [a], Qingwen Zhang [b,c], Bo Liedberg [d,e,***], Yi Wang [b,c,*]

[a] School of Materials Science and Engineering, Hunan Institute of Technology, Henghua Road 18, Hengyang, 421002, China
[b] School of Biomedical Engineering, School of Ophthalmology & Optometry, Eye Hospital, Wenzhou Medical University, Xueyuan Road 270, Wenzhou 325027, China
[c] Wenzhou Institute, University of Chinese Academy of Sciences, Xinsan Road 16, Wenzhou, 325001, China
[d] School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore, 639798, Singapore
[e] Centre for Biomimetic Sensor Science, School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore, 639798, Singapore

ARTICLE INFO

Keywords:
Non-antibody recognition elements
Colorimetric biosensor
Gold nanoparticles (AuNPs)
Naked-eye detection

ABSTRACT

Biosensing assays involving antibody-antigen interactions have been widely applied in diagnostics and healthcare in virtue of their superior selectivity and sensitivity. However, antibodies typically suffer from complex and fragile functional structures, tedious preparation (resource-intensive and time-consuming), and large molecular size. As a result, the application of antibody-based biosensors tends to be constrained by short shelf-life and limited on-site/remote applicability. To date, AuNP-based colorimetric assays have been widely employed for point-of-care diagnostics in virtue of their user-friendly nature, low cost, chemical versability, and great potential in naked-eye detection. In this review, recent advances in the development of colorimetric assays based on gold nanoparticles (AuNPs) functionalized/combined with non-antibody recognition elements (e.g., liposomes, peptides, aptamers, other chemical molecules) for naked-eye detection of various analytes (e.g., enzymes, viruses, DNAs and bacteria) are discussed in terms of performances and characteristics. Additionally, challenges and future opportunities of these assays are explored.

1. Introduction

As an analytical tool for detection of biological analytes [1–3], biosensors are becoming increasingly important for diagnostics and management of diseases in virtue of non-invasiveness [4,5], near real time feedback [6,7], high accuracy and reliability [8,9]. Owing to the great achievements over the past decade, the global market for commercial biosensors reached US$ 25.5 billion in 2021 and is projected to exceed US$ 36 billion in 2026 [10]. Indeed, biosensors have been intensively applied during the unexpected and catastrophic outbreak of COVID-19 [11–15], which was one of the most severe public health emergencies in human history [16–18]. Indeed, rapid yet effective screening for prevalent infections can undoubtedly save lives and protect healthcare facilities from being overrun. As a result, the global demand for point-of-care diagnostic kits such as biosensors for rapid detection has drastically increased over the past decades [19–21].

Among various optical biosensors, colorimetric biosensors have been intensively explored owing to several advantages. First, most colorimetric biosensors (e.g., COVID-19 test kits) are miniaturized and exhibit good portability [22–24]. Second, colorimetric biosensors generate visible color changes upon interaction with target molecules, making them suitable for naked-eye detection [25,26], which can hardly be realized by methods requiring advanced instruments (e.g., liquid chromatography - mass spectrometry (LC-MS)). Third, colorimetric sensing assays tend to be cost-effective [27] and user-friendliness [28,29] since neither sophisticated instrument nor tedious sample preparation is

* Corresponding author. School of Biomedical Engineering, School of Ophthalmology & Optometry, Eye Hospital, Wenzhou Medical University, Xueyuan Road 270, Wenzhou 325027, China.
** Corresponding author. School of Materials Science and Engineering, Hunan Institute of Technology, Henghua Road 18, Hengyang 421002, China.
*** Corresponding author. School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore, 639798, Singapore.
E-mail addresses: chenhu@hnit.edu.cn (H. Chen), bliedberg@ntu.edu.sg (B. Liedberg), yiwang@wmu.edu.cn (Y. Wang).
[1] These authors contributed equally.

https://doi.org/10.1016/j.trac.2024.117654
Received 20 September 2023; Received in revised form 10 February 2024; Accepted 12 March 2024
Available online 13 March 2024

required, as in the case of LC-MS. Colorimetric sensing is typically based on localized surface plasmon resonance (LSPR) occurring on the surface of conductive nanoparticles (e.g., metallic nanoparticles) under irradiation [30], wherein LSPR can be attributed to the confinement of surface plasmon in the two-dimensional structures [31]. Such biosensors offer naked-eye detection capabilities (qualitative) and can be integrated with smartphone imaging (quantitative) [32,33], both of which are suitable for near-patient testing. AuNP-based colorimetric bioassays have been effectively commercialized and served as a rapid and rationally accurate point-of-care diagnostic tools in the fight against pandemic outbreaks such as COVID-19 [34–36].

To date, a wide range of nanomaterials, including gold nanoparticles (AuNPs), silver nanoparticles (AgNPs) [37], and supermagnetic beads [38], have been employed for colorimetric biosensing. AuNPs constitute the most thoroughly explored nanoscale material for due to its ease of functionalization [39,40], facile fabrication [41], excellent chemical stability [42,43], extraordinary biocompatibility [44,45], and versatile and unique optical performance. Meanwhile, the optical properties of metal NPs, including LSPR, fluorescence, and surface enhanced Raman scattering (SERS), can be tuned by changing their shape, size and composition. To date, a variety of Au nanostructures have been reported, including nanospheres (AuNS) [46], nanorods (AuNR) [47], nanodisks (AuND) [48], nanoshells (AuNSh) [49], nanoprisms (AuNPr) [50], nanorings (AuNRg) [51], and nanocages (AuNC) [52], and each of these structures exhibits unique optical and chemical properties. Among various LSPR-exhibiting metal nanoparticles, AuNPs are essentially the most suitable ones for biosensing applications due to their noble nature, moderate cost and high accessibility [53–55]. Colorimetric assays indicate the presence of target molecules by wavelength shift caused by local changes in the refractive index and/or changes in the distance between particles (agglomeration in most cases), which is macroscopically reflected as color change (typically red to blue/purple) [56,57]. In the AuNP-based colorimetric bioassays, the NPs are typically functionalized/combined with recognition elements specific to the target molecules.

In the early days, most biosensing assays were developed on the basis of natural biomolecular pairs such as antibody/antigen owing to their extraordinary binding affinity and high sensitivity [58]. This is also the case for AuNP-based colorimetric assays. Great achievements have been made in biosensing assays based on natural biomolecular receptors. However, sensing assays based on natural biomolecular recognition elements suffer from several limitations. Firstly, natural biomolecules are vulnerable to denaturation/deactivation under typical working conditions as their functional structures are typically complex and fragile, resulting in short shelf-life and poor reproducibility of the assays [59]. Secondly, natural biomolecules are usually large molecules that may partly block binding sites (epitopes) during the interaction with the target molecules (steric hindrance) [60–62]; fewer natural biomolecules are available for the target molecules as the density of receptors immobilized on substrate per unit area is inversely proportional to their molecular sizes. Thirdly, synthesis of natural biomolecules tends to be time-consuming and resource-intensive [63], resulting in high cost of assays based on natural biomolecules as the recognition elements [64]. As a result, researchers have explored alternative molecular strategies by replacing natural recognition elements with less complex/synthetic analogues.

To date, various synthetic molecules have been proposed as recognition elements in colorimetric biosensing assays. Among them, liposomes [65,66], peptides [67], aptamers [68,69], and other chemical molecules [70] have been intensively explored and widely applied (Fig. 1). Several reviews on colorimetric assays based on AuNPs functionalized/combined with non-antibody molecules have been published, wherein specific sensing mechanisms were discussed [71–73]. Nevertheless, only a few of the review articles discuss the performance of colorimetric biosensing assays with respect to the recognition elements employed. Herein, we offer an overview of the colorimetric

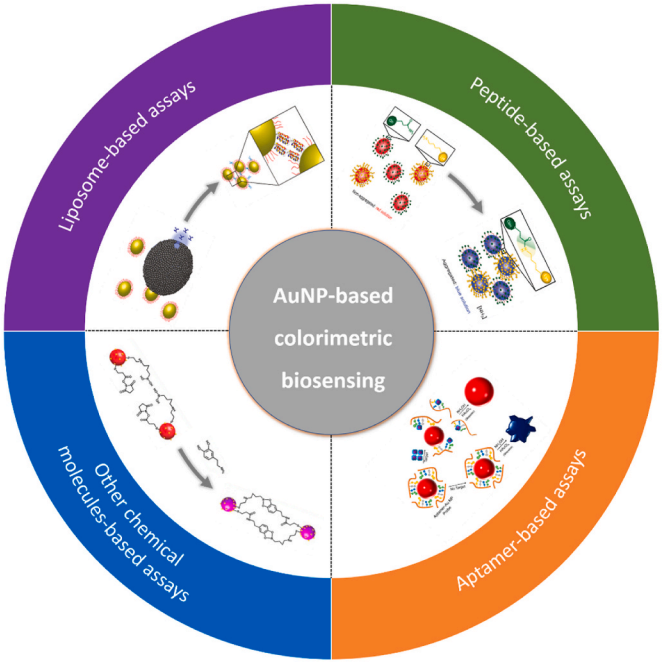

Fig. 1. Schematic illustration of the overall structure of the present review.

biosensing assays with non-antibody molecules as recognition elements, catalytic sites and carriers for signal molecules. Recent advances in the colorimetric assays with different categories of non-antibody recognition elements (liposomes, peptides, aptamers, and other chemical molecules) are presented, followed by chapters discussing each category of the recognition element. Meanwhile, biosensing assays based on different categories of non-antibody recognition elements were compared in order to clarify their respective pros and cons. Table 1 summarizes recent advances in the colorimetric biosensing assays based on gold nanoparticles functionalized/combined with different non-antibody recognition elements and assemblies/carriers. It highlights the target analyte, limit of detection (LoD), color change observed and characteristics of the assays. As indicated, such assays can detect a wide range of analytes (e.g., enzymes, proteins, viruses, DNAs, bacteria) at their clinically relevant concentrations. Additionally, a schematic summary of colorimetric biosensing assays based on gold nanoparticles functionalized/combined with different non-antibody recognition elements is presented in Fig. 1.

2. Colorimetric biosensing assays based on AuNPs functionalized/combined with liposomes

As self-assembled micro-vesicles prepared by hydration of lipid thin films, liposomes are artificial capsules with an aqueous compartment surrounded by a lipid bilayer (e.g., phospholipids and sterols) (Fig. S1) [100,101]. As a result, the liposomal leaflets that separate a hydrophobic interior are both hydrophilic in nature. In virtue of this unique structure, liposomes can theoretically encapsulate any water-soluble molecules (e.g., chemical molecules, enzymes, fluorescent dyes, nucleic acids) or nanoparticles [102–104] that may serve as signal markers. In this way, the signals can be amplified as one target molecule (e.g. a channel/pore forming molecule) can theoretically trigger the release of thousands of signal marker molecules, resulting in drastically enhanced sensitivity. Meanwhile, phospholipids, the basic building blocks of liposomes, exhibit numerous advantageous properties, including good biodegradability, non-toxicity, and excellent biocompatibility [105]. Additionally, the low cost of lipids makes liposome-based assays highly promising for commercialization. For these reasons, liposomes have been applied in food science [106],

Table 1
Colorimetric biosensing assays based on gold nanoparticles functionalized/combined with different non-antibody recognition elements (liposomes, peptides, aptamers, and other chemical molecules).

Recognition elements	Target analyte	Limit of detection	Assay time	Color change	Characteristics	Reference
Liposomes	Phospholipase A_2 (PLA_2)	700 pM	10–40 min (depending on the analyte concentration)	Red to blue	Ultrahigh sensitivity (picomolar range); one of the early assays with liposomes as recognition element	[66]
	Phospholipase A_2 (PLA_2)	1 nM (in serum)	<10 min	Green (polymer) to red (AuNPs)	First point-of-care detection in real sample (serum)	[74]
	Sphingomyelinase (SMase)	1.4 pM	5–30 min (depending on the analyte concentration)	Red to blue	Rapid and sensitive detection	[75]
	Enterovirus 71 (EV71)	16 copies/μL	5 min and above	Blue to red	Dual signal amplification	[76]
	Listeriolysin O (LLO)	~10 μg/mL	~5 min	Red to purple/blue	Naked-eye readout platform realized by explosive catalysis	[65]
	Pathogen	~1 pM	/	Red to dark-blue	Single-digit pathogen detection	[77]
Peptides	Human carbonic anhydrase II (HCAII)	~10 nM	<5 min	Remains red (red to purple in absence of analyte)	One of the pioneering colorimetric sensing assays based on peptide-functionalized AuNPs	[78]
	Matrilysin (MMP-7)	~5 nM (10 μg/mL)	<5 min	Red to blue	Ultrahigh sensitivity; both concentration and activity can be assessed	[79]
	Botulinum neurotoxin serotype A light chain (BoLcA)	0.1 nM	/	Remains red (red to pink in absence of analyte)	Naked-eye detection of toxin	[80]
	Blood coagulation Factor XIII	0.01 U/mL	30 min	Red to blue	Label-free detection at clinically relevant level	[81]
	Cardiac troponin I (cTnI)	8.4 pM (0.2 ng/mL)	<10 min	Red to purple	Rapid and sensitive taction in real sample	[67]
	Prostate specific antigen (PSA)	10 pg/mL	~5 min	Red to blue	Pt-decorated AuNPs; dual sensing mechanisms	[82]
	Glucose	0.2 mM	2–20 min (depending on the analyte concentration)	Red to colourless	qualitative (colorimetric) and quantitative (LSPR spectra-based) detection by involving smartphone	[32]
	Lead	~100 pM	/	Red to blue	Lowest LoD achieved for metallic molecules	[83]
	Rhodamine 6G (R6G)	1×10^{-5} fM	/	/	Lowest LoD achieved for chemical molecules	[84]
	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	10 copies per reaction	>60 min	/	Lowest LoD achieved for biomolecules	[85]
Aptamers	Oligonucleotide	10 fmol	/	Red to pink/purple	The first colorimetric assay based on aptamer-functionalized AuNPs	[33]
	Lead	/	120 min	Blue to purple and then to red	A prototype of colorimetric sensor based on aptamer-functionalized AuNPs	[86]
	Lead	0.4 μM	<10 min	Blue to red	Rapid detection of different analytes at room temperature	[87]
	Adenosine; Cocaine	300 μM for adenosine; 50 μM for cocaine	1–5 min (depending on the analyte concentration)	Purple to red	A generalized colorimetric assay that can be combined with any aptamer of interest	[88]
	Ochratoxin A; Cocaine; 7β-estradiol	1 nM for Ochratoxin A; 1 nM for cocaine; 0.2 nM for7β-estradiol	30 min	Dark purple to pink	Naked eye detection of analyte in real samples at ultra-low concentration	[89]
	Adenosine triphosphate (ATP)	10 nM	30 min	Remains red (red to purple in absence of analyte)	Real sample (urine) detection	[90]
	Ochratoxin A; Aflatoxins B1	0.5 ng/mL for Ochratoxin A; 5 ng/mL for Aflatoxins B1	10 min	Colourless to yellow for Ochratoxin A; Blue to colourless for Aflatoxins B1	Simultaneous detection of two analytes	[91]
	Thrombin; Cocaine; Hg (II)	10 nM for thrombin; 10 μM for cocaine; 50 μM for Hg (II)	5–10 min	Remains red (red to blue in absence of analyte)	A rapid and universal biosensor that can be used for any target of interest	[92]
Other chemical molecules	Cr^{3+}; Fe^{2+}	23.66 nm for Cr^{3+}; 11.21 nm for Fe^{2+}	30 min	Red to Blue	Application at wide pH range (3–8)	[93]
	S. aureus; *M. luteus*; *B. subtilis*	1×10^9 cells/mL	/	Red to black (owing to reduction of silver ions on the surface of AuNPs)	Ultra-sensitive detection in real sample (orange juice and tap water)	[94]
	S. aureus; *P. aeruginosa*	10^6 CFU/mL	1 h	Pink to yellow	Real sample detection	[95]

(*continued on next page*)

Table 1 (*continued*)

Recognition elements	Target analyte	Limit of detection	Assay time	Color change	Characteristics	Reference
	Transition metal ions (Ni^{2+}, Cu^{2+}, Fe^{3+})	1.4–11.2 nM	10 min	Red to purple	Ultra-high sensitivity	[96]
	Dopamine	<5 μM	30 min	Red to pink	Detection of target in living cells	[70]
	Co^{2+}	10 nM	15 min	Red to blue	No additional recognition element (AuNP as the recognition element)	[97]
	Vitamin B1	3 ppb	<10 min	Red to blue	No additional recognition element (AuNP as the recognition element)	[98]
	DNA	1.47 nM	/	Remains red (Turns blue in absence of analyte)	Gold nanorods instead of gold nanospheres are employed as the probe	[99]

biosensing [66], and drug delivery [107]. The application of liposomes in biosensing was first reported decades ago and liposomes have played a key role in optical biosensing approaches since then [108,109]. Liposome-based optical assays have been employed for detections of various analytes, including enzymes [66], nucleic acids [110], and viruses [77]. Nevertheless, approaches based on conventional optical methodologies (e.g. fluorescence, surface plasmon resonance [111]) are inherently limited by cross-talk issues and the requirement for sophisticated instrumentation and tedious sample preparation, making such approaches not ideal candidates for point-of-care applications. Therefore, liposome-based colorimetric biosensors, which are cost effective, rapid, and portable, have also been intensively investigated in recent years owing to their great potential in clinical diagnosis [112]. Indeed, the signal amplification capability of liposomes as carriers of signal molecules (as mentioned above) is of great significance owing to the relatively low sensitivity of colorimetric assays [113].

2.1. Early assays

Since the proposal of the first liposome immunosensor in 1980 [108], a variety of liposome-based colorimetric biosensing assays have been reported, especially in recent years. In 2011, Aili et al. proposed a flexible phospholipase assay based on liposomes and AuNPs (Fig. 2a). In this assay, rupture of liposomes, which is triggered by the target analyte (phospholipase A_2), leads to release of encapsulated polypeptides from the liposomes, which in turn induces aggregation of AuNPs that are functionalized with polypeptides associate and fold with the polypeptides released from the liposomes. As a result, a color change can be detected within 5 min [66]. Then, real sample detection has been thoroughly explored. Chapman et al. demonstrated a liposome-based lateral flow assay for real sample detection of the same target analyte (phospholipase A_2) in complex fluids (Fig. 2b). Herein, polymers encapsulated within the liposomes are released on the interaction with the target analyte, resulting in the generation of multivalent nanoparticle networks with such polymers as linkers. This process is feasible in human serum, which is of great significance to clinical applications. Also, a red test line is generated and easily detected with no additional instrument involved, which is of great significance to point-of-care diagnosis. The LoD is 1 nM (in serum) and the assay time is less than 10 min [74].

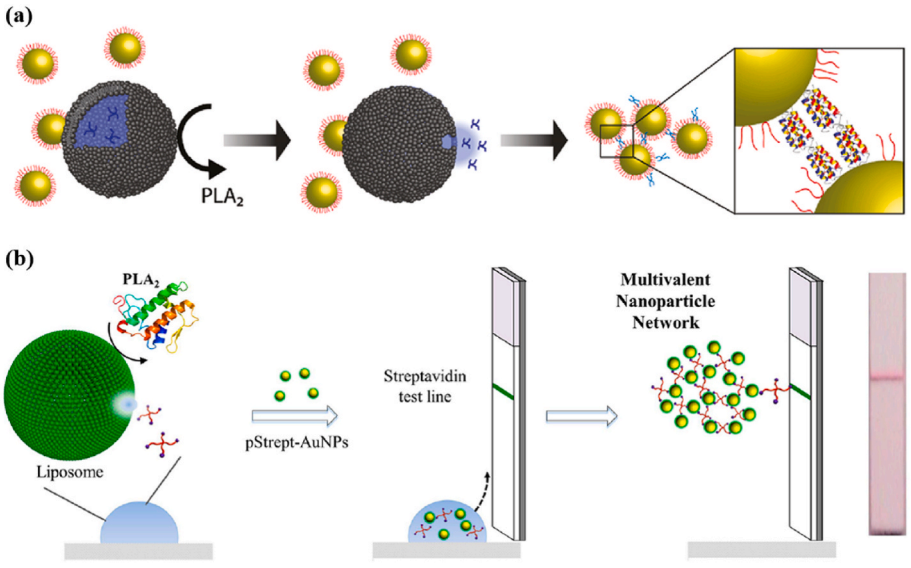

Fig. 2. (a) Colorimetric detection of phospholipase A_2 (PLA_2): AuNPs are functionalized with Polypeptide A (JR2EC) and liposomes are loaded with Polypeptide B ($JR2KC_2$), wherein Polypeptide A and Polypeptide B are complementary; PLA_2-mediated hydrolysis of the lipids leads to liposome rupture, resulting in release of Polypeptide B; Polypeptide B interacts with Polypeptide A on AuNPs to form a four-helix bundle, resulting in bridging and aggregation of AuNPs (with permission from American Chemical Society) [66]. (b) Liposome-based lateral flow assay for real sample detection of PLA_2: liposomes are loaded with biotinylated PEG linkers and incubation with PLA_2 leads to release of the linkers; the acquired solution is mixed with a solution containing AuNPs functionalized with polystreptavidin so that polystreptavidin is linked in the presence of the released PEG linkers to generate AuNP aggregations; the solution is then added into a lateral flow device, wherein the test line is pre-printed-with polystreptavidin, once the linker molecules and AuNP aggregations reach the test line, the AuNP aggregations would adhere by forming multivalent nanoparticle networks, thereby generating a color change (with permission from American Chemical Society) [74]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.2. Efforts in performance improvement

Extensive efforts have been devoted to improving the performance of such assays. Holme et al. demonstrated a colorimetric assay for detection of sphingomyelinase (SMase) (Fig. 3a). Herein, target analyte triggers the release of cysteine encapsulated in the liposomes, which in turn induces aggregation of AuNPs, resulting in a colorimetric read-out visible to the naked eye. The proposed assay exhibits extraordinary advantages over currently available commercial kits and assays as the LoD is 1.4 pM and the assay time can be down to 5 min, although the assay time is negatively related to the analyte concentration [75]. Xiong et al. reported an immunoassay for naked-eye detection of viral entities (Fig. 3b). Herein, enzyme molecules (trypsin) encapsulated within the liposomes are released to the solution in the presence of the target analyte; the released trypsin boost the disassembly of peptide-functionalized AuNPs that are otherwise aggregated. Dual signal amplification is achieved in this assay by means of liposome encapsulation (one analyte molecule can trigger the release of thousands of enzyme molecules) and explosive catalysis (enzyme molecules can serve as catalyst in cleavage of multiple peptide links in the AuNP-peptide aggregates). The LoD is 16 copies/μL and the assay time can be down to 5 min [76]. Despite the use of antibodies as the receptors, the mechanism of dual signal amplification can be used for future assays where no antibody receptors are used. Mazur et al. demonstrated a liposome-AuNP integrated sensing platform for detection of *Listeriolysin O* (LLO) (Fig. 3c). The target analyte interacts with cysteine-encapsulating liposomes so that pores are generated across the leaflets; the released cysteine induces aggregation of AuNPs, which is reflected as a color change from red to purple/blue. The assay time can be down to 5 min [65]. To date, the LoD of liposome-based assays has been optimized to single molecule detection. For instance, Bui et al. achieved detection of a single pathogen by a color change from red to dark-blue that was visible to the naked eye (Fig. 3d) [77].

2.3. Future challenges

Despite the great advances achieved, further improvements are needed in several aspects. Firstly, liposomes are typically limited by low stability (leakage, fusion and lipid oxidation) compared with other synthetic molecules (e.g., peptides, aptamers, other chemical molecules [114], resulting in lower reproducibility and reliability. Then, the encapsulation rates and levels are still low and need to be further improved as the signal amplification is dependent on the amount of encapsulated signal molecules [114]. Additionally, the pore forming or rupture process triggered by the analyte, which is typically time-consuming, should be accelerated to reduce the overall assay time.

3. Colorimetric biosensing assays based on AuNPs functionalized/combined with peptides

As short chains of amino acid oligomers linked by peptide bonds, peptides possess the same building blocks as proteins [115]. Owing to performances varying with length and amino acid composition, peptides can effectively replace antibodies in the clinical and diagnostic applications by mimicking natural protein interactions or providing completely different structural and chemical functionalities on the interaction with the target analytes [116–121]. Peptides exhibit some distinctive advantages over antibodies and other synthetic receptors. Firstly, peptides exhibit a high affinity to particular analytes, which can be attributed to their protein-like nature [122]. Secondly, peptides are typically small and robust compared with proteins and enable facile incorporation of functional groups for directed immobilisation and further modification. Thirdly, peptides exhibit excellent intrinsic stability in the presence of chemical and thermal denaturants owing to their short-chain structures [123]. Fourthly, peptide synthesis is facile and cost-effective once the sequence information is isolated from the phage display [124], making peptide-based biosensing assays highly promising for commercialization. For these reasons, peptides are excellent candidates for synthetic receptors in biosensing assays, especially those designed for applications in harsh environments (e.g., high/low temperature, high pressure, high acidity/alkalinity, in the presence of chemical and thermal denaturants).

3.1. Early assays

In 2006, functionalization of AuNPs with synthetic peptides to enable control of particle aggregation in a switchable manner was reported [125]. Based on that, Aili et al. demonstrated colorimetric sensing by controlled assembly of peptide-functionalized AuNPs (Fig. 4a). In absence of analyte molecules, addition of Zn^{2+} ions triggers peptide folding and subsequently aggregation of AuNPs, resulting in color change from red to purple. In the presence of analyte molecules, they bind to peptides so that folding-induced aggregation is precluded and the dispersion color remains red [78]. This is one of the pioneering colorimetric sensing assays based on peptide-functionalized AuNPs. Following that, Chen et al. reported a similar colorimetric sensing assay, wherein aggregation of AuNPs indicates the presence of the target analyte (Fig. 4b). In this assay, both concentration and activity of the target analyte can be assessed, which are of a great significance to protein detection. Additionally, the LoD achieved has been optimized to be ~5 nM, which was superior compared with its peers reported then [79]. Liu et al. reported a colorimetric assay based on biofunctionalized AuNPs (Fig. 4c). Herein, a color change from pink/transparent to red, which is induced by dispersion of AuNPs, indicates the presence of the target analyte (botulinum neurotoxin serotype A light chain) as it causes cleavage of surface peptides in this case [80]. Chandrawati et al. proposed a highly sensitive sensing assay where AuNPs are functionalized with two peptides (Fig. 4d). The presence of activated target analyte leads to crosslinking of the two peptide chains, resulting in aggregation of AuNPs and consequently a color change from red to blue; the LoD achieved was 0.01 U/mL, which is comparable to the clinically relevant level of the target analyte (0.05 U/mL) [81]. Liu et al. reported a colorimetric biosensing assay involving peptide-functionalized AuNPs and demonstrated the proposed assay using cardiac troponin I (cTnI) (Fig. 5a). Herein, the peptide serves as the recognition element as it binds to the target analyte with high affinity and color change (red to transparent) serves as the detection signal. The LoD achieved was 0.2 ng/mL (8.4 pM) in real samples (diluted serum) and the assay time was no more than 10 min. Additionally, the effects of size and concentration of AuNPs on the assay performance were explored [67]. In order to further enhance the sensitivity, Pt-decorated AuNPs were employed for colorimetric biosensing assay. Herein, two sensing mechanisms (plasmonics and catalysis) are involved (Fig. 5b). The LoD achieved by Pt-decorated AuNPs were two orders of magnitude higher than that achieved by bare AuNPs [82]. Despite that the recognition element used was antibody, it is reasonable to deduce that a similar assay with peptide as the recognition element is feasible. In order to facilitate commercialization and practical applications, Wang et al. reported a smartphone spectrometer for colorimetric biosensing, wherein light-emitting diode flash and camera of the smartphone are employed as the light source and the detector, respectively (Fig. 5c). This assay is capable of both qualitative (colorimetric) and quantitative (LSPR spectra-based) detection of biological analyte using a portable platform (smartphone) [32].

3.2. Efforts in performance improvement

Recently, great advances have been reported in various aspects of peptide-based colorimetric bio-sensing. In terms of sensitivity, the lowest LoD achieved by colorimetric assays based on peptide-functionalized AuNPs to date is 98.7 pM for metallic molecules (lead) [83], 1×10^{-5} fM for chemical molecules [84], and single-molecule level for biomolecules [85]. In terms of efficiency, the detection time

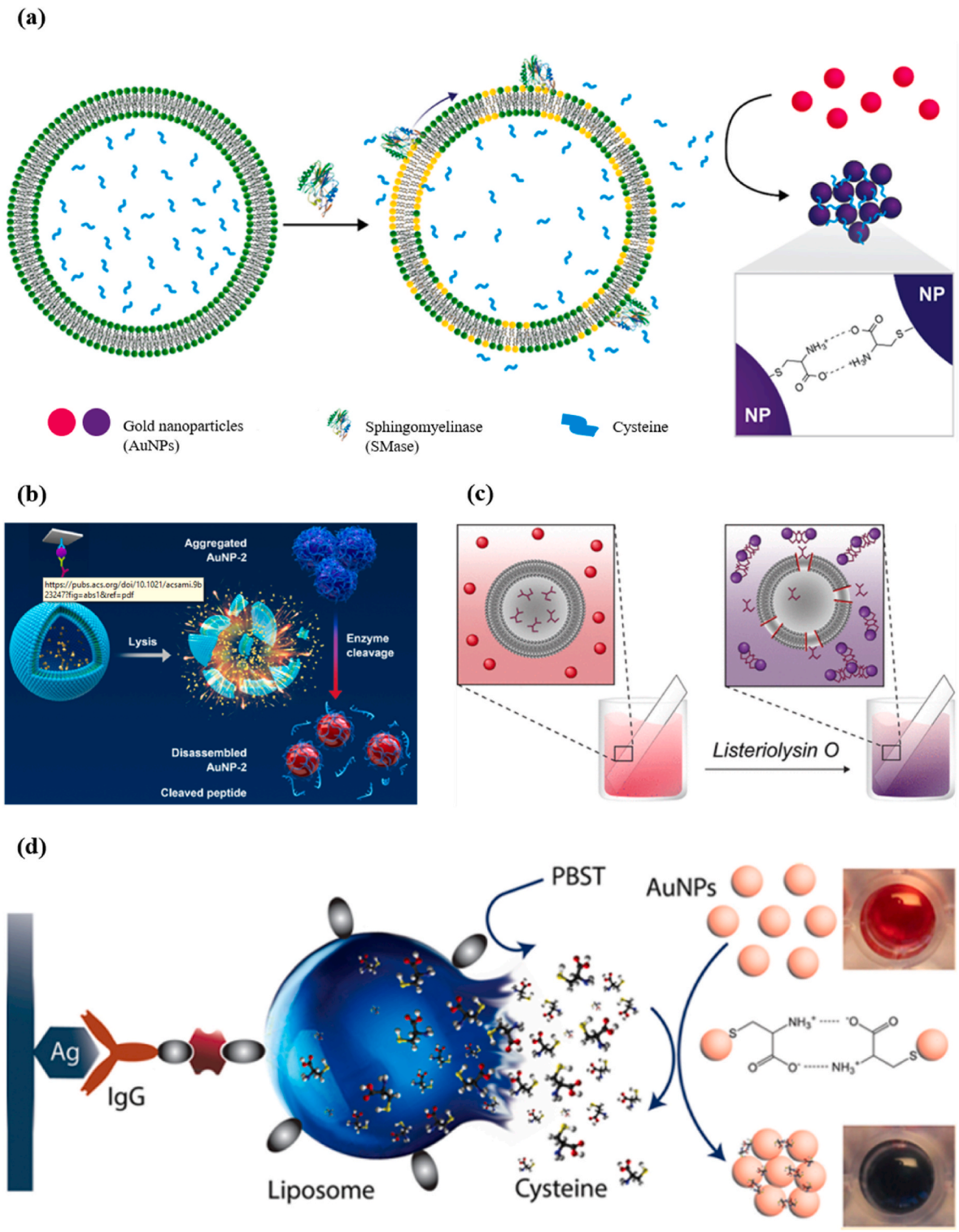

Fig. 3. (a) A liposome-based platform for colorimetric detection of sphingomyelinase (SMase): the presence of SMase leads to membrane phase change of cysteine-encapsulating liposomes, which allows leakage of cysteine; dispersed AuNPs are then added into the solution, and AuNP aggregates are generated by formation of hydrogen bonds between cysteine molecules (with permission from American Chemical Society) [75]. (b) An immunoassay for colorimetric detection of virus: enzyme molecules (trypsin) encapsulated within the liposomes are released to the solution in the presence of the target analyte, and boost the disassembly of peptide-functionalized AuNPs that are otherwise aggregated. Dual signal amplification is achieved in this assay by means of liposome encapsulation (one analyte molecule can trigger the release of thousands of enzyme molecules) and explosive catalysis (enzyme molecules can serve as catalyst of cleavage of peptides linking the AuNPs) (with permission from American Chemical Society) [76]. (c) A liposome-AuNP integrated sensing platform for detection of *Listeriolysin O* (LLO). LLO interacts with cysteine-encapsulating liposomes and pores are generated on the liposomes, so that cysteine molecules are released; the released cysteine induces aggregation of AuNPs, which is reflected as a color change from red to purple/blue (with permission from American Chemical Society) [65]. (d) Liposome-amplified plasmonic immunoassay for naked-eye detection of pathogen: the presence of a single pathogen can trigger a chemical cascade reaction leading to aggregation of AuNPs (with permission from American Chemical Society) [77]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

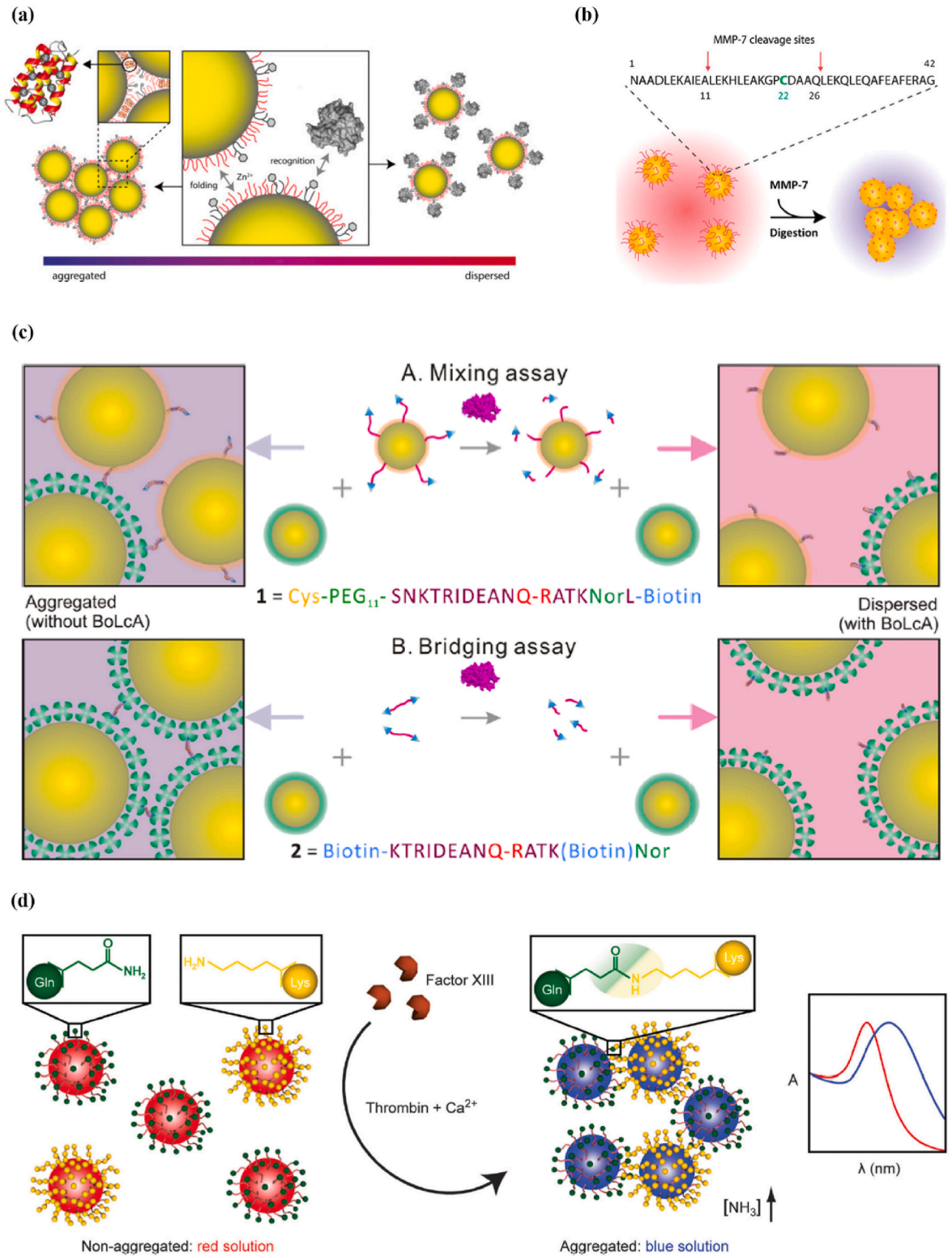

Fig. 4. (a) Colorimetric sensing by controlled assembly of peptide-functionalized AuNPs: in absence of analyte molecules (human carbonic anhydrase II (HCAII)), addition of Zn^{2+} triggers peptide folding and subsequently aggregation of AuNPs, resulting in color change from red to purple; in presence of analyte molecules, they bind to peptides so that folding-induced aggregation is precluded and the dispersion color remains red (with permission from Royal Society of Chemistry) [78]. (b) Colorimetric sensing based on aggregation of AuNPs: the target analyte (matrilysin, MMP-7) triggers cleavage of peptides on AuNP surface, which induces aggregation of AuNPs; both concentration and activity of the target analyte can be assessed in this assay (with permission from Royal Society of Chemistry) [79]. (c) Colorimetric sensing based on re-dispersion of AuNPs: AuNPs functionalized with peptide aggregate, and the target analyte (BoLcA) can cleave the peptides so that AuNPs are re-dispersed (with permission from American Chemical Society) [80]. (d) Label-free, colorimetric detection of blood coagulation Factor XIII: AuNPs are functionalized with two different peptides, and the presence of activated target analyte leads to crosslinking of the two peptide chains on AuNP surface (with permission from Royal Society of Chemistry) [81]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

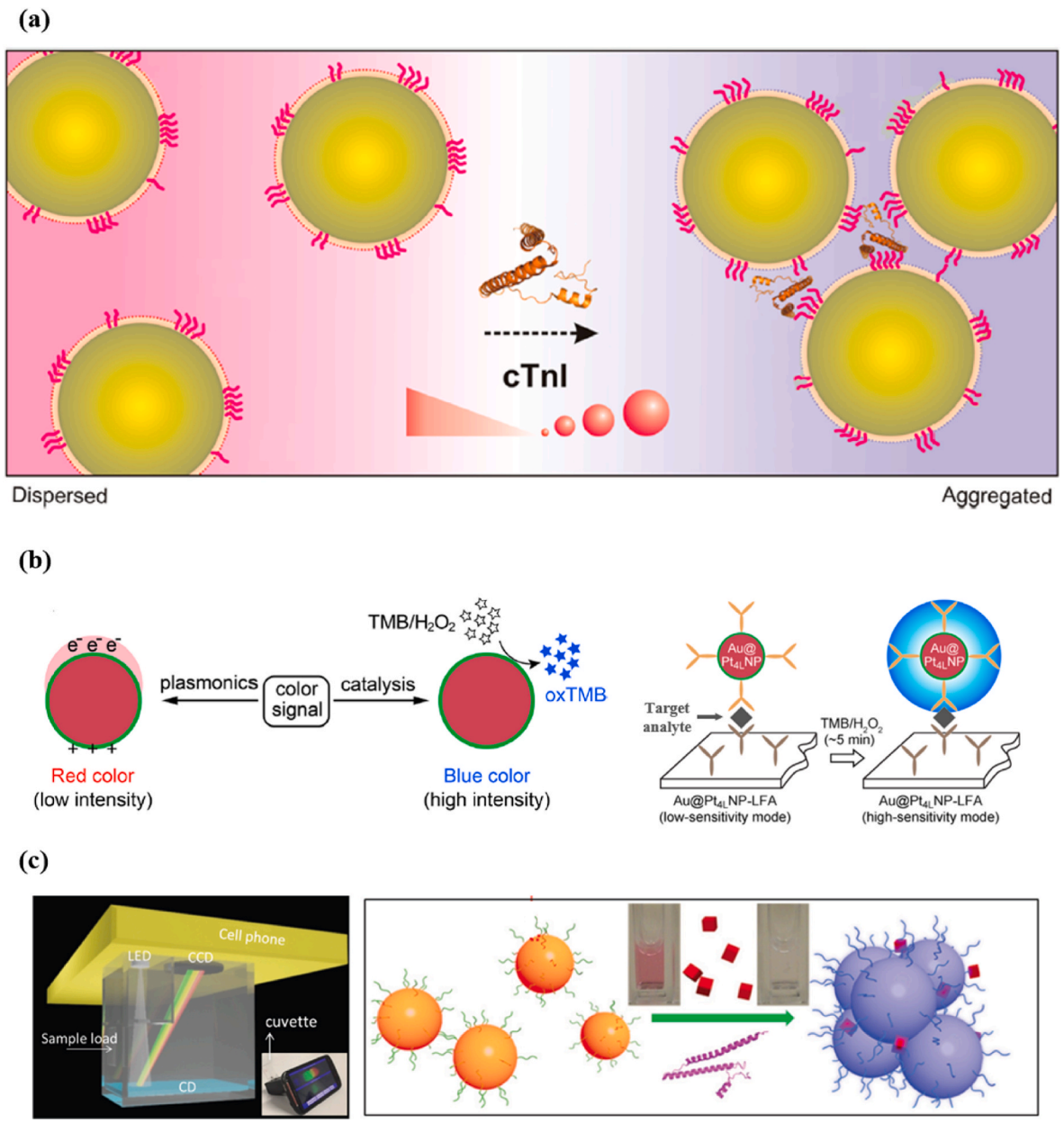

Fig. 5. (a) Colorimetric detection of cardiac troponin I (cTnI) using AuNPs of different sizes and concentrations: the peptide serves as the recognition element as it binds to the target analyte with high affinity and color change (red to transparent) serves as the detection signal. Additionally, the effects of size and concentration of AuNPs on the assay performance were explored (with permission from American Chemical Society) [67]. (b) Colorimetric biosensing assay based on Pt-decorated AuNPs. Herein, dual sensing mechanisms (plasmonics and catalysis) are involved, resulting in two different color signals (with permission from American Chemical Society) [82]. (c) colorimetric biosensing based on a portable platform (smartphone), wherein light-emitting diode flash and camera of the smartphone are employed as the light source and the detector, respectively (with permission from Royal Society of Chemistry) [32]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

was below 10 min [126,127], which is a clinically relevant level for most application scenarios, although further reduction is limited by the intrinsic features of protein-protein interactions; in terms of real sample detection, peptide-based colorimetric bio-sensing assays have been demonstrated for analyte detection in complex matrices, including serum [128], whole blood, urine [129], saliva [130], and sweat [131].

3.3. Future challenges

Currently, a reporter molecule is required in most peptide-based assays as peptides do not directly generate a measurable signal in response to a binding event [132], indicating that label-free detection is an inherent challenge for these assays, although several label-free peptide-based assays have been proposed [81]. Additionally, the selectivity of peptide-based sensing assays shall be further optimized as various peptides exhibit significant and comparable binding affinity towards multiple cells/molecules.

4. Colorimetric biosensing assays based on AuNPs functionalized/combined with aptamers

As analogue to protein-based antibodies, aptamers are essentially short, single-stranded nucleic acid ligands (DNA or RNA) with high binding affinity and specificity towards any molecule of interest (e.g., protein and inorganic molecules) [133,134]. In virtue of the folding capability upon binding [135], affinity and specificity of the

aptamer/target interactions are superior compared with other synthetic receptors and even comparable to those of antibody/antigen interactions [136–138]. For this reason, nucleic acid aptamers are termed as "chemical antibodies" in a wide range of applications [139]. More importantly, aptamers exhibit excellent stability in harsh environments and are not subject to denaturization. Additionally, a non-disposable biosensor can be realized using aptamers as their interactions with target molecules are indeed reversible (by intermolecular hybridizations) [140]. In virtue of their unprecedented advantages (e.g., flexible structure, low cost, small physical size, absence of immunogenicity, and versatile chemical modification, high stability) over natural receptors, aptamers have been thoroughly investigated and widely applied in the field of diagnostics [141] and healthcare [142].

Currently, the most commonly used method for aptamer preparation is the systematic evolution of ligands by the exponential enrichment (SELEX) (Fig. S2) [143–146], despite that non-SELEX methods have also been reported [147,148]. Specifically, a fundamental library of nucleic acids is established, followed by incubation with the molecule/ligand of interest. Then, unbound sequences and molecules are removed, and the bound nucleic acids are collected and eluted. After that, the eluted sequences were amplified by means of polymerase chain reaction (PCR). As a result, an enriched library is obtained. This enriched library is employed as the starting library in the next cycle. Eventually, the final library obtained after multiple cycles (typically 6–12 consecutive cycles) is cloned and sequenced [149]. Upon sequence determination by SELEX, aptamers can be synthesized by using cost-effective and reproducible chemical methods. In other words, the SELEX enables *in vitro* selection of aptamers so that *in vivo* immunization of animals, as in the case of antibody production, is not required for aptamers.

4.1. Early assays

In 1997, Elghanian et al. proposed the first colorimetric sensing assay based on aptamer-functionalized AuNPs and demonstrated the proposed assay for detection of a single-stranded oligonucleotide. Herein, the presence of target molecules led to aggregation of AuNPs, thereby a red-to-pinkish/purple color change visible to the naked eye. The LoD achieved for the target oligonucleotide was 10 fmol [33]. Storhoff et al. investigated the correlation of aptamer length with optical properties (e.g., color) of aptamer-functionalized AuNPs and found that the aptamer length could kinetically control the size of AuNP aggregates, thereby controlling their optical properties. In other words, the optical properties of AuNPs are dependent on its aggregate size [150]. Following that, various assays with similar sensing mechanisms have been reported. Liu et al. reported a colorimetric sensing assay based on aptamer-functionalized AuNPs for detection of metallic ions (Pb^{2+}) (Fig. 6a). This assay is a generalized one that may be applied for various analytes of interest as aptamers with high binding affinity to a specific

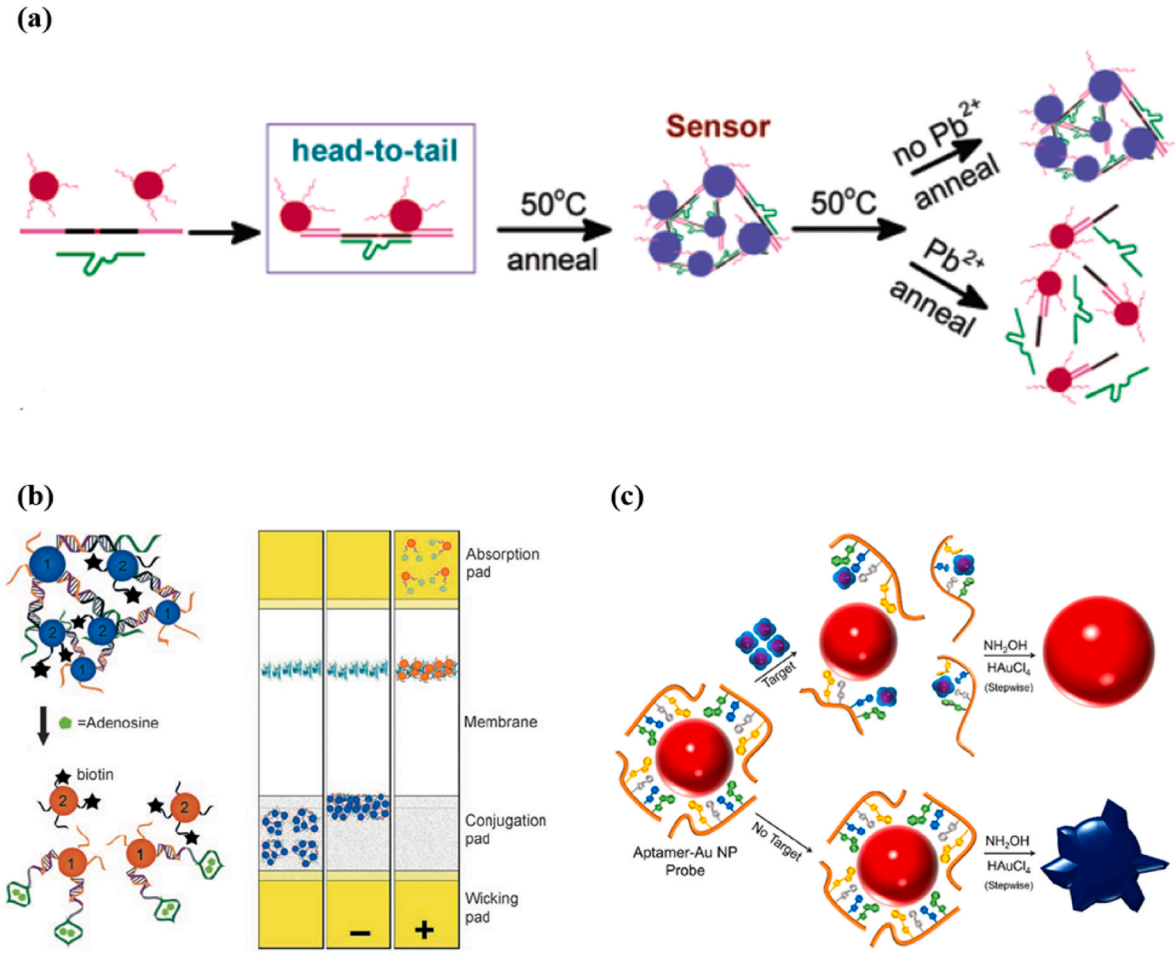

Fig. 6. (a) Colorimetric sensing assay based on aptamer-functionalized AuNPs for detection of metallic ions (Pb^{2+}). This assay can be applied for detection of various analytes of interest as aptamers with high binding affinity to a specific analyte can be generated by *in vitro* selection (mostly SELEX) (with permission from American Chemical Society) [87]. (b) A general colorimetric sensing assay based on the disassembly of AuNP aggregates linked by aptamers, wherein no special features are required for the aptamers (with permission from Wiley-VCH) [88]. (c) Colorimetric detection of small molecules (ochratoxin A, cocaine, and 7β-estradiol) in real samples. The specific mechanism was target-mediated growth of aptamer-functionalized AuNPs, which equips this assay with sufficient selectivity for real sample detections (with permission from American Chemical Society) [89].

analyte can be generated by *in vitro* selection (mostly SELEX) [86]. However, this assay is tedious as a 2-h cooling process is required before the color change can be observed. Hence, Liu et al. developed an improved version of such assay by increasing the size of AuNPs from 13 nm to 42 nm, as well as optimizing the AuNP alignment, the temperature and the aptamer used. This improved assay could achieve rapid (assay time <10 min) and sensitive (LoD = 0.4 μM) detection of Pb^{2+} at room temperature, making it more suitable for practical applications [87]. After that, a general colorimetric sensing assay based on the disassembly of AuNP aggregates linked by aptamers was proposed by the same group (Fig. 6b). Herein, no special features are required for the aptamers, and the proposed assay is supposed to be applicable to any aptamer of interest [88]. As a complementary, Liu et al. reported optimized preparation of aptamer-functionalized AuNP aggregates [151]. Additionally, Soh et al. proposed a colorimetric assay for detection of small molecules (ochratoxin A, cocaine, and 7β-estradiol) in real samples (Fig. 6c). The specific mechanism was target-mediated growth of aptamer-functionalized AuNPs, which equips this assay with sufficient selectivity for real sample detections [89].

4.2. Efforts in performance improvement

Assays mentioned above are based on disassembly of AuNP aggregates, which are highly unstable in real samples (e.g., serum, saliva, urine, and sweat) or after long-term storage. As a result, the real sample sensitivity and the shelf life of biosensors based on such assays are by no

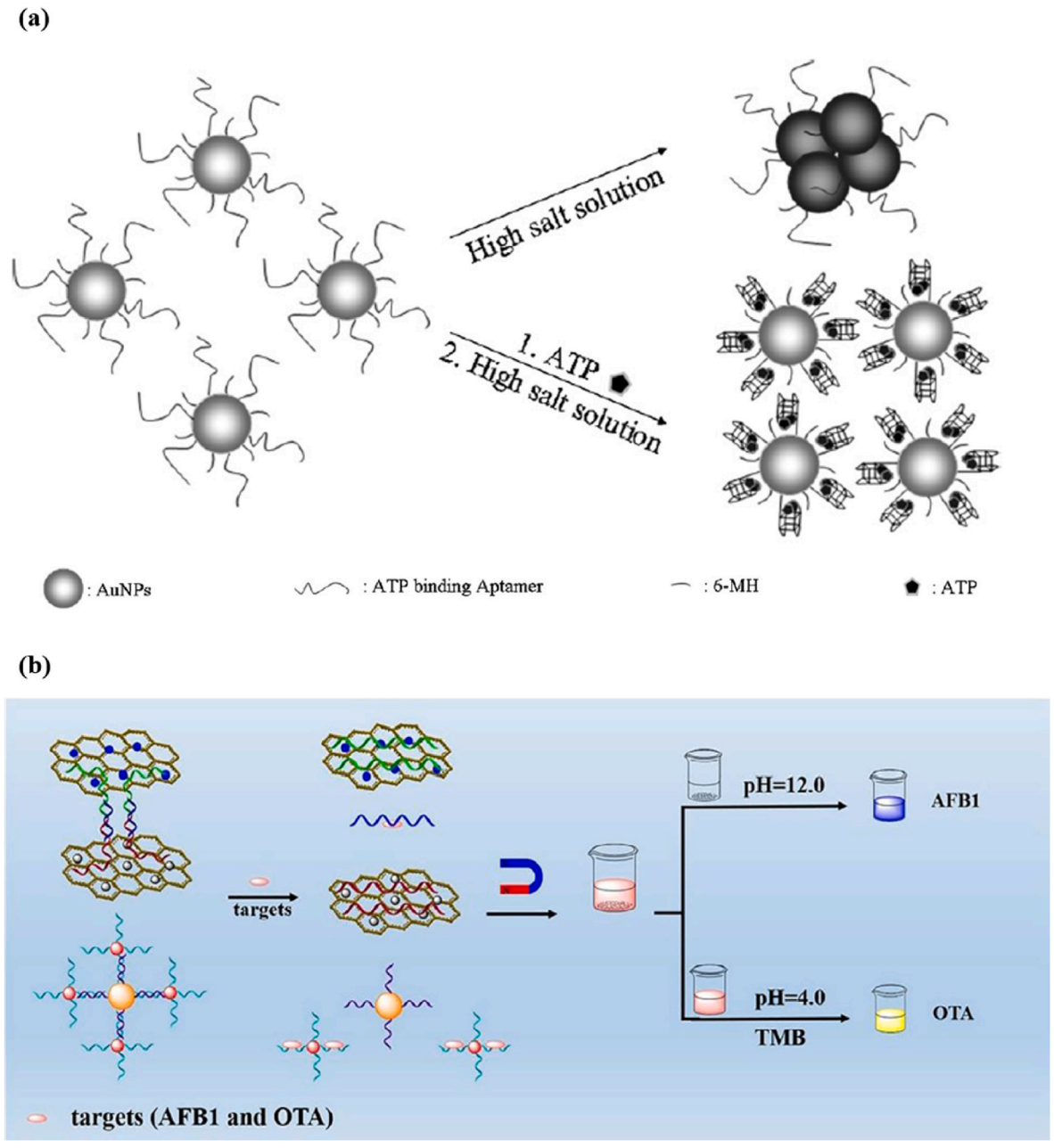

Fig. 7. (a) Colorimetric detection of adenosine triphosphate (ATP) based on controlled aggregation of AuNPs: the target molecules prevents aggregation of aptamer-functionalized AuNPs, which is observed in absence of the target molecules (with permission from Elsevier B.V.) [90]. (b) Colorimetric sensing assay for simultaneous detection of two targets (ochratoxin A and aflatoxins B1). This assay is a breakthrough in terms of simultaneous detection of multiple target, although color changed induced by AuNP aggregation is responsible for one of the targets only (with permission from Elsevier B.V.) [91]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

means ideal. For this reason, Chen et al. introduced a colorimetric assay for detection of adenosine triphosphate (ATP) (Fig. 7a) [90]. In this assay, the target molecules prevents aggregation of AuNPs, which is observed in absence of the target molecules; the LoD achieved was 10 nM, indicating a significantly enhanced sensitivity compared with previous assays [88]. However, the aptamer-functionalized AuNPs can only be applied to a specific target and detection of multiple targets require repeated nanoparticle functionalization by different aptamers, which could take hours. To solve this problem, Zhu et al. reported a colorimetric sensing assay for simultaneous detection of two targets (ochratoxin A and aflatoxins B1) (Fig. 7b). This is indeed a breakthrough in simultaneous detection of multiple target, although the color change induced by AuNP aggregation is responsible for one of the targets only [91]. Xia et al. demonstrated a colorimetric sensing assay based on aptamers and AuNPs. Instead of being functionalized with aptamers, AuNPs were combined with different aptamers according to the target to be detected (Fig. 8a). Hence, this biosensor is essentially a universal device that can be used for any target of interest. In this article, detections of proteins, small molecules, and ions were demonstrated (Fig. 8b) [92].

4.3. Future challenges

Despite the great advances in colorimetric assays using aptamers as the recognition elements, such assays are facing several challenges. Primarily, SELEX is an extremely time-consuming process as each round typically takes 24 h [152] and the entire process may take a few weeks [153]. Hence, acceleration of the SELEX process is urgently needed; alternatively, a substitute preparation method may also be a solution. Secondly, aptamers are readily exposed to digestion by enzymes [154,

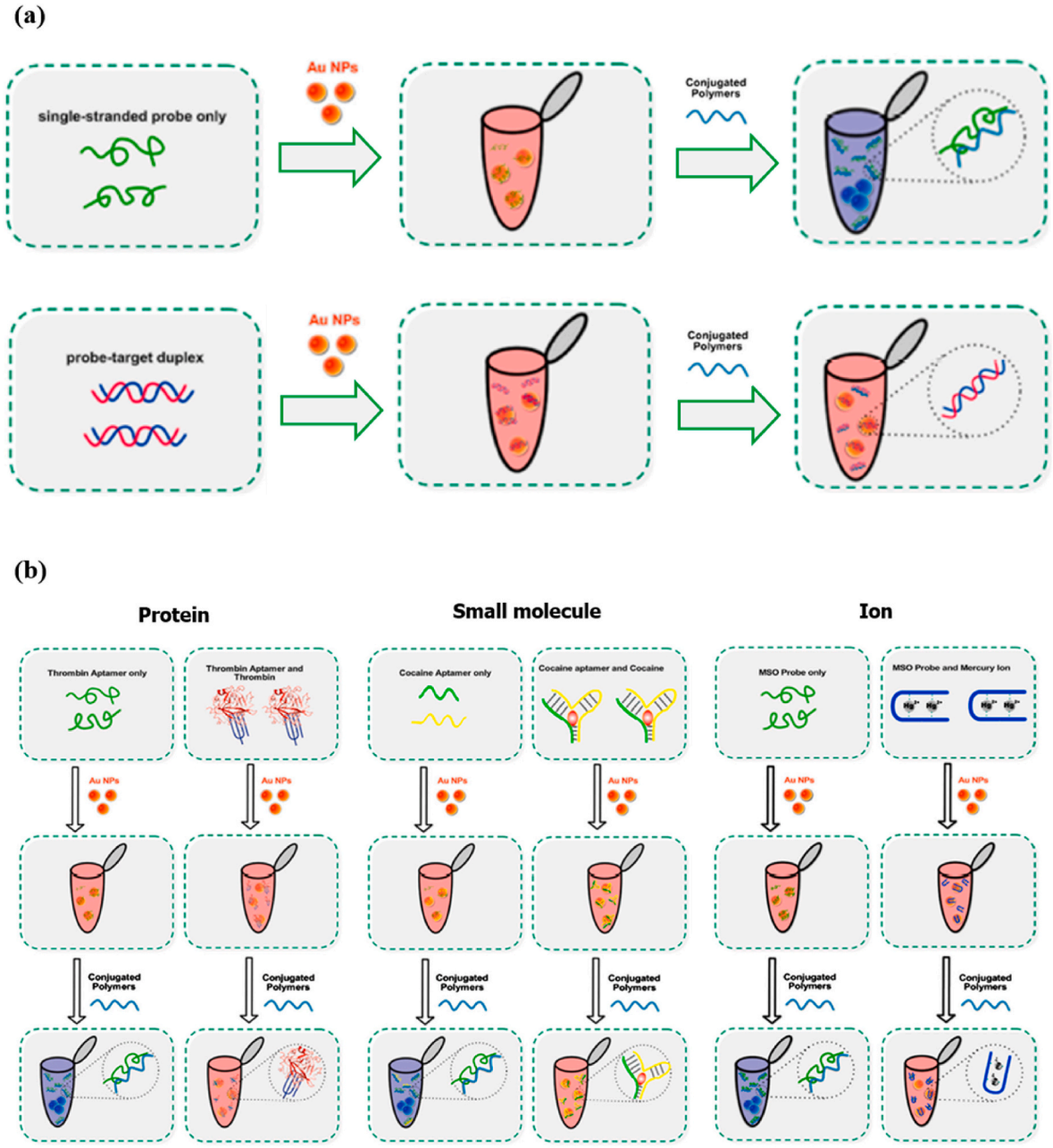

Fig. 8. (a) Colorimetric sensing assay based on aptamers and AuNPs. Instead of being functionalized with aptamers, AuNPs are combined with different aptamers according to the target to be detected. Hence, this biosensor is essentially a universal device that can be used for any target of interest; (b) detections of proteins (thrombin), small molecules (cocaine), and ions (Hg^{2+}) were demonstrated (with permission from National Academy of Sciences) [92].

155], which are abundant in blood. As a result, aptamer-based sensing assays tend to inherently exhibit limited performance in real sample detection and aptamers shall be modified accordingly (e.g., phosphate backbone modifications) to minimize the digestion.

5. Colorimetric biosensing assays based on AuNPs functionalized/combined with other chemical molecules

Besides the synthetic receptors mentioned above, AuNPs have also been functionalized/combined with other chemical molecules for colorimetric biosensing. In order to focus on recent advances in this field, only representative assays reported in 2018 and later are summarized and discussed.

5.1. Early assays

Salimi et al. demonstrated colorimetric detection of metallic ions (Cr^{3+} and Fe^{2+}) using AuNPs modified with methylene blue (Fig. 9a). The proposed assay is highly sensitive (LoD = 23.66 nM for Cr^{3+} and 11.21 nM for Fe^{2+}) and applicable in a wide pH range (pH = 3–8) [93], making it promising for real sample detections. You et al. demonstrated a colorimetric sensing assay based on vancomycin-modified AuNPs for detection of bacteria in real-life samples (orange juice and tap water) (Fig. 9b). The naked eye LoD was 1×10^9 cells/mL for all three bacteria involved (*S. aureus, M. luteus, and B. subtilis*) [94]. Landa et al. proposed sialic acid-functionalized AuNPs for colorimetric detection of pathogenic bacteria (*S. aureus* and *P. aeruginosa*) in real samples (human serum and urine). The LoD achieved was 10^6 CFU/mL [95]. Čonková et al. reported a colorimetric method based on AuNPs functionalized with Schiff base and demonstrated it for the detection of transition metal

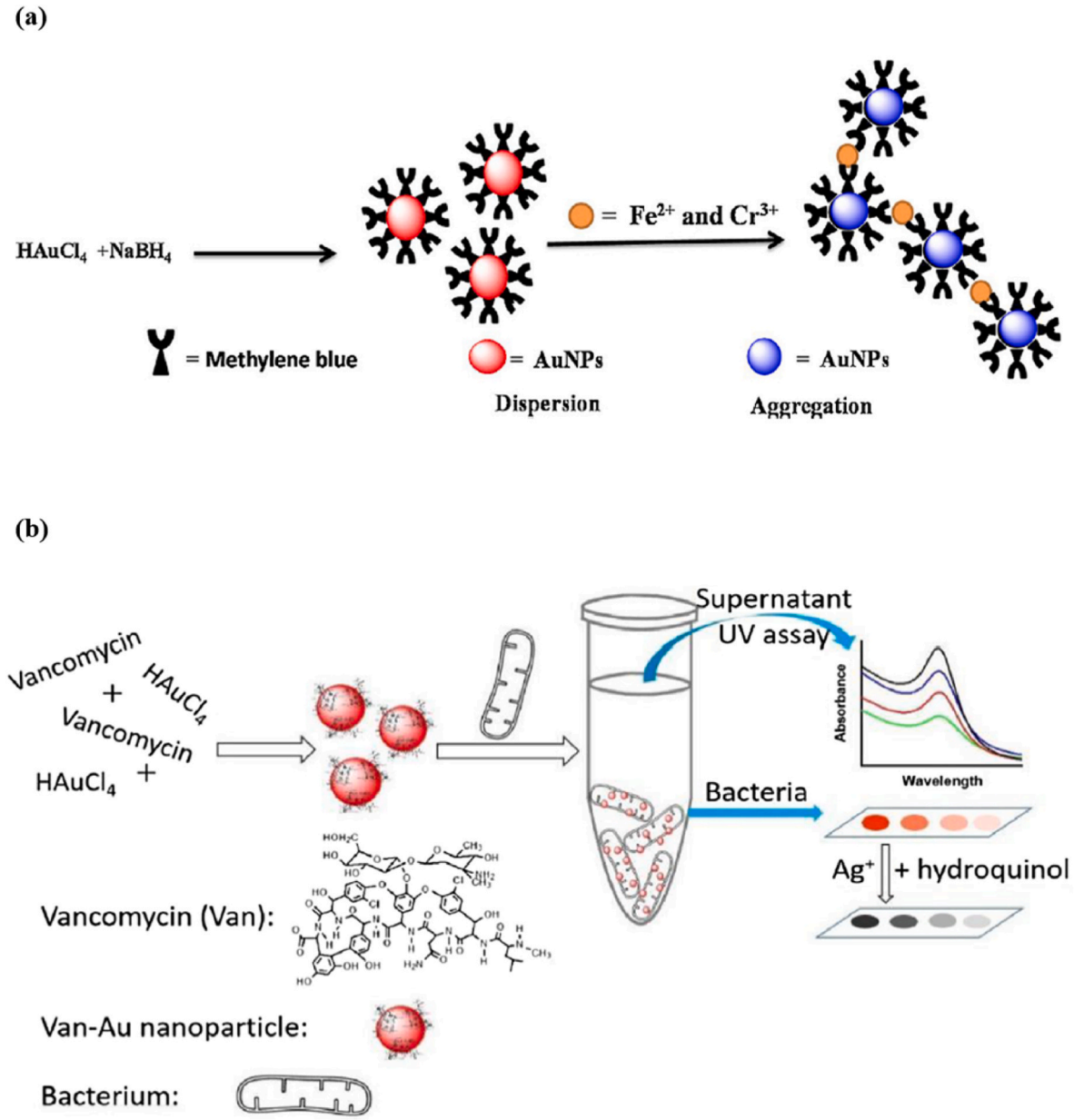

Fig. 9. (a) Colorimetric detection of metallic ions (Cr^{3+} and Fe^{2+}) using AuNPs modified with methylene blue (with permission from Elsevier B.V.) [93]. (b) Colorimetric sensing assay based on vancomycin-modified AuNPs for detection of bacteria (*S. aureus, M. luteus, and B. subtilis*) in real-life samples (orange juice and tap water) (with permission from Elsevier B.V.) [94]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

ions (Ni^{2+}, Cu^{2+}, Fe^{3+}) (Fig. 10a). The LoDs achieved for the transition metal ions were in the range of 1.4–11.2 nM, which were two orders of magnitude lower than the LoDs suggested by European Union (EU) [96]. Recently, detection of targets in living cells has attracted great attention. For instance, Ren et al. reported colorimetric sensing of dopamine in living cells and retina using AuNPs functionalized with *N*-hydroxysuccinimide ester (Fig. 10b). In this study, localized dopamine levels in retina tissues were determined by the proposed assay and the LoD achieved was estimated to be below 5 μM [70].

5.2. Efforts in performance improvement

AuNP modification is typically a complicated and tedious process, and the long-term stability of modified AuNPs tends to be limited. Therefore, efforts have been made to eliminate the need for an additional receptor. For instance, Mazur et al. developed a colorimetric biosensor based on core-satellite AuNP and demonstrated it by detection of Co^{2+}. Herein, the core-satellite AuNP, which is linked by cysteine, is exposed to architectural transformation in presence of Co^{2+}. In this way, the core-satellite AuNP itself serves as the receptor and no additional recognition element is needed [97]. Duenchay et al. developed a transparent sheet-based colorimetric sensor based on unmodified AuNPs. Herein, the negatively charged AuNPs can specifically interact with the positively charged vitamin B1 via an electrostatic effect and no surface modification is required for the AuNPs [98]. Besides spherical nanoparticles, AuNPs of other shapes have also been explored. For instance, Xu et al. developed a colorimetric assay based on unmodified AuNR for the detection of DNA. The LoD achieved was 1.47 nM, which is three times determinations of the blank solution. Different from spherical AuNS, rod-shaped AuNR is an anisotropic nanoparticle with two distinctive absorption bands, which exhibits great potential in biosensing [99].

6. Conclusions and perspectives

This review has discussed recent advances in colorimetric biosensing assays based on AuNPs functionalized/combined with non-antibody recognition elements such as liposomes, peptides, aptamers, and other chemical molecules. These assays are ideal alternatives to conventional assays based on natural receptors such as antibodies, which are limited by complicated yet fragile functional structures, tedious and costly preparation, and large molecular size. To date, naked-eye detection of various analytes, including enzymes, viruses, DNAs and bacteria, at clinically relevant concentrations using the colorimetric assays based on AuNPs functionalized/combined with non-antibody recognition elements has been demonstrated.

Each category of assays has their respective strengths and limitations: liposome-based assays exhibit advantages such as high sensitivity due to signal amplification (one analyte molecule can theoretically trigger the release of thousands of signal marker molecules) and great potential for commercialization, but suffer from low stability (leakage, fusion and lipid oxidation) and time-consuming rupture process; peptide-based assays exhibit high sensitivity owing to high affinity of protein-like peptides and wide applicability owing to excellent intrinsic stability of peptides in harsh environments (e.g., in the presence of chemical and thermal denaturants), but suffer from challenges in label-free detection (peptides do not directly generate a measurable signal in response to a binding event in most cases) and low specificity (a peptide may exhibit significant and comparable binding affinity towards multiple cells/molecules); aptamer-based assays are characterized by high specificity owing to the folding capability of aptamers upon binding, good stability in harsh environments (low probability of denaturization) and potential for non-disposable biosensors owing to reversible interactions of aptamers with target molecules, but suffer from time-consuming SELEX process and high sensitivity to hydrolytic digestion by nucleases, which are abundant in human blood.

Despite the great advances achieved in colorimetric sensing based on AuNPs functionalized/combined with non-antibody recognition elements mentioned above (liposomes, peptides, aptamers, other chemical molecules), several challenges remain to be tackled in this promising field before wide application and commercialization of such biosensors.

(1) Limited sensitivity: The sensitivity of colorimetric sensing assays is intrinsically low compared with other methods involving advanced instrument. One of the most effective ways to improve the sensitivity of these assays is to tune the size of AuNPs. Theoretically, decreasing single particle size leads to increased specific surface area of AuNPs, thereby enhanced sensitivity. Practically, however, neither too large nor too small AuNPs can deliver ideal sensing performances, indicating the presence of an optimized particle size for each assay. Another solution is dual-signal output methods combined with other analytical strategies (e.g., SERS, fluorescence, and electrochemistry) [156], wherein the colorimetric result may serve as a preliminary indication; the dual-signal output also enhances sensitivity by reducing the probability of false positive results.

(2) Simultaneous detection of multiple targets: For practical applications, simultaneous detection of more than one target by one device is essentially in various scenarios [157]. Nevertheless, a majority of colorimetric assays based on AuNPs functionalized/combined with non-antibody recognition elements have no capability of simultaneous detection of multiple targets, especially quantitative detection. A possible solution is sensor arrays assisted by machine learning tools [158]. Such assays can theoretically achieve simultaneous detection of dozens of targets, provided that the array is sufficiently large. Alternatively, the combination of colorimetric assays with microfluidic systems with multiple channels may also be a promising strategy for simultaneous detection of multiple targets [159]. Indeed, colorimetric analysis in microfluidic environments is related to device miniaturization, low sample/reagent consumption, and facile measurement of flowing samples.

(3) Restrained commercialization: Practical application and commercialization are the ultimate objective of all biosensors. Colorimetric biosensors are supposed to be advantageous in terms of commercialization owing to its intrinsic potential in point-of-care diagnostics [160] and monitoring [161]. To date, colorimetric biosensors based on AuNPs have been successfully commercialized and well-known examples include pregnancy test kits and diabetic glucose meters [162,163]. However, several challenges remain to be tackled to achieve further advances in its commercialization. Firstly, the cost of AuNP functionalization, which is typically a time-consuming and labour-intensive process, shall be further reduced [164]. This may be relieved by integrating AuNP preparation and surface functionalization into one step [165]. Secondly, the shelf-life of colorimetric biosensors based on AuNPs shall be further improved. In virtue of improved receptor stability compared with those involving antibodies, colorimetric biosensors based on AuNPs functionalized/combined with non-antibody recognition elements exhibit prolonged shelf-life [78]. However, the shelf-lives of currently available colorimetric biosensors based on AuNPs are still beyond the requirement of commercial products. Thirdly, the assay time of colorimetric biosensors based on AuNPs. As indicated, most colorimetric assays based on AuNPs functionalized/combined with non-antibody recognition elements take more than 10 min to deliver the result, especially at low analyte concentrations (typically 30 min) [166,167]. Although assay time is not the most sensitive index in representative scenarios, reduced waiting time would be always appealing to users and can reduce the rate of missed positive result.

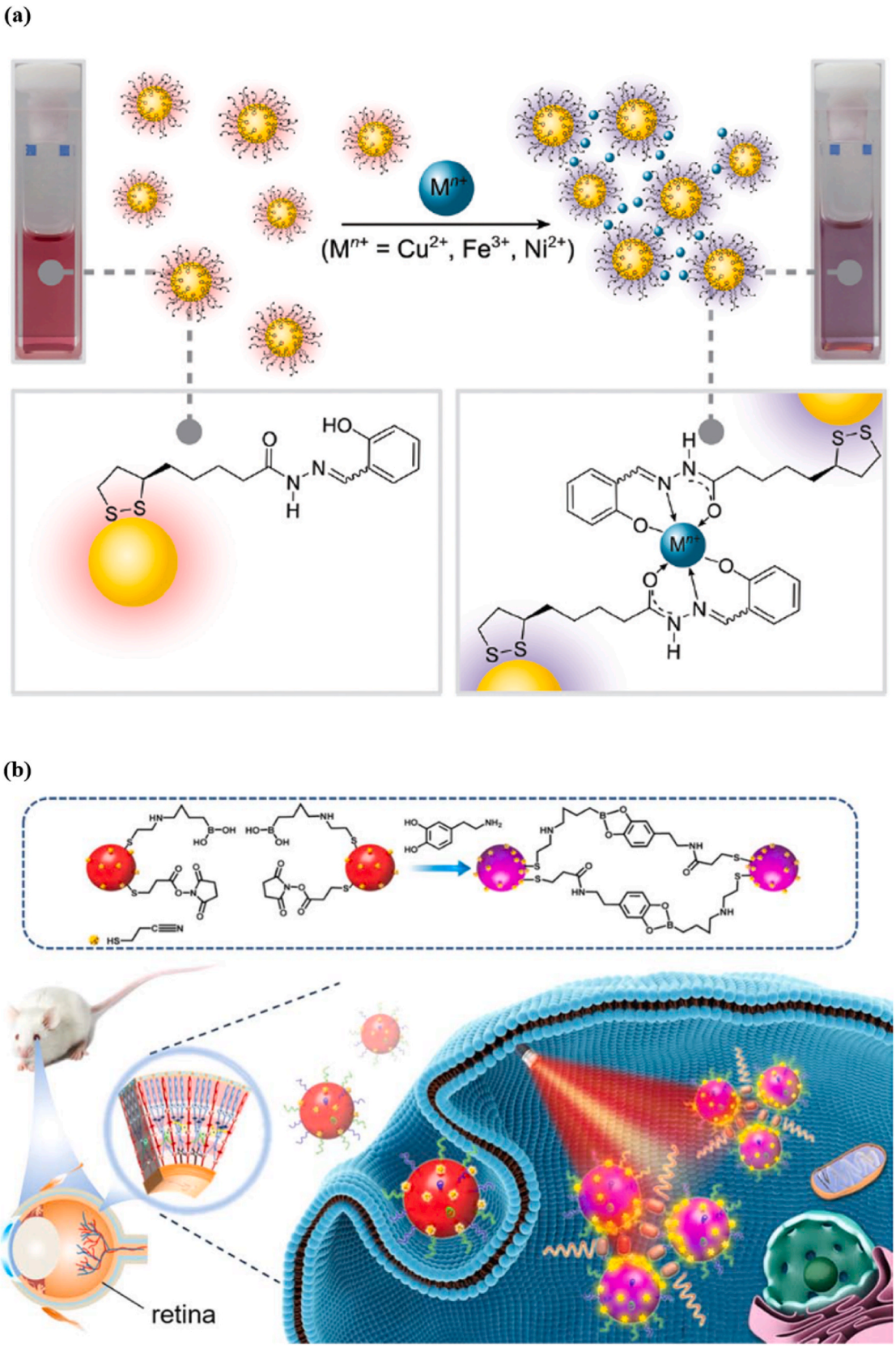

Fig. 10. (a) Colorimetric method based on AuNPs functionalized with Schiff base and demonstrated it for the detection of transition metal ions (Ni^{2+}, Cu^{2+}, Fe^{3+}). The LoDs achieved for the transition metal ions were in the range of 1.4–11.2 nM, which were two orders of magnitude lower than the limits suggested by European Union (EU) (with permission from Royal Society of Chemistry) [96]. (b) Colorimetric sensing of dopamine in living cells and retina using AuNPs functionalized with *N*-hydroxysuccinimide ester. The LoD achieved was estimated to be below 5 μM (with permission from American Chemical Society) [70].

CRediT authorship contribution statement

Hu Chen: Conceptualization, Writing – original draft, Writing – review & editing. **Songtao Cai:** Formal analysis. **Jianxin Luo:** Funding acquisition, Supervision. **Xiaohu Liu:** Investigation. **Lijuan Ou:** Methodology. **Qingwen Zhang:** Validation. **Bo Liedberg:** Writing – original draft, Writing – review & editing. **Yi Wang:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgement

This project was financially supported by Zhejiang Province Natural Science Fund for Distinguished Young Scholars (LR19H180001), Public Projects of Wenzhou (G2020005), Hunan Provincial Natural Science Foundation (2023JJ50100), the Characteristic Application Discipline of Material Science Engineering in Hunan Province (Grants No. [2022] 351), the Science and Technology Innovation Program of Hunan Province, Hunan Provincial Open Fund for Applied Characteristic Discipline (KFB22006), and Guidance Planning Project of Hengyang, China (202222015692).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trac.2024.117654.

References

[1] P. Ugo, et al., Introduction to bioanalytical assays and biosensors, in: Bioanalytical Chemistry, De Gruyter, 2021, pp. 61–102.
[2] W.F. DeGrado, Biosensor design, Nature 423 (2003) 132–133, https://doi.org/10.1038/423132a.
[3] M. Malmqvist, Biospecific interaction analysis using biosensor technology, Nature 361 (1993) 186–187, https://doi.org/10.1038/361186a0.
[4] A. Salim, S. Lim, Recent advances in noninvasive flexible and wearable wireless biosensors, Biosens. Bioelectron. 141 (2019) 111422, https://doi.org/10.1016/j.bios.2019.111422.
[5] L. García-Carmona, et al., Pacifier biosensor: toward noninvasive saliva biomarker monitoring, Anal. Chem. 91 (2019) 13883–13891, https://doi.org/10.1021/acs.analchem.9b03379.
[6] L. Wang, et al., Flexible, graphene-coated biocomposite for highly sensitive, real-time molecular detection, Adv. Funct. Mater. 26 (2016) 8623–8630, https://doi.org/10.1002/adfm.201603550.
[7] A. Romeo, et al., Smart biosensors for multiplexed and fully integrated point-of-care diagnostics, Lab Chip 16 (2016) 1957–1961, https://doi.org/10.1039/C6LC90046A.
[8] Y. Wu, et al., Challenges and solutions in developing ultrasensitive biosensors, J. Am. Chem. Soc. 141 (2019) 1162–1170, https://doi.org/10.1021/jacs.8b09397.
[9] J.-F. Zhang, et al., An ultrasensitive biosensor for high-resolution kinase activity imaging in awake mice, Nat. Chem. Biol. 17 (2021) 39–46, https://doi.org/10.1038/s41589-020-00660-y.
[10] F. Clemente, et al., Last trends in point-of-care (POC) diagnostics for the management of Hematological indices in home care patients, Biosensors 13 (2023) 345.
[11] M. Asif, et al., The role of biosensors in coronavirus disease-2019 outbreak, Curr. Opin. Electrochem. 23 (2020) 174–184, https://doi.org/10.1016/j.coelec.2020.08.011.
[12] A. Gowri, et al., Recent advances in nanomaterials based biosensors for point of care (PoC) diagnosis of Covid-19 – a minireview, TrAC, Trends Anal. Chem. 137 (2021) 116205, https://doi.org/10.1016/j.trac.2021.116205.
[13] J. Kudr, et al., COVID-19: a challenge for electrochemical biosensors, TrAC, Trends Anal. Chem. 136 (2021) 116192, https://doi.org/10.1016/j.trac.2021.116192.
[14] H. Rahimi, et al., CRISPR systems for COVID-19 diagnosis, ACS Sens. 6 (2021) 1430–1445, https://doi.org/10.1021/acssensors.0c02312.
[15] R. Funari, et al., Nanoplasmonic multiplex biosensing for COVID-19 vaccines, Biosens. Bioelectron. 208 (2022) 114193, https://doi.org/10.1016/j.bios.2022.114193.
[16] S. Hsiang, et al., The effect of large-scale anti-contagion policies on the COVID-19 pandemic, Nature 584 (2020) 262–267, https://doi.org/10.1038/s41586-020-2404-8.
[17] S. Lai, et al., Effect of non-pharmaceutical interventions to contain COVID-19 in China, Nature 585 (2020) 410–413, https://doi.org/10.1038/s41586-020-2293-x.
[18] F. Wu, et al., A new coronavirus associated with human respiratory disease in China, Nature 579 (2020) 265–269, https://doi.org/10.1038/s41586-020-2008-3.
[19] R.W. Peeling, et al., Diagnostics for COVID-19: moving from pandemic response to control, Lancet 399 (2022) 757–768, https://doi.org/10.1016/S0140-6736(21)02346-1.
[20] A. Parihar, et al., Point-of-Care biosensor-based diagnosis of COVID-19 holds promise to combat current and future pandemics, ACS Appl. Bio Mater. 3 (2020) 7326–7343, https://doi.org/10.1021/acsabm.0c01083.
[21] S. Suleman, et al., Point of care detection of COVID-19: advancement in biosensing and diagnostic methods, Chem. Eng. J. 414 (2021) 128759, https://doi.org/10.1016/j.cej.2021.128759.
[22] Y. Qi, et al., Portable colorimetric photonic indicator for ethanol concentration sensing, Chem. Eng. J. 457 (2023) 141184, https://doi.org/10.1016/j.cej.2022.141184.
[23] X. Wang, et al., Self-referenced smartphone-based nanoplasmonic imaging platform for colorimetric biochemical sensing, Anal. Chem. 89 (2017) 611–615, https://doi.org/10.1021/acs.analchem.6b02484.
[24] D. Zhang, Q. Liu, Biosensors and bioelectronics on smartphone for portable biochemical detection, Biosens. Bioelectron. 75 (2016) 273–284, https://doi.org/10.1016/j.bios.2015.08.037.
[25] C. Zhao, et al., Design and fabrication of a highly sensitive and naked-eye distinguishable colorimetric biosensor for chloramphenicol detection by using ELISA on nanofibrous membranes, Talanta 217 (2020) 121054, https://doi.org/10.1016/j.talanta.2020.121054.
[26] Z. Zhang, et al., Highly sensitive on-site detection of glucose in human urine with naked eye based on enzymatic-like reaction mediated etching of gold nanorods, Biosens. Bioelectron. 89 (2017) 932–936, https://doi.org/10.1016/j.bios.2016.09.090.
[27] Y. Chen, et al., Low cost smart phone diagnostics for food using paper-based colorimetric sensor arrays, Food Control 82 (2017) 227–232, https://doi.org/10.1016/j.foodcont.2017.07.003.
[28] E. Schoolaert, et al., Colorimetric nanofibers as optical sensors, Adv. Funct. Mater. 27 (2017) 1702646, https://doi.org/10.1002/adfm.201702646.
[29] N. Idros, D. Chu, Triple-Indicator-based multidimensional colorimetric sensing platform for heavy metal ion detections, ACS Sens. 3 (2018) 1756–1764, https://doi.org/10.1021/acssensors.8b00490.
[30] P. Singh, SPR biosensors: historical perspectives and current challenges, Sensor. Actuator. B Chem. 229 (2016) 110–130, https://doi.org/10.1016/j.snb.2016.01.118.
[31] E. Mauriz, Clinical applications of visual plasmonic colorimetric sensing, Sensors 20 (2020) 6214.
[32] Y. Wang, et al., Smartphone spectrometer for colorimetric biosensing, Analyst 141 (2016) 3233–3238, https://doi.org/10.1039/C5AN02508G.
[33] R. Elghanian, et al., Selective colorimetric detection of polynucleotides based on the distance-dependent optical properties of gold nanoparticles, Science 277 (1997) 1078–1081, https://doi.org/10.1126/science.277.5329.1078.
[34] M. Alafeef, et al., RNA-extraction-free nano-amplified colorimetric test for point-of-care clinical diagnosis of COVID-19, Nat. Protoc. 16 (2021) 3141–3162, https://doi.org/10.1038/s41596-021-00546-w.
[35] H.N. Kozlowski, et al., A colorimetric test to differentiate patients infected with influenza from COVID-19, Small Structures 2 (2021) 2100034, https://doi.org/10.1002/sstr.202100034.
[36] B. Liedberg, et al., Biosensing with surface plasmon resonance — how it all started, Biosens. Bioelectron. 10 (1995) i–ix, https://doi.org/10.1016/0956-5663(95)96965-2.
[37] A. Amirjani, D.H. Fatmehsari, Colorimetric detection of ammonia using smartphones based on localized surface plasmon resonance of silver nanoparticles, Talanta 176 (2018) 242–246, https://doi.org/10.1016/j.talanta.2017.08.022.
[38] Y. Wang, et al., A colorimetric biosensor using Fe3O4 nanoparticles for highly sensitive and selective detection of tetracyclines, Sensor. Actuator. B Chem. 236 (2016) 621–626, https://doi.org/10.1016/j.snb.2016.06.029.
[39] J. Zong, et al., Peptide-functionalized gold nanoparticles: versatile biomaterials for diagnostic and therapeutic applications, Biomater. Sci. 5 (2017) 872–886, https://doi.org/10.1039/C7BM00006E.
[40] S. Guo, et al., Enhanced gene delivery and siRNA silencing by gold nanoparticles coated with charge-reversal polyelectrolyte, ACS Nano 4 (2010) 5505–5511, https://doi.org/10.1021/nn101638u.
[41] M. Huang, et al., Fast microwave heating-based one-step synthesis of DNA and RNA modified gold nanoparticles, Nat. Commun. 13 (2022) 968, https://doi.org/10.1038/s41467-022-28627-8.
[42] A. Gupta, et al., Ultrastable and biofunctionalizable gold nanoparticles, ACS Appl. Mater. Interfaces 8 (2016) 14096–14101, https://doi.org/10.1021/acsami.6b02548.

[43] P. Nativo, et al., Uptake and intracellular fate of surface-modified gold nanoparticles, ACS Nano 2 (2008) 1639–1644, https://doi.org/10.1021/nn800330a.
[44] R.J. Kadhim, et al., Biocompatibility of gold nanoparticles: in-vitro and In-vivo study, Mater. Today: Proc. 42 (2021) 3041–3045, https://doi.org/10.1016/j.matpr.2020.12.826.
[45] Y. Wang, et al., Nuclear targeting dynamics of gold nanoclusters for enhanced therapy of HER2+ breast cancer, ACS Nano 5 (2011) 9718–9725, https://doi.org/10.1021/nn2032177.
[46] C. Hanske, et al., Large-Scale plasmonic pyramidal supercrystals via templated self-assembly of monodisperse gold nanospheres, J. Phys. Chem. C 121 (2017) 10899–10906, https://doi.org/10.1021/acs.jpcc.6b12161.
[47] Y.-S. Chen, et al., Miniature gold nanorods for photoacoustic molecular imaging in the second near-infrared optical window, Nat. Nanotechnol. 14 (2019) 465–472, https://doi.org/10.1038/s41565-019-0392-3.
[48] W.-S. Chang, et al., Tuning the acoustic frequency of a gold nanodisk through its adhesion layer, Nat. Commun. 6 (2015) 7022, https://doi.org/10.1038/ncomms8022.
[49] Y. Ma, et al., Gold nanoshell nanomicelles for potential magnetic resonance imaging, light-triggered drug release, and photothermal therapy, Adv. Funct. Mater. 23 (2013) 815–822, https://doi.org/10.1002/adfm.201201663.
[50] P. Si, et al., Gold nanoprisms as optical coherence tomography contrast agents in the second near-infrared window for enhanced angiography in live animals, ACS Nano 12 (2018) 11986–11994, https://doi.org/10.1021/acsnano.8b03862.
[51] T.H. Chow, et al., Colloidal gold nanorings and their plasmon coupling with gold nanospheres, Small 15 (2019) 1902608, https://doi.org/10.1002/smll.201902608.
[52] S.E. Skrabalak, et al., Gold nanocages: synthesis, properties, and applications, Accounts Chem. Res. 41 (2008) 1587–1595, https://doi.org/10.1021/ar800018v.
[53] S. Zeng, et al., A review on functionalized gold nanoparticles for biosensing applications, Plasmonics 6 (2011) 491–506, https://doi.org/10.1007/s11468-011-9228-1.
[54] F. Wang, et al., Cysteine-mediated aggregation of Au nanoparticles: the development of a H2O2 sensor and oxidase-based biosensors, ACS Nano 7 (2013) 7278–7286, https://doi.org/10.1021/nn402810x.
[55] J.M. Zook, et al., Measuring agglomerate size distribution and dependence of localized surface plasmon resonance absorbance on gold nanoparticle agglomerate size using analytical ultracentrifugation, ACS Nano 5 (2011) 8070–8079, https://doi.org/10.1021/nn202645b.
[56] C. Sönnichsen, et al., A molecular ruler based on plasmon coupling of single gold and silver nanoparticles, Nat. Biotechnol. 23 (2005) 741–745, https://doi.org/10.1038/nbt1100.
[57] J. Sun, et al., Colorimetric sensor array based on gold nanoparticles: design principles and recent advances, TrAC, Trends Anal. Chem. 122 (2020) 115754, https://doi.org/10.1016/j.trac.2019.115754.
[58] R.M.T. de Wildt, et al., Antibody arrays for high-throughput screening of antibody–antigen interactions, Nat. Biotechnol. 18 (2000) 989–994, https://doi.org/10.1038/79494.
[59] M. Kundu, et al., Recent developments in biosensors to combat agricultural challenges and their future prospects, Trends Food Sci. Technol. 88 (2019) 157–178, https://doi.org/10.1016/j.tifs.2019.03.024.
[60] A. Bhattacharyya, et al., Performance assessment of new dual-pocket vertical heterostructure tunnel FET-based biosensor considering steric hindrance issue, IEEE Trans. Electron. Dev. 66 (2019) 3988–3993, https://doi.org/10.1109/TED.2019.2928850.
[61] J. Liu, Y. Lu, Stimuli-Responsive disassembly of nanoparticle aggregates for light-up colorimetric sensing, J. Am. Chem. Soc. 127 (2005) 12677–12683, https://doi.org/10.1021/ja053567u.
[62] Y. Wang, et al., Improving nanoparticle-enhanced surface plasmon resonance detection of small molecules by reducing steric hindrance via molecular linkers, Talanta 198 (2019) 350–357, https://doi.org/10.1016/j.talanta.2019.02.035.
[63] R. Cánovas, et al., Are aptamer-based biosensing approaches a good choice for female fertility monitoring? A comprehensive review, Biosens. Bioelectron. 220 (2023) 114881, https://doi.org/10.1016/j.bios.2022.114881.
[64] P. Wentworth, Antibody design by man and nature, Science 296 (2002) 2247–2249, https://doi.org/10.1126/science.296.5576.2247.
[65] F. Mazur, et al., Rapid detection of Listeriolysin O toxin based on a nanoscale liposome–gold nanoparticle platform, ACS Appl. Nano Mater. 3 (2020) 7270–7280, https://doi.org/10.1021/acsanm.0c01602.
[66] D. Aili, et al., Hybrid Nanoparticle−Liposome detection of phospholipase activity, Nano Lett. 11 (2011) 1401–1405, https://doi.org/10.1021/nl1024062.
[67] X. Liu, et al., Peptide functionalized gold nanoparticles with optimized particle size and concentration for colorimetric assay development: detection of cardiac troponin I, ACS Sens. 1 (2016) 1416–1422, https://doi.org/10.1021/acssensors.6b00493.
[68] X. Liu, et al., Dopamine and melamine binding to gold nanoparticles dominates their aptamer-based label-free colorimetric sensing, Anal. Chem. 92 (2020) 9370–9378, https://doi.org/10.1021/acs.analchem.0c01773.
[69] C.-C. Chang, et al., Aptamer-based colorimetric detection of proteins using a branched DNA cascade amplification strategy and unmodified gold nanoparticles, Biosens. Bioelectron. 78 (2016) 200–205, https://doi.org/10.1016/j.bios.2015.11.051.
[70] X. Ren, et al., Dopamine imaging in living cells and retina by surface-enhanced Raman scattering based on functionalized gold nanoparticles, Anal. Chem. 93 (2021) 10841–10849, https://doi.org/10.1021/acs.analchem.1c01108.
[71] C.I.L. Justino, et al., Recent developments in recognition elements for chemical sensors and biosensors, TrAC, Trends Anal. Chem. 68 (2015) 2–17, https://doi.org/10.1016/j.trac.2015.03.006.
[72] A. Sharma, et al., Point of care testing of sports biomarkers: potential applications, recent advances and future outlook, TrAC, Trends Anal. Chem. 142 (2021) 116327, https://doi.org/10.1016/j.trac.2021.116327.
[73] M. Sharafeldin, J.J. Davis, Point of care sensors for infectious pathogens, Anal. Chem. 93 (2021) 184–197, https://doi.org/10.1021/acs.analchem.0c04677.
[74] R. Chapman, et al., Multivalent nanoparticle networks enable point-of-care detection of human phospholipase-A2 in serum, ACS Nano 9 (2015) 2565–2573, https://doi.org/10.1021/nn5057595.
[75] M.N. Holme, et al., A robust liposomal platform for direct colorimetric detection of sphingomyelinase enzyme and inhibitors, ACS Nano 12 (2018) 8197–8207, https://doi.org/10.1021/acsnano.8b03308.
[76] L.-H. Xiong, et al., Ultrasensitive visualization of virus via explosive catalysis of an enzyme muster triggering gold nano-aggregate disassembly, ACS Appl. Mater. Interfaces 12 (2020) 12525–12532, https://doi.org/10.1021/acsami.9b23247.
[77] M.-P.N. Bui, et al., Single-digit pathogen and attomolar detection with the naked eye using liposome-amplified plasmonic immunoassay, Nano Lett. 15 (2015) 6239–6246, https://doi.org/10.1021/acs.nanolett.5b02837.
[78] D. Aili, et al., Colorimetric protein sensing by controlled assembly of gold nanoparticles functionalized with synthetic receptors, Small 5 (2009) 2445–2452, https://doi.org/10.1002/smll.200900530.
[79] P. Chen, et al., Peptide functionalized gold nanoparticles for colorimetric detection of matrilysin (MMP-7) activity, Nanoscale 5 (2013) 8973–8976, https://doi.org/10.1039/C3NR03006G.
[80] X. Liu, et al., Biofunctionalized gold nanoparticles for colorimetric sensing of botulinum neurotoxin A light chain, Anal. Chem. 86 (2014) 2345–2352, https://doi.org/10.1021/ac402626g.
[81] R. Chandrawati, M.M. Stevens, Controlled assembly of peptide-functionalized gold nanoparticles for label-free detection of blood coagulation Factor XIII activity, Chem. Commun. 50 (2014) 5431–5434, https://doi.org/10.1039/C4CC00572D.
[82] Z. Gao, et al., Platinum-decorated gold nanoparticles with dual functionalities for ultrasensitive colorimetric in vitro diagnostics, Nano Lett. 17 (2017) 5572–5579, https://doi.org/10.1021/acs.nanolett.7b02385.
[83] M. Solra, et al., Optical pico-biosensing of lead using plasmonic gold nanoparticles and a cationic peptide-based aptasensor, Chem. Commun. 56 (2020) 289–292, https://doi.org/10.1039/C9CC07407D.
[84] H. Guo, et al., Ordered gold nanoparticle arrays on the tip of silver wrinkled structures for single molecule detection, Sensor. Actuator. B Chem. 300 (2019) 126846, https://doi.org/10.1016/j.snb.2019.126846.
[85] H. Ye, et al., Plasmonic LAMP: improving the detection specificity and sensitivity for SARS-CoV-2 by plasmonic sensing of isothermally amplified nucleic acids, Small 18 (2022) 2107832, https://doi.org/10.1002/smll.202107832.
[86] J. Liu, Y. Lu, A colorimetric lead biosensor using DNAzyme-directed assembly of gold nanoparticles, J. Am. Chem. Soc. 125 (2003) 6642–6643, https://doi.org/10.1021/ja034775u.
[87] J. Liu, Y. Lu, Accelerated color change of gold nanoparticles assembled by DNAzymes for simple and fast colorimetric Pb2+ detection, J. Am. Chem. Soc. 126 (2004) 12298–12305, https://doi.org/10.1021/ja046628h.
[88] J. Liu, Y. Lu, Fast colorimetric sensing of adenosine and cocaine based on a general sensor design involving aptamers and nanoparticles, Angew. Chem. Int. Ed. 45 (2006) 90–94, https://doi.org/10.1002/anie.200502589.
[89] J.H. Soh, et al., Colorimetric detection of small molecules in complex matrixes via target-mediated growth of aptamer-functionalized gold nanoparticles, Anal. Chem. 87 (2015) 7644–7652, https://doi.org/10.1021/acs.analchem.5b00875.
[90] S.-J. Chen, et al., Colorimetric determination of urinary adenosine using aptamer-modified gold nanoparticles, Biosens. Bioelectron. 23 (2008) 1749–1753, https://doi.org/10.1016/j.bios.2008.02.008.
[91] W. Zhu, et al., A colorimetric biosensor for simultaneous ochratoxin A and aflatoxins B1 detection in agricultural products, Food Chem. 319 (2020) 126544, https://doi.org/10.1016/j.foodchem.2020.126544.
[92] F. Xia, et al., Colorimetric detection of DNA, small molecules, proteins, and ions using unmodified gold nanoparticles and conjugated polyelectrolytes, Proc. Natl. Acad. Sci. USA 107 (2010) 10837–10841, https://doi.org/10.1073/pnas.1005632107.
[93] F. Salimi, et al., Colorimetric sensor of detection of Cr (III) and Fe (II) ions in aqueous solutions using gold nanoparticles modified with methylene blue, Optik 158 (2018) 813–825, https://doi.org/10.1016/j.ijleo.2018.01.006.
[94] Q. You, et al., Colorimetric and test stripe-based assay of bacteria by using vancomycin-modified gold nanoparticles, Sensor. Actuator. B Chem. 281 (2019) 408–414, https://doi.org/10.1016/j.snb.2018.10.103.
[95] G. Landa, et al., Selective point-of-care detection of pathogenic bacteria using sialic acid functionalized gold nanoparticles, Talanta 234 (2021) 122644, https://doi.org/10.1016/j.talanta.2021.122644.
[96] M. Čonková, et al., Schiff base capped gold nanoparticles for transition metal cation sensing in organic media, Chem. Commun. 58 (2022) 5773–5776, https://doi.org/10.1039/D2CC00497F.
[97] F. Mazur, et al., Core-satellite gold nanoparticle biosensors for monitoring cobalt ions in biological samples, Sensor. Actuator. B Chem. 268 (2018) 182–187, https://doi.org/10.1016/j.snb.2018.04.089.
[98] P. Duenchay, et al., Application of modifier-free gold nanoparticle colorimetric sensing for rapid screening and detection of vitamin B1, New J. Chem. 44 (2020) 9223–9229, https://doi.org/10.1039/D0NJ01401J.

[99] C. Xu, et al., An unmodified gold nanorods-based DNA colorimetric biosensor with enzyme-free hybridization chain reaction amplification, Sensor. Actuator. B Chem. 273 (2018) 642–648, https://doi.org/10.1016/j.snb.2018.06.035.
[100] B.M. Discher, et al., Polymersomes: tough vesicles made from diblock copolymers, Science 284 (1999) 1143–1146, https://doi.org/10.1126/science.284.5417.1143.
[101] L. Zhang, A. Eisenberg, Multiple morphologies and characteristics of "crew-cut" micelle-like aggregates of polystyrene-b-poly(acrylic acid) diblock copolymers in aqueous solutions, J. Am. Chem. Soc. 118 (1996) 3168–3181, https://doi.org/10.1021/ja953709s.
[102] R.A. Schwendener, H. Schott, Liposome formulations of hydrophobic drugs, in: G. G.M. D'Souza (Ed.), Liposomes: Methods and Protocols, Springer, New York, 2017, pp. 73–82.
[103] N.V. Beloglazova, et al., Quantum dot loaded liposomes as fluorescent labels for immunoassay, Anal. Chem. 85 (2013) 7197–7204, https://doi.org/10.1021/ac401729y.
[104] H. Chen, et al., Reporter-encapsulated liposomes on graphene field effect transistors for signal enhanced detection of physiological enzymes, Phys. Chem. Chem. Phys. 17 (2015) 3451–3456, https://doi.org/10.1039/C4CP04644G.
[105] J. Li, et al., A review on phospholipids and their main applications in drug delivery systems, Asian J. Pharm. Sci. 10 (2015) 81–98, https://doi.org/10.1016/j.ajps.2014.09.004.
[106] W. Liu, et al., Research progress on liposomes: application in food, digestion behavior and absorption mechanism, Trends Food Sci. Technol. 104 (2020) 177–189, https://doi.org/10.1016/j.tifs.2020.08.012.
[107] J.-S. Kim, Liposomal drug delivery system, Journal of Pharmaceutical Investigation 46 (2016) 387–392, https://doi.org/10.1007/s40005-016-0260-1.
[108] M. Haga, et al., Liposome immunosensor for theophylline, Biochem. Biophys. Res. Commun. 95 (1980) 187–192, https://doi.org/10.1016/0006-291X(80)90722-6.
[109] M. Haga, et al., Drug sensor: liposome immunosensor for theophylline, Anal. Biochem. 118 (1981) 286–293, https://doi.org/10.1016/0003-2697(81)90584-4.
[110] J. Liu, et al., CRISPR-/Cas12a-Mediated liposome-amplified strategy for the surface-enhanced Raman scattering and naked-eye detection of nucleic acid and application to food authenticity screening, Anal. Chem. 93 (2021) 10167–10174, https://doi.org/10.1021/acs.analchem.1c01163.
[111] B. Liedberg, et al., Surface plasmon resonance for gas detection and biosensing, Sensor. Actuator. 4 (1983) 299–304, https://doi.org/10.1016/0250-6874(83)85036-7.
[112] A.B. Ganganboina, et al., Dual modality sensor using liposome-based signal amplification technique for ultrasensitive norovirus detection, Biosens. Bioelectron. 157 (2020) 112169, https://doi.org/10.1016/j.bios.2020.112169.
[113] L. Guo, et al., Oriented gold nanoparticle aggregation for colorimetric sensors with surprisingly high analytical figures of merit, J. Am. Chem. Soc. 135 (2013) 12338–12345, https://doi.org/10.1021/ja405371g.
[114] Q. Liu, B.J. Boyd, Liposomes in biosensors, Analyst 138 (2013) 391–409, https://doi.org/10.1039/C2AN36140J.
[115] H. Chen, et al., A review on electronic bio-sensing approaches based on non-antibody recognition elements, Analyst 141 (2016) 2335–2346, https://doi.org/10.1039/C5AN02623G.
[116] D. Aili, M.M. Stevens, Bioresponsive peptide–inorganic hybrid nanomaterials, Chem. Soc. Rev. 39 (2010) 3358–3370, https://doi.org/10.1039/B919461B.
[117] H. Chen, et al., Detection of matrilysin activity using polypeptide functionalized reduced graphene oxide field-effect transistor sensor, Anal. Chem. 88 (2016) 2994–2998, https://doi.org/10.1021/acs.analchem.5b04663.
[118] X. Liu, et al., Rational design of functional peptide–gold hybrid nanomaterials for molecular interactions, Adv. Mater. 32 (2020) 2000866, https://doi.org/10.1002/adma.202000866.
[119] Y. Wang, et al., Time-resolved botulinum neurotoxin A activity monitored using peptide-functionalized Au nanoparticle energy transfer sensors, Chem. Sci. 5 (2014) 2651–2656, https://doi.org/10.1039/C3SC53305K.
[120] G. Goyal, et al., Stoichiometric tuning of PNA probes to Au0.8Ag0.2 alloy nanoparticles for visual detection of nucleic acids in plasma, ACS Sens. 5 (2020) 2476–2485, https://doi.org/10.1021/acssensors.0c00667.
[121] S. Yeasmin, et al., Colorimetric urinalysis for on-site detection of metabolic biomarkers, ACS Appl. Mater. Interfaces 12 (2020) 31270–31281, https://doi.org/10.1021/acsami.0c09179.
[122] G.J. Cotton, et al., Insertion of a synthetic peptide into a recombinant protein framework: a protein biosensor, J. Am. Chem. Soc. 121 (1999) 1100–1101, https://doi.org/10.1021/ja983804b.
[123] P.C. Lyu, et al., Side chain contributions to the stability of alpha-helical structure in peptides, Science 250 (1990) 669–673, https://doi.org/10.1126/science.2237416.
[124] R.B. Merrifield, Solid phase peptide synthesis. I. The synthesis of a tetrapeptide, J. Am. Chem. Soc. 85 (1963) 2149–2154, https://doi.org/10.1021/ja00897a025.
[125] D. Aili, et al., Aggregation-induced folding of a de novo designed polypeptide immobilized on gold nanoparticles, J. Am. Chem. Soc. 128 (2006) 2194–2195, https://doi.org/10.1021/ja057056j.
[126] J.I. Lee, et al., Colorimetric allergenic fungal spore detection using peptide-modified gold nanoparticles, Sensor. Actuator. B Chem. 327 (2021) 128894, https://doi.org/10.1016/j.snb.2020.128894.
[127] Z. Jin, et al., A charge-switchable zwitterionic peptide for rapid detection of SARS-CoV-2 main protease, Angew. Chem. Int. Ed. 61 (2022) e202112995, https://doi.org/10.1002/anie.202112995.
[128] L. Liu, et al., A colorimetric strategy for assay of protease activity based on gold nanoparticle growth controlled by ascorbic acid and Cu(II)-coordinated peptide, Sensor. Actuator. B Chem. 266 (2018) 246–254, https://doi.org/10.1016/j.snb.2018.03.116.
[129] S. Feng, et al., Colorimetric detection of creatinine using its specific binding peptides and gold nanoparticles, New J. Chem. 44 (2020) 15828–15835, https://doi.org/10.1039/D0NJ03860A.
[130] A. Kaur, et al., Gliadin-coated gold nanoparticles for rapid colorimetric test for celiac disease, Materials Advances 1 (2020) 2483–2491, https://doi.org/10.1039/D0MA00495B.
[131] E. Tu, et al., Comparison of colorimetric analyses to determine cortisol in human sweat, ACS Omega 5 (2020) 8211–8218, https://doi.org/10.1021/acsomega.0c00498.
[132] S. Pavan, F. Berti, Short peptides as biosensor transducers, Anal. Bioanal. Chem. 402 (2012) 3055–3070, https://doi.org/10.1007/s00216-011-5589-8.
[133] A.D. Ellington, J.W. Szostak, In vitro selection of RNA molecules that bind specific ligands, Nature 346 (1990) 818–822, https://doi.org/10.1038/346818a0.
[134] C. Tuerk, L. Gold, Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase, Science 249 (1990) 505–510, https://doi.org/10.1126/science.2200121.
[135] T. Hermann, D.J. Patel, Adaptive recognition by nucleic acid aptamers, Science 287 (2000) 820–825, https://doi.org/10.1126/science.287.5454.820.
[136] A. Chen, S. Yang, Replacing antibodies with aptamers in lateral flow immunoassay, Biosens. Bioelectron. 71 (2015) 230–242, https://doi.org/10.1016/j.bios.2015.04.041.
[137] R. de la Rica, et al., Enzyme-responsive nanoparticles for drug release and diagnostics, Adv. Drug Deliv. Rev. 64 (2012) 967–978, https://doi.org/10.1016/j.addr.2012.01.002.
[138] G. Ammanath, et al., Colorimetric and fluorometric profiling of advanced glycation end products, ACS Appl. Mater. Interfaces 14 (2022) 94–103, https://doi.org/10.1021/acsami.1c16261.
[139] J. Zhou, J. Rossi, Aptamers as targeted therapeutics: current potential and challenges, Nat. Rev. Drug Discov. 16 (2017) 181–202, https://doi.org/10.1038/nrd.2016.199.
[140] S.L. Bidinger, et al., Pulsed transistor operation enables miniaturization of electrochemical aptamer-based sensors, Sci. Adv. 8 (2022) eadd4111, https://doi.org/10.1126/sciadv.add4111.
[141] S. Song, et al., Aptamer-based biosensors, TrAC, Trends Anal. Chem. 27 (2008) 108–117, https://doi.org/10.1016/j.trac.2007.12.004.
[142] H. Li, et al., Dual-reporter drift correction to enhance the performance of electrochemical aptamer-based sensors in whole blood, J. Am. Chem. Soc. 138 (2016) 15809–15812, https://doi.org/10.1021/jacs.6b08671.
[143] K. Sefah, et al., Development of DNA aptamers using Cell-SELEX, Nat. Protoc. 5 (2010) 1169–1185, https://doi.org/10.1038/nprot.2010.66.
[144] D.A. Daniels, et al., A tenascin-C aptamer identified by tumor cell SELEX: systematic evolution of ligands by exponential enrichment, Proc. Natl. Acad. Sci. USA 100 (2003) 15416–15421, https://doi.org/10.1073/pnas.2136683100.
[145] Y. Wang, et al., Recent advance of RNA aptamers and DNAzymes for MicroRNA detection, Biosens. Bioelectron. 212 (2022) 114423, https://doi.org/10.1016/j.bios.2022.114423.
[146] W. Zhang, et al., Functional nucleic acids as modular components against SARS-CoV-2: from diagnosis to therapeutics, Biosens. Bioelectron. 201 (2022) 113944, https://doi.org/10.1016/j.bios.2021.113944.
[147] M. Berezovski, et al., Non-SELEX selection of aptamers, J. Am. Chem. Soc. 128 (2006) 1410–1411, https://doi.org/10.1021/ja056943j.
[148] M.V. Berezovski, et al., Non-SELEX: selection of aptamers without intermediate amplification of candidate oligonucleotides, Nat. Protoc. 1 (2006) 1359–1369, https://doi.org/10.1038/nprot.2006.200.
[149] G. Mayer, et al., Fluorescence-activated cell sorting for aptamer SELEX with cell mixtures, Nat. Protoc. 5 (2010) 1993–2004, https://doi.org/10.1038/nprot.2010.163.
[150] J.J. Storhoff, et al., What controls the optical properties of DNA-linked gold nanoparticle assemblies? J. Am. Chem. Soc. 122 (2000) 4640–4650, https://doi.org/10.1021/ja993825l.
[151] J. Liu, Y. Lu, Preparation of aptamer-linked gold nanoparticle purple aggregates for colorimetric sensing of analytes, Nat. Protoc. 1 (2006) 246–252, https://doi.org/10.1038/nprot.2006.38.
[152] K. Szeto, et al., RAPID-SELEX for RNA aptamers, PLoS One 8 (2013) e82667, https://doi.org/10.1371/journal.pone.0082667.
[153] J. Wu, et al., Recent trends in SELEX technique and its application to food safety monitoring, Mikrochim. Acta 181 (2014) 479–491, https://doi.org/10.1007/s00604-013-1156-7.
[154] H. Yu, et al., Advances and challenges in small-molecule DNA aptamer isolation, characterization, and sensor development, Angew. Chem. Int. Ed. 60 (2021) 16800–16823, https://doi.org/10.1002/anie.202008663.
[155] J. Canoura, et al., High-throughput quantitative binding analysis of DNA aptamers using exonucleases, Nucleic Acids Res. 51 (2023), https://doi.org/10.1093/nar/gkac1210 e19-e19.
[156] J. Yang, et al., Recent advances in colorimetric sensors based on gold nanoparticles for pathogen detection, Biosensors 13 (2023) 29.
[157] Y. Shen, et al., Recent advances in nanotechnology for simultaneous detection of multiple pathogenic bacteria, Nano Today 38 (2021) 101121, https://doi.org/10.1016/j.nantod.2021.101121.
[158] Z. Xu, et al., Machine learning assisted dual-emission fluorescence/colorimetric sensor array detection of multiple antibiotics under stepwise prediction strategy, Sensor. Actuator. B Chem. 359 (2022) 131590, https://doi.org/10.1016/j.snb.2022.131590.

[159] J. Tang, et al., Optical-switch-Enabled microfluidics for sensitive multichannel colorimetric analysis, Anal. Chem. 93 (2021) 6784–6791, https://doi.org/10.1021/acs.analchem.1c00674.
[160] J. Liu, et al., Point-of-care testing based on smartphone: the current state-of-the-art (2017–2018), Biosens. Bioelectron. 132 (2019) 17–37, https://doi.org/10.1016/j.bios.2019.01.068.
[161] B. Liu, et al., Recent advances in the design of colorimetric sensors for environmental monitoring, Environ. Sci.: Nano 7 (2020) 2195–2213, https://doi.org/10.1039/D0EN00449A.
[162] H. Jans, Q. Huo, Gold nanoparticle-enabled biological and chemical detection and analysis, Chem. Soc. Rev. 41 (2012) 2849–2866, https://doi.org/10.1039/C1CS15280G.
[163] W. Zhou, et al., Gold nanoparticles for in vitro diagnostics, Chem. Rev. 115 (2015) 10575–10636, https://doi.org/10.1021/acs.chemrev.5b00100.
[164] R. Wang, et al., Cost effective surface functionalization of gold nanoparticles with a mixed DNA and PEG monolayer for nanotechnology applications, RSC Adv. 7 (2017) 3676–3679, https://doi.org/10.1039/C6RA26791B.
[165] B. Baruah, et al., One-phase synthesis of surface modified gold nanoparticles and generation of SERS substrate by seed growth method, Langmuir 28 (2012) 15168–15176, https://doi.org/10.1021/la302861b.
[166] X. Mao, et al., Disposable nucleic acid biosensors based on gold nanoparticle probes and lateral flow strip, Anal. Chem. 81 (2009) 1660–1668, https://doi.org/10.1021/ac8024653.
[167] A. Alizadeh, et al., Rapid and selective lead (II) colorimetric sensor based on azacrown ether-functionalized gold nanoparticles, Nanotechnology 21 (2010) 315503, https://doi.org/10.1088/0957-4484/21/31/315503.

Hu Chen is currently a research associate professor at Hunan Institute of Technology. He obtained his B. Eng. (Hons) degree in 2012 from Nanyang Technological University and Ph.D. degree in 2016 from the same university. His research interests include development of electrical and optical biosensors based on non-antibody recognition elements.

Bo Liedberg is a retired professor of materials science and director of the Center for Biomimetic Sensor Science, Nanyang Technological University, Singapore. He was formerly a full professor of sensor science and molecular physics at Linköping University, Sweden (2015). His research interests include soft materials science (surface chemistry, self-assembly, supramolecular chemistry, and biomimetics), and development of new biosensor and diagnostic tools for field applications.

Yi Wang is currently a full professor at Wenzhou Medical University and Wenzhou Institute, University of Chinese Academy of Sciences. He obtained his Ph.D. degree in 2010 from the Max-Planck Institute for Polymer Research in Mainz, Germany. After that, he worked as a research fellow at the Austrian Institute of Technology, Austria, and Nanyang Technological University, Singapore, from 2011 to 2015. His research interests include the development of plasmonic nanostructures, nanocomposites, novel polymers, and peptide-functionalized materials for optical and electrical biosensors.