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Emerging Biohybrids of Aptamer-Based Nano-Biosensing Technologies for Effective Early Cancer Detection

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Abstract
Cancer is a leading global cause of mortality, which underscores the imperative of early detection for improved patient outcomes. Biorecognition molecules, especially aptamers, have emerged as highly effective tools for early and accurate cancer cell identification. Aptamers, with superior versatility in synthesis and modification, offer enhanced binding specificity and stability compared with conventional antibodies. Hence, this article reviews diagnostic strategies employing aptamer-based biohybrid nano-biosensing technologies, focusing on their utility in detecting cancer biomarkers and abnormal cells. Recent developments include the synthesis of nano-aptamers using diverse nanomaterials, such as metallic nanoparticles, metal oxide nanoparticles, carbon-derived substances, and biohybrid nanostructures. The integration of these nanomaterials with aptamers significantly enhances sensitivity and specificity, promising innovative and efficient approaches for cancer diagnosis. This convergence of nanotechnology with aptamer research holds the potential to revolutionize cancer treatment through rapid, accurate, and non-invasive diagnostic methods.

Key Points

This article reviews diagnostic strategies employing aptamer-based biohybrid nano-biosensing technologies, focusing on their utility in detecting cancer biomarkers and abnormal cells.

The integration of nanomaterials with aptamers significantly enhances sensitivity and specificity, promising innovative and efficient approaches for early cancer diagnosis.

The convergence of nanotechnology with aptamer research holds the potential to revolutionize cancer treatment through rapid, accurate, and non-invasive diagnostic methods.

1 Introduction

Cancer is a fatal disease characterized by the uncontrolled growth and proliferation of cells, which has been a leading cause of mortality among humans for decades [1, 2]. In advanced stages of cancer, these abnormal cells spread to other parts of the human body [3]. In fact, the mortality rate of the cancer depends on the cancer type as summarized in Fig. S1 of the Electronic Supplementary Material (ESM) [4, 5]. Early diagnosis and detection of cancer have a significant impact on the cancer patients' survival rate and quality of life [6, 7]. At present, cancer diagnosis involves histopathology, cytology, and imaging techniques [8]. Histopathology can be used to examine the cell shape and tissue distribution regularities and diagnose cancer-affected organs or tissues as well as their malignancy level [9, 10]. However, certain limitations such as sampling errors, needle tract seeding,

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and a small morbidity risk exist in histopathology, which limits their application for specific cancer detection [11]. Further, cytology is the analysis of cancer cell types in fluid specimens, which is safe, simple, quick, and a cost-effective method for cancer diagnosis [12]. However, the results of cytology are not always accurate and can be used only as a preliminary cancer diagnostic tool, not as a confirmatory test [13]. Furthermore, imaging techniques, such as a computed tomography scan [14], a magnetic resonance imaging scan [15], breast magnetic resonance imaging [16], radiographic tests including X-ray analysis [17], mammography [18], nuclear medicine scans [19], and ultrasound [20] are recently utilized for the early or precision cancer diagnosis. However, radiation exposure, poor soft-tissue contrast, low spatial resolution, low acquisition time, limited sensitivity, and expensiveness are the limitations of these methods [21]. Additionally, all these diagnostic methods suffer from poor sensitivity as a common limitation [22]. Thus, the early detection of cancer remains a huge challenge and requires a novel material that can detect several cancer types with high sensitivity.

Antibodies and aptamers, as biorecognition molecules, have been effectively utilized for the early and accurate detection of cancer cells [23]. Compared with antibodies, which are considered first-generation ligands, aptamers offer more flexibility in synthesis and modification for targeting specific analytes [24]. For example, nucleic acid aptamers can efficiently target cancer biomarkers through a more straightforward approach, whereas the production of antibodies targeting such biomarkers involves more complex and stringent processes [25, 26]. The superior attributes of aptamers, such as high affinity and specificity, ease of synthesis, excellent reproducibility, long-term stability, and ease of transportation, position them as superior detection materials compared with antibodies. These qualities make aptamers valuable in biorecognition for both disease diagnosis and therapeutic applications [27]. The integration of aptamers with nanoparticles (NPs) has opened new frontiers in the enhancement of biosensing performance, particularly in the field of cancer detection. Nanoparticles, with their unique physicochemical properties such as a high surface area [28], optical and electronic characteristics [29], and the ability to facilitate signal amplification [30] complement the high specificity and affinity of aptamers towards their target molecules [31]. This synergy enhances the overall sensitivity and selectivity of biosensors [32], where the aptamer targets specific cancer-related markers and NP amplifies the signals to elevate biosensing ability [33]. This article discusses various diagnostic strategies developed using aptamer-based nanobiosensing technologies for effective cancer diagnosis. This involves the detection of cancer biomarkers or cells. Additionally, it discusses recent advancements in the synthesis of nano-aptamers by incorporating various nanomaterials, including metallic NPs, metal-oxide NPs, carbon-derived materials, and biohybrid nanostructured materials. These innovations represent a significant stride in cancer diagnostics, offering new possibilities for sensitive, specific, and efficient cancer detection.

2 Overview of Aptamers for Biosensor Applications

Recently, it can be noted that the publications with the keywords 'aptamer' and 'biosensors' have been increasing gradually from 1998 as shown in Fig. S2(A) of the ESM. This reveals that there is an extensive research in the field of aptamers for biosensor applications, which has been further improved from 2010 to 2019. The summary of publications from 2010 to 2019 with keywords 'aptasensor' and 'nanomaterials' is presented in Fig. S2(B) of the ESM, which shows that the inclusion of nanomaterials with aptamer-based sensors are gaining attention among researchers to improve their biomolecule monitoring capability.

Aptamers are primarily DNA or RNA oligonucleotides that possess a three-dimensional structure, playing a significant role in highly specific target binding with biomolecules. They are widely used in diagnostic and therapeutic tools and can be obtained through a process known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX), as shown in Fig. 1 [34].

2.1 DNA Aptamer

DNA aptamers identified by the SELEX approach can be successfully employed in biosensor applications as biomarkers without the specific requirement for antibodies as shown in Fig. 2 [35]. Recently, Pundir et al. designed a novel DNA aptamer that is specific to salivary melatonin, proving beneficial for the diagnosis of circadian clock and sleep disorders. The circular dichroism studies showed that the conformational structure of the aptamer was modified via a cationic effect upon melatonin recognition. Additionally, the study emphasized that the truncated hairpin-structured aptamer possesses the lowest detection limit and highest binding affinity towards salivary melatonin [36]. Furthermore, Joseph and colleagues produced a novel biomarker named HMGB1 to detect *Plasmodium falciparum*. This biomarker, having a folded three-dimensional structure, can detect the parasite through all stages of blood infection. It has been identified that single-stranded DNA nucleotide-based aptamers can tightly bind to recognize HMGB1, where the specificity of the aptamer was improved by 14 SELEX cycles. A fluorescent probe was also introduced to monitor the molecular interaction between the bound and unbound state of the ligand with aptamers, which eventually

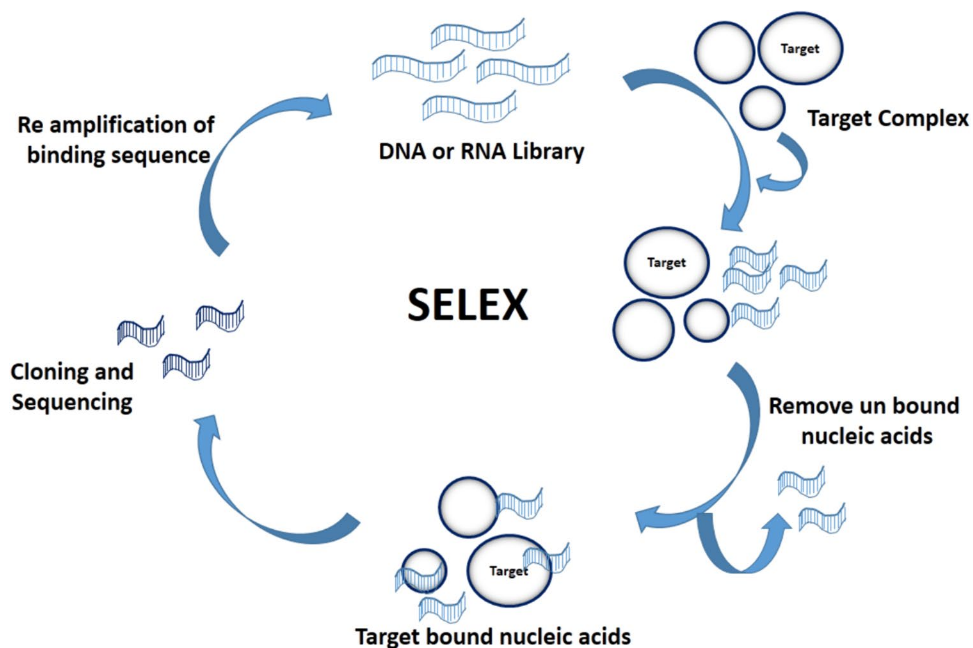

Fig. 1 Mechanism of the SELEX (Systematic Evolution of Ligands by Exponential Enrichment) process for the generation of aptamers

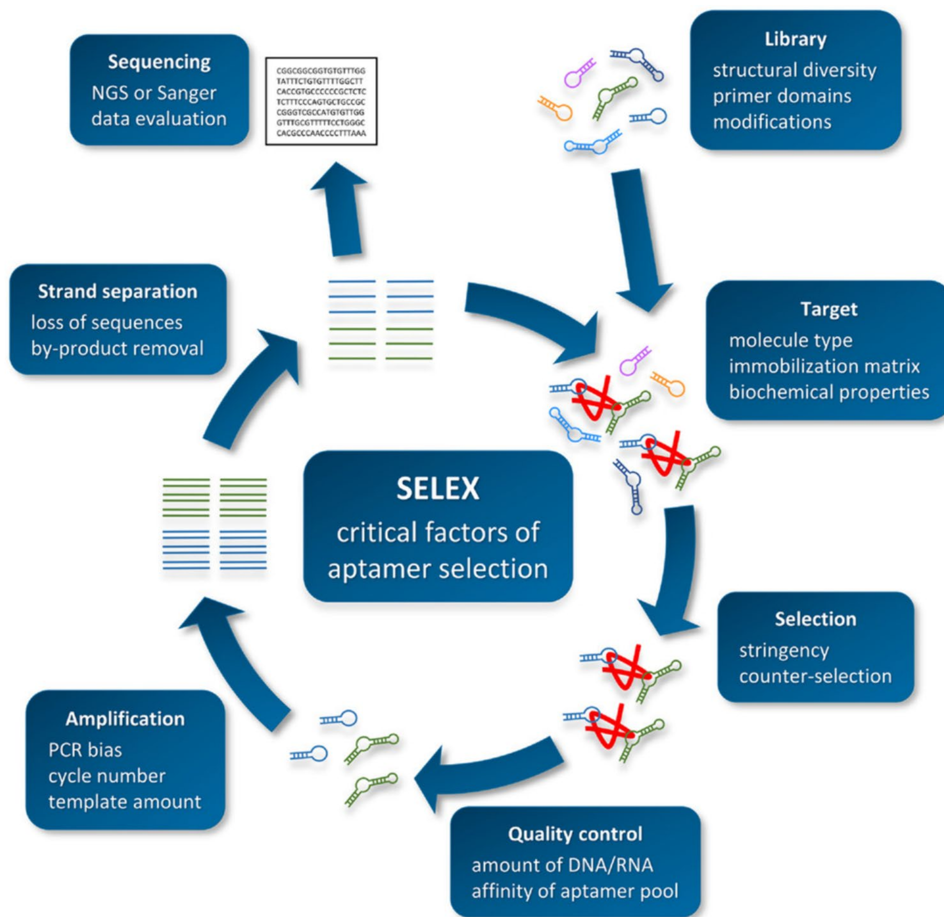

Fig. 2 Scheme of SELEX (Systematic Evolution of Ligands by Exponential Enrichment) procedure for the successful selection of aptamers. *NGS* next-generation sequencing, *PCR* polymerase chain reaction. Reproduced with permission from Kohlberger et al. (2022) [35], ©International Union of Biochemistry and Molecular Biology, 2024

helped identify the mechanism of aptamers in biomarker detection [37]. Thus, DNA-based aptamers are reportedly used as a specific receptor for the biomarker to diagnose malaria in low-income countries. Additionally, Kushwaha et al. introduced the Systematic Enrichment of Ligands by Competitive Selection (SELCOS) approach for the selection of multiple site-targeting aptamers. The selected aptamers were monitored by the electrochemical sensing method, targeting subtypes of the influenza A virus, namely H1N1 and H3N2. The core advantage of this selection method is that aptamers can selectively bind to relative targets with high specificity. Differential pulse voltammetry results indicated that the selected aptamer exhibited stronger affinity towards the specific target, compared with conventional SELEX aptamers. Theoretical studies proved that SELCOS is more convenient compared with the polymerase chain reaction method, as it reduces a few process steps [38]. Moreover, Stoltenburg et al. established the Capture-SELEX procedure to select DNA aptamers for solute targets. In this approach, the DNA sequence, after the docking process, was immobilized on magnetic beads that exhibit high affinity towards specific target molecules. During the aptamer selection process, target molecules were immobilized on the solid surface. DNA aptamers synthesized using this approach were constructed to selectively target the aminoglycoside antibiotic kanamycin A via hydrogen bonds [39]. Recently, Wang et al. fabricated a novel inhibitory DNA aptamer to target the apurinic/apyrimidinic endonuclease 1 enzyme, which is crucial for the base excision repair pathway during DNA repair. The study emphasized that the aptamer possesses a high binding affinity toward the enzyme with a dissociation constant (K_d) of 1.306 ± 0.1418 nanomolar (nM) [40]. Likewise, Yin et al. prepared a novel DNA aptamer named VDBA14 for the effective monitoring of 25-hydroxyvitamin D3, which is beneficial for the rapid diagnosis of vitamin D deficiency. The aptamers were immobilized on a gold (Au) surface via a disulfide linker, and their electrochemical response was monitored using systematic characterization approaches such as square wave voltammetry, cyclic voltammetry, and electrochemical impedance spectroscopy. The results showed that the electrochemical aptamer-based sensor possesses a wide linear range of 1–1000 nm with a limit of detection of 0.085 nM and high selectivity and sensitivity for detecting 25-hydroxyvitamin D3 in human serum samples [41]. Additionally, Mann et al. selected an in vitro single-stranded DNA aptamer for its effective binding with the small moiety ethanolamine as the target biomolecule, even at a nanomolar concentration. In this study, the aptamers were marked by a fluorescent label for the quantification of DNA, and target molecules were immobilized on a magnetic bead, selectively binding with the aptamers, and further amplified using polymerase chain reaction. The K_d study proved that the aptamers successfully target and bind with ethanolamine. The study also revealed that the selected aptamers could be used to target mono-ethanolamine, di-ethanolamine, and tri-ethanolamine [42]. Thus, it is noteworthy that DNA aptamers possess enhanced stability and a relatively simple selection process as potential advantages for use in biosensor applications, compared with RNA aptamers [43]. However, these aptamers have been identified to degrade rapidly in blood within a few minutes, which is a short period for the detection of biomolecules [44].

2.2 RNA Aptamer

Similar to DNA aptamers, RNA-based aptamers are also currently utilized in biosensor applications, especially for disease diagnosis. Shien Yeoh et al. recently synthesized a novel RNA aptamer, named LepRapt-11, that is specific to a major leptospiral outer membrane protein known as LipL32, which exists in pathogenic *Leptospira* bacterial species for the diagnosis of leptospirosis. In this study, a modified SELEX approach named 'tripartite-hybrid SELEX' with three distinct partitioning strategies, such as microtiter plate, nitrocellulose filter membrane, and native polyacrylamide gel electrophoresis-based separation, was used. The aptamer specific to the LipL32 protein was eventually applied in the development of a direct enzyme-linked aptamer sorbent assay for disease diagnosis [45]. Similarly, Ospina-Villa et al. selected an RNA aptamer using the SELEX method to target a polyadenylation factor named EhCFIm25 protein of *Entamoeba histolytica* to induce cell death. The target protein was recognized by the GUUG motif because of electrostatic interactions. The RNA loops were folded to form alpha-helix-like structures known as molecular switches, which act as an RNA-binding pocket for the effective binding of the EhCFIm25 protein. The selected aptamers, named C4 and C5, alter the poly(A) site and inhibit the growth of parasites. These RNA aptamers were also found to possess high affinity and selectivity towards *Trypanosoma cruzi* [46]. Likewise, myco-lactone, a lipid chemical produced by *Mycobacterium ulcerans*, is responsible for their virulent nature. Sakyi et al. described the use of RNA aptamers to target mycolactone for the diagnosis of Buruli ulcer [47]. Moreover, Weiss et al. modified RNA aptamers for the recognition of a fusion of Syrian golden hamster prion protein named rPrP23-231 (rPrPc) to glutathione *S*-transferase. The study showed that the unmodified RNA aptamers could not recognize the fusion owing to the absence of 67 amino acids in the N-terminal of the rPrPc protein. Modified RNA aptamers were added to brain homogenates from scrapie-infected mice, and a western blot assay was used to detect the protein. The results revealed that the aptamer detected proteinase K-resistant PrP27-30, which indicated that PrPc was soluble and sensitive in uninfected brain homogenate for the effective diagnosis of transmissible spongiform encephalopathies

[48]. It is evident from these studies that RNA aptamers possess advantages, such as high affinity and specificity towards specific targets, that are approved by the US Food and Drug Administration for biosensor applications [49]. However, RNA aptamers are prone to rapid degradation owing to their interaction with biomolecules in biological media, which is their major limitation for use in biosensors [50]. Additionally, it can be noted that DNA aptamers are highly stable with low manufacturing costs, whereas RNA aptamers have stronger intra-strand RNA-RNA interactions with diverse three-dimensional conformations, leading to increased binding specificity and affinity [51]. All these studies highlight that aptamers are highly beneficial for the binding of target biomolecules and are useful as efficient disease diagnosis agents, compared with antibodies.

3 Aptamers in Cancer Diagnosis

Cancer is one of the major leading causes of death worldwide [52]. Environmental pollution, changes in lifestyle, and heredity are the significant factors that have elevated the incidence and risk of cancer in recent times [53]. Early diagnosis of cancer remains a challenge that could have a great impact on the death rate and also improve the quality of patients' lives [54, 55]. Hence, specific, low-cost biomarkers with high affinity are required to detect cancer at an early stage [56]. Several studies have identified that aptamers have great potential to detect cancer because of their unique properties [57, 58]. These aptamers could be linked to various diagnostic agents based on the type of cancer through physical or chemical conjugation to improve their diagnostic efficiency [59].

3.1 Breast Cancer

Breast cancer is the second leading cause of death among women worldwide [60]. The diagnosis of breast cancer using aptamers has gained more attention owing to their exclusive properties, such as high specificity, non-immunogenicity, stability, and repeated mention of 'affinity' corrected [61]. Recently, Liu et al. utilized a biotin-labeled human epidermal growth factor receptor 2 (HER2)-specific aptamer for the targeted recognition of HER2. The aptamers were labeled with streptavidin-alkaline phosphatase as detection probes for electrochemical signal generation, which could be beneficial as a potential electrochemical biosensor for breast cancer diagnosis as shown in Fig. 3. The biosensor has been reported to have an efficiency for the detection of about 0.23 pg/mL of HER2 within a 1.0 pg/mL to 100 ng/mL linear range, as well as reproducibility and accuracy [62]. Likewise, Liu et al. produced an MF3 single-stranded DNA aptamer against MCF-7 breast cancer cells. The Cell-SELEX method was used to select the aptamers, and fluorescence intensity measurements indicated better specificity of the selected aptamers. These MF3 aptamers were stable in serum for about 4 h. In vivo studies showed higher fluorescence efficiency in tumor-bearing mice at 1 h. These results demonstrated that the MF3 aptamers could be employed for the successful diagnosis of MCF-7 breast cancer cells [63]. Similarly, Li et al. selected the M3 aptamer to diagnose circulating breast cancer cells. In this study, aptamers tagged with a fluorescent label were used for the detection of cancer cells. Flow cytometry studies revealed that these aptamers possess the ability to detect highly metastatic MDA-MB-231 cells, which was reflected by higher fluorescence intensity. In vitro cell line studies proved that the M3 aptamers can specifically bind to the breast cancer cell line (target) without any affinity towards normal cells [64].

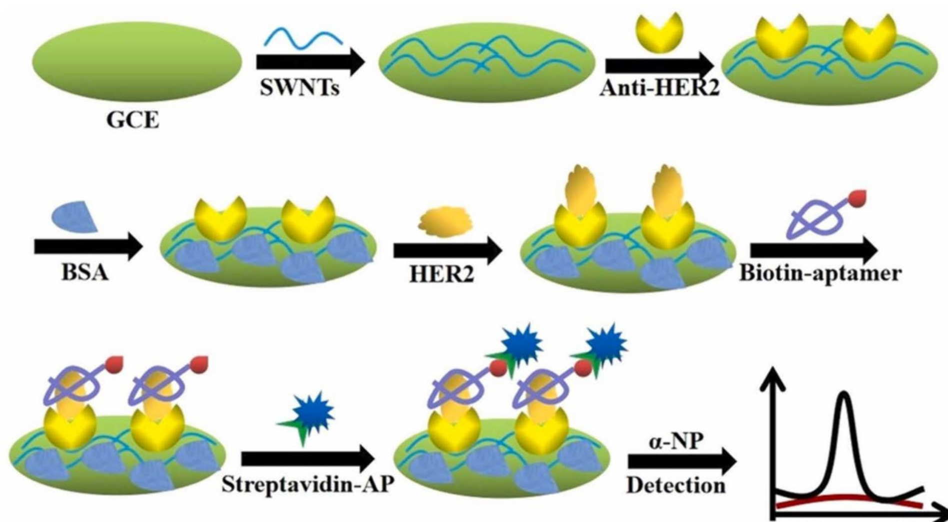

Fig. 3 Schematics of electrochemical immunosensor with biotin-aptamer specific to human epidermal growth factor receptor 2 (HER2) for breast cancer diagnosis. *AP* alkaline phosphatase, *BSA* bovine serum albumin, *GCE* glassy carbon electrode, *NP* nanoparticle, *SWNTs* single-walled nanotubes. Reproduced with permission from Liu et al. (2023) [62], ©Elsevier, 2023

3.2 Prostate Cancer

Prostate cancer is one of the most common cancer types diagnosed among the male population [65]. This type of cancer affects the prostate gland of the patient, which is a part of the male reproductive system [66]. Numerous research groups have reported the use of aptamers for the diagnosis of prostate cancer. Recently, Takita et al. demonstrated the design of an electrochemical biosensor in combination with the transduction of methylene blue-labeled RNA-based aptamer using differential pulse voltammetry. The biosensor was proposed to be useful for the detection of prostate cancer with the help of an aptamer specific to prostate-specific antigen gene 3 (PCA3), where methylene blue is used as a redox indicator. The biosensor was identified to possess a low detection limit of 0.1 pM with an affinity constant (K_D) of 3.0×10^{-8} M [56]. Furthermore, Wang et al. reported that the novel Wy-5a DNA aptamer possesses an enhanced ability to detect prostate cancer. The prostatic adenocarcinoma (PC-3) cells have been isolated from a patient with androgen-independent cancer diagnosed with bone metastasis. The target cells exhibited a high intensity because of the binding of the aptamer, compared with control cells, as evidenced through flow cytometry studies [67]. In addition, Duan et al. fabricated novel DML-7 aptamers for the diagnosis of metastatic prostate cancer. The flow cytometry results showed the binding ability of the aptamers to the cancer cells. The results revealed that the Cy5-labeled DML-7 aptamer exhibits excellent binding affinity and high selectivity for prostate cancer cells [68]. Moreover, Campos et al. described the use of modified oligonucleotides for prostate cancer detection. The modified mA4 aptamer was chemically stable owing to the putative binding sites in the protein structure. The three-dimensional structured aptamers were identified to have high-affinity binding sites towards their target (prostate cancer). In vitro studies indicated that the aptamers were able to bind to the surface of neoplastic human prostate cells (PC-3 cells) and could be used as a potential diagnostic tool [69]. Additionally, Huang et al. synthesized the Xq-2-C1 aptamer for the diagnosis of prostate cancer. In this study, four specific aptamers were selected after the 13th cycle of the SELEX process, which are highly selective to prostate cancer cells. The hairpin loop structure of the aptamer was identified to be crucial for the binding interactions with the target. The laser confocal microscopic images emphasized that the Xq-2-C1 aptamer possesses an enhanced ability to effectively recognize prostate cancer tissues [70].

3.3 Lung Cancer

Globally, lung cancer remains one of the most serious cancerous conditions with a high death rate [71]. Recently, Chen et al. utilized an S1 aptamer to design a novel multivalent activatable probe to specifically recognize lung adenocarcinoma (A549) cells. The study showed that the aptameric probe possesses excellent sensitivity and specificity, with a reduced background signal and a lowest detection limit of 6 cells per 200 μL [72], as shown in Fig. 4. Furthermore, non-small-cell lung cancer (NSCLC) is a common type of lung cancer that affects about 85% of patients [73]. Wang et al. reported that a bifunctional synthetic RNA aptamer and its truncated form, named syn-RA16 and trans-RA16 RNA aptamers prepared via in vivo SELEX, can potentially target and inhibit NSCLC. The truncated trans-RA16 RNA aptamer has been shown to possess a binding affinity toward NCI-H460 (NSCLC) cells with a K_D value of 63.20 ± 0.91 nM and a cell growth inhibition rate of 39.32 ± 3.25% at 150 nM. Thus, the aptamer was proposed to be beneficial for the construction of a novel biosensor for NSCLC detection [74]. Additionally, Zhao et al. developed single-stranded aptamers for the diagnosis of lung cancer. The fluorescein isothiocyanate-labeled aptamers have been evaluated by flow cytometry. The study identified that the target-specific aptamer possesses an enhanced ability to bind with NSCLC and recognize only the NSCLC subtype [75].

3.4 Colorectal Cancer

Colorectal cancer is the third leading cause of cancer-related mortality worldwide [76, 77]. About 50% of patients with colorectal cancer are diagnosed at the metastatic stage [78]. Early diagnosis of colorectal cancer is crucial to improving the survival rates of these patients [79]. Recently, Chinnappan et al. utilized an anti-CD63 aptamer as a recognition element for the effective detection of colorectal cancer exosomes. In this study, a novel integrated lab-on-a-chip platform was developed using aptamers for the pre-concentration and detection of colorectal cancer-specific exosomes. The results showed that the aptamer-based platform could detect exosomes with a detection limit of 1457 particles/mL [57]. Furthermore, Li et al. used the W3 aptamer, selected via the subtractive cell-SELEX approach, for the effective detection of colorectal cancer cells. The study revealed that this specific aptamer is highly beneficial in recognizing metastatic colorectal cancer and highlighted the W3 aptamer's effective binding with the Ephrin type-A receptor 2 for the efficient capture of circulating tumor cells in colorectal cancer cell blood samples [80]. Similarly, Liu et al. adapted the Cell-SELEX approach to select aptamers that recognize only LoVo cells and exhibit high selectivity for metastatic colorectal cancer cells [81]. Finally, Hung et al. developed three nucleic acid aptamers for the rapid diagnosis of colorectal cancer. The fluorescently labeled aptamers were identified to specifically bind to targeted colorectal HCT-8 cells with high affinity, and the dissociation constants of the aptamers

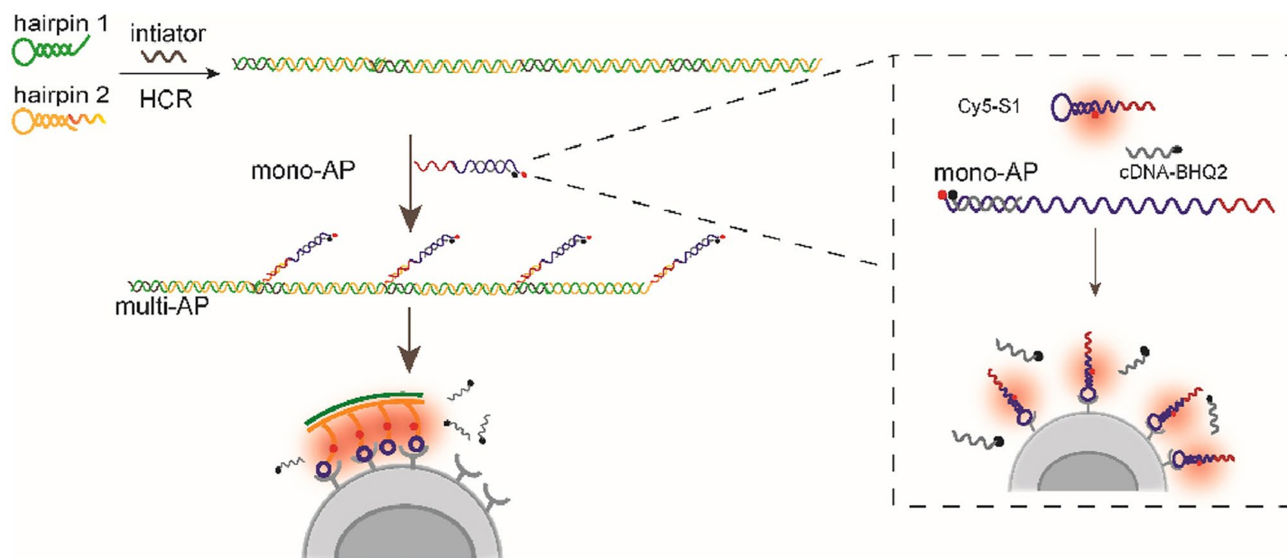

Fig. 4 Schematic of novel aptameric probe for the detection of lung cancer. *AP* alkaline phosphatase, *cDNA* complementary DNA (deoxyribonucleic acid), *HCR* hybridization chain reaction. Reproduced with permission from Chen et al. (2023) [72], © Elsevier, 2023

were at the nanomolar level. Confocal microscopic studies confirmed that these aptamers can specifically bind to colorectal cancer cells with high selectivity [82].

3.5 Leukemia

Leukemia is a type of cancer that is most common in children, caused by the growth of abnormal white blood cells in the bone marrow [83]. It is a lethal cancer that can result in death for most affected patients [84]. The leukemia cells can easily affect or damage normal blood cells, making early diagnosis highly essential to reduce mortality rates [85]. Recently, Rus et al. utilized a novel AB3 aptamer for the effective detection of oncofetal antigen/immature laminin receptor protein-positive cells for the diagnosis of hematologic malignancies, including acute myeloid leukemia. The study revealed that the aptasensor showed affinity towards the targeted leukemia-induced Jurkat cells, evaluated and identified via electrochemical approaches. The results showed that the aptasensor has a detection limit of 3.3×10^3 cells/mL for the target molecule, i.e., 16 cells in a 5-μL suspension [86]. Furthermore, Poturnayová et al. utilized sgc8c DNA aptamers, which are specific to protein tyrosine kinase 7. Their study used single-molecule force spectroscopy and an acoustic method with a thickness shear mode for the enhanced detection of leukemia cells, such as Jurkat lymphocyte cell lines and protein tyrosine kinase 7-negative MOLT-4 and U266 myeloid leukemia cells. The results indicated that the aptamer could be used for fabricating a label-free biosensor with high sensitivity and a limit of detection of 195 ± 20 cells per mL for leukemia cells [87]. Similarly, Yang et al. produced a DNA aptamer for the diagnosis of acute myelogenous leukemia. About ten SELEX cycles were employed to screen suitable aptamers, with the fluorescence intensity indicating a significant ability to recognize the targeted leukemia cells [88]. Likewise, Zeng et al. isolated a stable oligonucleotide aptamer for the detection of lymphoma tumors. The oligonucleotide aptamer was labeled with the Cy3 fluorochrome, and the site-specific in vivo targeting of the tumor was monitored using a confocal microscope with minimal accumulation in other organs. The aptamer was found to be highly stable in human serum [89]. Moreover, Yang et al. developed a novel S30 aptamer for targeting the CD33 antigen expressed in leukemia cells. The selected aptamers demonstrated excellent stability in human serum and could bind to target cells from a mixed-cell population with high selectivity and binding affinity. The in vivo studies showed that the aptamer could recognize tumor cells for approximately 12 h [90]. Finally, Yu et al. reported the hybrid combination of aptamers with semiconductor quantum dots labeled with streptavidin and biotin to capture leukemia cells. The selected aptamers were identified as selectively recognizing the target cells without causing any toxic reaction [91].

4 Limitations of Mediated *Cancer* Diagnosis

Early diagnosis of cancer can significantly reduce mortality and increase the likelihood of patient recovery [92]. Aptamers are extensively utilized in cancer diagnostics because of their desirable features, such as low immunogenicity, ease of cell-free chemical synthesis, in vitro selection, and effective

tissue penetration owing to their size [93]. Cancer cells often overexpress certain proteins that are not present in normal cells [94]. Aptamers can target these overexpressed proteins, forming the basis for cancer imaging applications [95]. Further, the sensitivity of aptamers is high [96], where low concentrations of these overexpressed proteins secreted in the early stage of cancer can be detected with the help of optical [97], electrochemical [98], microscopic studies [99], and surface-enhanced Raman spectroscopy [99]. However, there are limitations in using aptamers for commercial cancer diagnostic applications [100]. The cell-SELEX method for selecting reliable aptamers is constrained by several factors [101]. The chosen aptamers may not target unknown proteins because of the complexity of living cell surfaces, which can also undergo changes in protein expression upon cell death [102]. High-throughput sequencing technology can help avoid high-affinity aptamers with altered cloning sequences [103]. The aptamer selection process is intricate, requiring additional screening to enhance specificity, particularly in the face of cancer cell heterogeneity [104]. Isolating multi-target aptamers is challenging because of the diverse structures of overexpressed proteins [105]. MUC1 is commonly overexpressed in various cancer cells, and its molecular recognition has become routine in diagnostics using the same aptamer sequence for different cancers [106]. Yet, the specificity of aptamers is challenged by the wide variety of targets, including untargeted or subtype proteins, which may bind non-specifically [107]. One major limitation of the aptamer-based cancer diagnostic approach is the difficulty in conducting systematic and precise in vivo studies because of complexities associated with live cells [108]. While aptamers are advantageous for biosensor applications, each type has its limitations [109]. RNA aptamers, for example, are susceptible to rapid degradation in biological fluids [44], and the binding affinity of DNA aptamers can be influenced by the composition and pH of the reaction medium [110]. Moreover, oligonucleotide aptamers face challenges in therapeutic applications, such as poor pharmacokinetic properties, which can lead to high rates of renal filtration [111]. Therefore, to enhance their specificity and stability, aptamers should be combined with novel materials.

5 Aptameric Nanosensors for *Cancer* Diagnosis

Nanoscience is a branch of science that deals with the study and application of particles/materials smaller than 100 nm [112]. Nanoscale materials have revolutionized various fields because of their tunable size, high surface area-to-volume ratio, and unique properties [113]. Nanosensors, which operate at the nanoscale, can detect forces, chemical, and/or biological signals with high sensitivity [81]. Consequently, the pursuit of early, rapid, and straightforward diagnostic methods for cancer, long sought after, is now more attainable with the use of aptamers. Aptamers conjugated to NPs are emerging as potent diagnostic tools in cancer research [114]. These high-affinity aptamers can be attached to NPs composed of metals, semiconductors, or polymers, exploiting the intrinsic electrochemical, optical, mechanical, and magnetic properties of NPs to offer multi-functional theranostic capabilities for cancer diagnosis [115, 116]. Multi-target aptamers can be immobilized on NPs to enhance selectivity toward a variety of targets [117]. Moreover, metal NPs can augment detection sensitivity through their signal-amplifying electrocatalysis property [118]. The conjugation with metal NPs reduces the reliance on enzymes and serves as a catalyst in the development of aptasensors [119].

Integrating nanosystems with aptamers has broadened the scope of biological applications [120]. In particular, specificity, sensitivity, and the limit of detection of the nano-aptamer-based sensing techniques are remarkably enhanced and non-specific sensing is highly reduced, owing to the optical catalytic magnetic properties of the specifically utilized nanomaterials [121]. Conjugation helps to detect specific in vivo cancer cell targets required for early diagnosis via aptamers by improving their binding energy and their signal for detection is enhanced by using NPs [122] along with potential synergistic effects of enhanced detection [123]. Gold and silver NPs, in particular, display remarkable optical properties characterized by their high extinction coefficients and surface plasmon resonance, making them ideal for constructing colorimetric biosensors for the detection of various analytes [124].

5.1 Aptameric Metal Nanosensors

Aptameric metal nanosensors harness the distinct properties of metal NPs such as Au, platinum, silver, selenium, copper, and palladium for targeted molecule detection. Gold NPs are favored for optical sensors because of their strong surface plasmon resonance [125]. Platinum excels in electrochemical sensors because of its high electrocatalytic activity [126], while silver and selenium are used for their enhanced optical and antimicrobial properties [127, 128], respectively. When these metals are combined with aptamers, which are specialized to bind with specific analytes, the result is a powerful, sensitive, and versatile array of sensors for detecting cancer markers and other critical biomolecules.

5.1.1 Aptameric Gold Nanosensors

Gold NPs exhibit size-dependent optical properties [129]. Chun et al. demonstrated the diagnosis of breast cancer using an aptasensor mediated by Au NPs. The developed aptasensor displayed properties such as low resistance, good conductivity, and an enhanced current response, with a detection range for recombinant HER2 from 10^{-5} to 10^{2} ng/mL. It detects low levels of HER2 without cross-reacting with other biomolecules in serum, showcasing its high binding affinity toward the target. The aptasensor's regeneration was achieved by adjusting the pH, with the highest desorption rate at pH 4, maintaining its selectivity and affinity for the target upon regeneration [130]. Zhu et al. created a bio-conjugated aptasensor by depositing hydrazine onto a Au-aptamer complex (Hyd-Au NPs-Apt) to detect breast cancer cells. The cancer cells were stained with silver to enhance quantification using the aptasensor, with hydrazine reducing the silver ions. The results showed selectivity towards SK-BR-3 breast cancer cells, with the target cells appearing black and enlarged owing to silver deposition, revealing a detection limit of 26 cells/mL for the aptasensor with Au NPs [131]. Borghei et al. analyzed the colorimetric response of Au NPs crosslinked with aptamers for cancer cell detection as shown in Fig. 5. Using the DNA aptamer AS1411, modified with Au NPs to target nucleolin, they observed a high affinity for cancer cells overexpressing the nucleolin receptor. The Au NP-aptamer complex turned the solution red when bound to MCF-7 cells owing to cellular internalization, while a purple color indicated a lower cellular concentration, demonstrating its specificity towards cancer cells, unlike the unchanged color with normal cells [132]. Li et al. synthesized fluorescent Au NPs conjugated with the nucleolin aptamer AS1411, exhibiting low toxicity and specific binding to human lung adenocarcinoma cells (A549), where nucleolin was highly expressed, with an intense computed tomography signal intensity observed between 10 and 40 mg/mL in mouse models [133]. Yaiwong et al. developed a novel portable biosensor using a toluidine blue/oligonucleotide aptamer complex on polyethyleneimine-coated Au NPs for the effective electrochemical label-free detection of alpha-fetoprotein, achieving a detection limit of 9.5 pg/mL and a range of 10–50,000 pg/mL [134].

5.1.2 Aptameric Silver Nanosensors

Silver NPs conjugated with aptamers for cancer diagnosis are in the research spotlight because of their unique optical attributes, such as biocompatibility, stability, and the

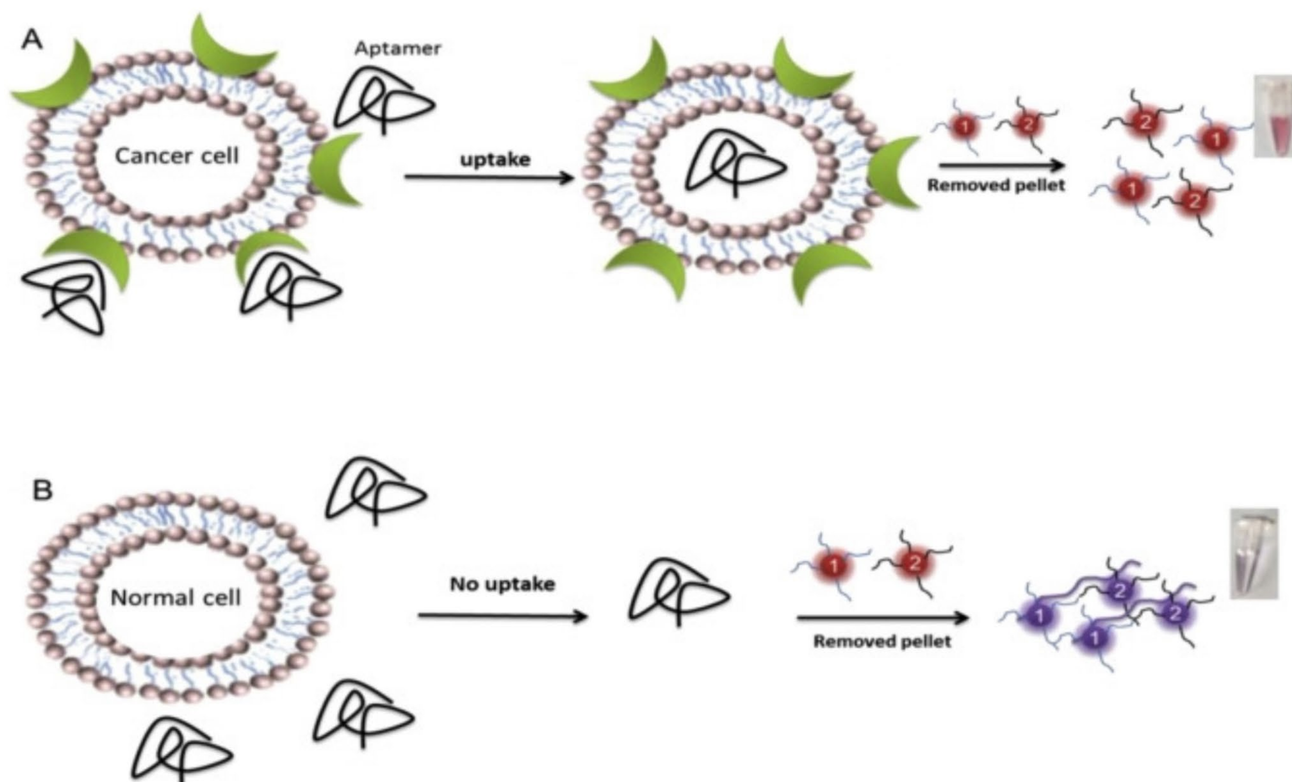

Fig. 5 Scheme of selective colorimetric approach for cancer cell detection via 1, 2 functionalized gold nanoparticles via a DNA probe and AS1411 aptamer. Reproduced with permission from Borghei et al. (2016) [132], ©Elsevier, 2016

light-scattering effect at plasmon resonance frequencies, which facilitates microscopic imaging [135]. Park and Ban recently crafted an innovative, one-shot, aptamer-based dual fluorescence nanosensor for sensitive, rapid, and label-free detection of periostin in blood for cancer diagnostics as shown in Fig. 6. They engineered Au and silver NP probes in a core-satellite configuration using PL5truc aptamers, which regain fluorescence owing to increased proximity, achieving detection limits of 106.68 pM in a buffer and 463.3 pM in serum-spiked samples without signal amplification or extra washing, within half an hour [136]. In a similar vein, Zhou et al. introduced aptamer-tagged silver nanoclusters for the selective targeting of MUC1 and MCF-7 cancer cells. Interaction with MUC1 prompted a marked fluorescence reduction in the aptamer-tagged clusters, while incubation with MCF-7 cells resulted in green cell membranes and enhanced fluorescence with longer incubation times [137]. Yin et al. designed fluorescent aptamer-silver nanoclusters with a hybridization process sensitive to conformational changes induced by target recognition, where the constructs were adept at binding to protein tyrosine kinase-7 on cancer cell membranes, specifically binding to human acute lymphoblastic leukemia cells as verified by confocal microscopy [138]. Additionally, Shan et al. created an aptamer-based quartz crystal microbalance biosensor, which uses silver NPs on its substrate for signal enhancement and acridine orange staining on the sensor electrode. This sensor efficiently captures target leukemia cells in T-cell acute lymphoblastic leukemia cell lines, confirmed by the fluorescent green appearance of detected cells, underlining its supreme selectivity [139].

5.1.3 Aptameric Platinum Nanosensors

Platinum NPs are known for their exceptional catalytic activity, large specific surface area, good electrical conductivity, and biocompatibility, making them ideal for use in electrochemical biosensors [140]. These properties have spurred research into aptasensors that incorporate platinum for the effective detection of cancer [141]. Gao et al. developed a novel platinum NP-based nanozyme that was linked with a covalent organic framework and thiol-terminated AS1411 aptamers, creating a nanoplatform for targeted tumor screening. They used a stable platinum-sulfide

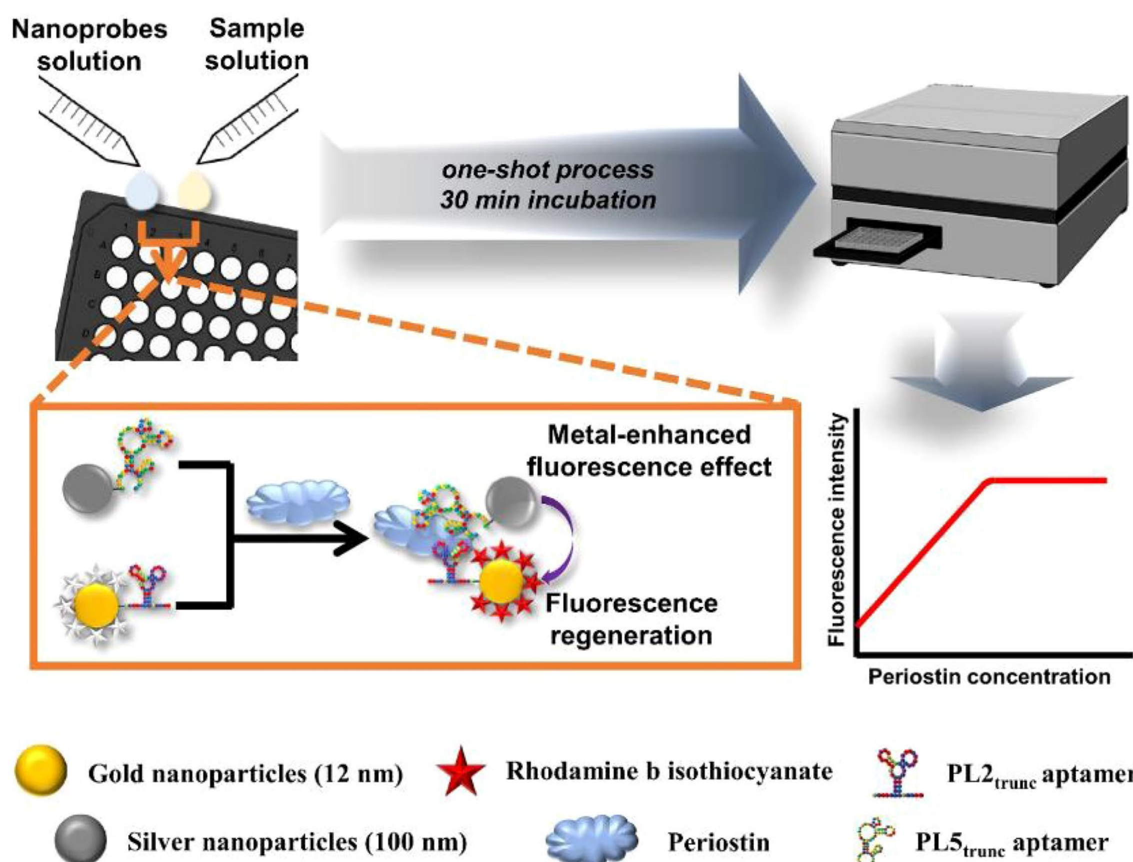

Fig. 6 Scheme of dual aptamer-based fluorescence nanosensors for periostin detection. *min* minute. Reproduced with permission from Park and Ban (2023) [136], ©Springer Nature, 2023

bond for the robust attachment of aptamers onto the NP surface, finding that this nanoplatform demonstrated a 2.5-fold increase in intra-tumoral accumulation compared with isolated NPs in a mouse model [142]. In another approach, Bharti et al. utilized electrodeposition to create Au-platinum bimetallic NPs on a carboxylated graphene oxide electrode for MUC1 protein detection. MUC1 is a transmembrane protein that is overexpressed in the early stages of breast cancer. Applying streptavidin to the carboxylated graphene oxide electrode surface enhanced its hydrophilicity because of the oxygen-containing functional groups in carboxylated graphene oxide. The bimetallic NPs increased the electrode's current owing to improved electron transfer. However, aptamer binding to streptavidin reduced the current response because of the negatively charged phosphate backbone, with a further decrease upon MUC1 binding to the aptasensor. Notably, the aptasensor maintained stability for up to 15 days, and the regenerated sensor continued to detect cancer cells effectively [143]. Additionally, Jiang et al. constructed a sensor using a layer-by-layer arrangement of DNA-platinum NPs with thiolated TLS11a aptamers immobilized on an indium tin oxide glass electrode as shown in Fig. 7. Platinum NPs, noted for their high catalytic activity, enhanced the conductivity of the indium tin oxide electrode with Au NPs, thus reducing impedance. Conjugation with platinum NPs resulted in moderate resistance, which decreased upon detecting target cells, indicating the aptasensor's efficacy. The sensor's selectivity was validated by the significant current change observed in the presence of live HepG2 cells, without interference from other cancer cells. The sensor also retained 80–90% functionality after regeneration [144].

5.1.4 Aptameric Palladium Nanosensors

Palladium NPs have been widely used in the fabrication of electrochemical aptasensors for the detection of cancer cells, owing to their high electrocatalytic properties [145]. Some researchers have reported that palladium NPs are beneficial for the diagnosis and therapy of cancer [146]. Recently, Bi et al. employed palladium NPs that were decorated on

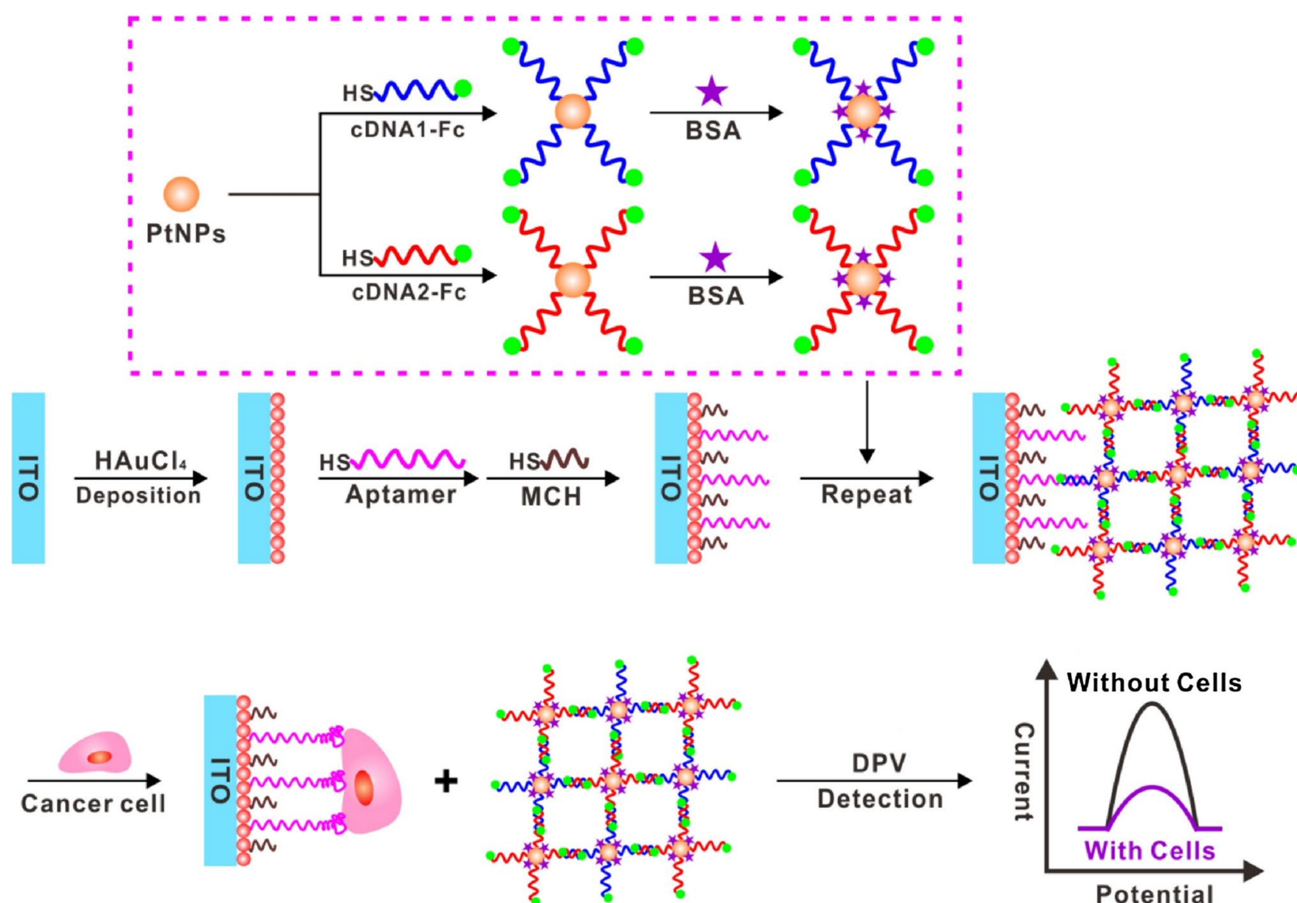

Fig. 7 Scheme of competitive electrochemical aptasensor fabrication using platinum nanoparticles for the detection of cancer cells. *BSA* bovine serum albumin, *DPV* differential pulse voltammetry, *HS* hot start aptamer, *ITO* indium tin oxide, *MCH* 6-mercapto-1-hexanol. Reproduced with permission from Jiang et al. (2018) [144], ©Elsevier, 2018

halloysite nanotubes and carbon composites for the fabrication of electrochemical aptasensors to detect breast cancer. In this study, the aptasensor was designed for the effective detection of the breast cancer biomarker known as HER2. The results showed that the aptasensor has a wide linear range of 0.03–9 ng/mL and a detection limit of 8 pg/mL [147]. Similarly, Tabrizi et al. fabricated a sandwich-type electrochemical aptasensor for the detection of human leukemic lymphoblasts, where Au and palladium NPs were decorated with an aptamer. The Nyquist diameter and current of the sensor decreased after the cancer cells were captured. The detection limit of the sensor was 8 cells/mL, and it exhibited the highest selectivity towards human leukemic lymphoblasts compared with other cancer cells [148]. Sun et al. detected human liver cancer cells in blood using a microfabricated chip-based electrochemical aptasensor with Au/Pd functionalized ZnO nanorods (ZnO@Au-Pd) to act as a potential nanocarrier as shown in Fig. 8. The TLS11a aptamer was introduced onto the electrode, which specifically recognizes HepG2 cells, and the optimized time for electrodeposition was 20 s. Notably, about 10 cells/mL were determined by an increase in the electron transfer resistance of the electrode after cancer cell interaction. Additionally, a low current response was observed in HepG2 cell lysates by the electrochemical sensor in the tested cancer cell mixture, indicating the high selectivity of the sensor [149]. Furthermore, Ou et al. developed a sandwich-type electrochemical aptasensor for the diagnosis of cancer cells. Tetrahedral DNA nanostructure aptamers acted as recognition probes and were immobilized on an Au electrode. A manganese–palladium–platinum (Mn_3O_4/Pd@Pt) composite decorated with aptamers exhibited high catalytic activity. Electrophoretic mobility studies indicated that the DNA aptamer moved more slowly owing to the pyramid-like

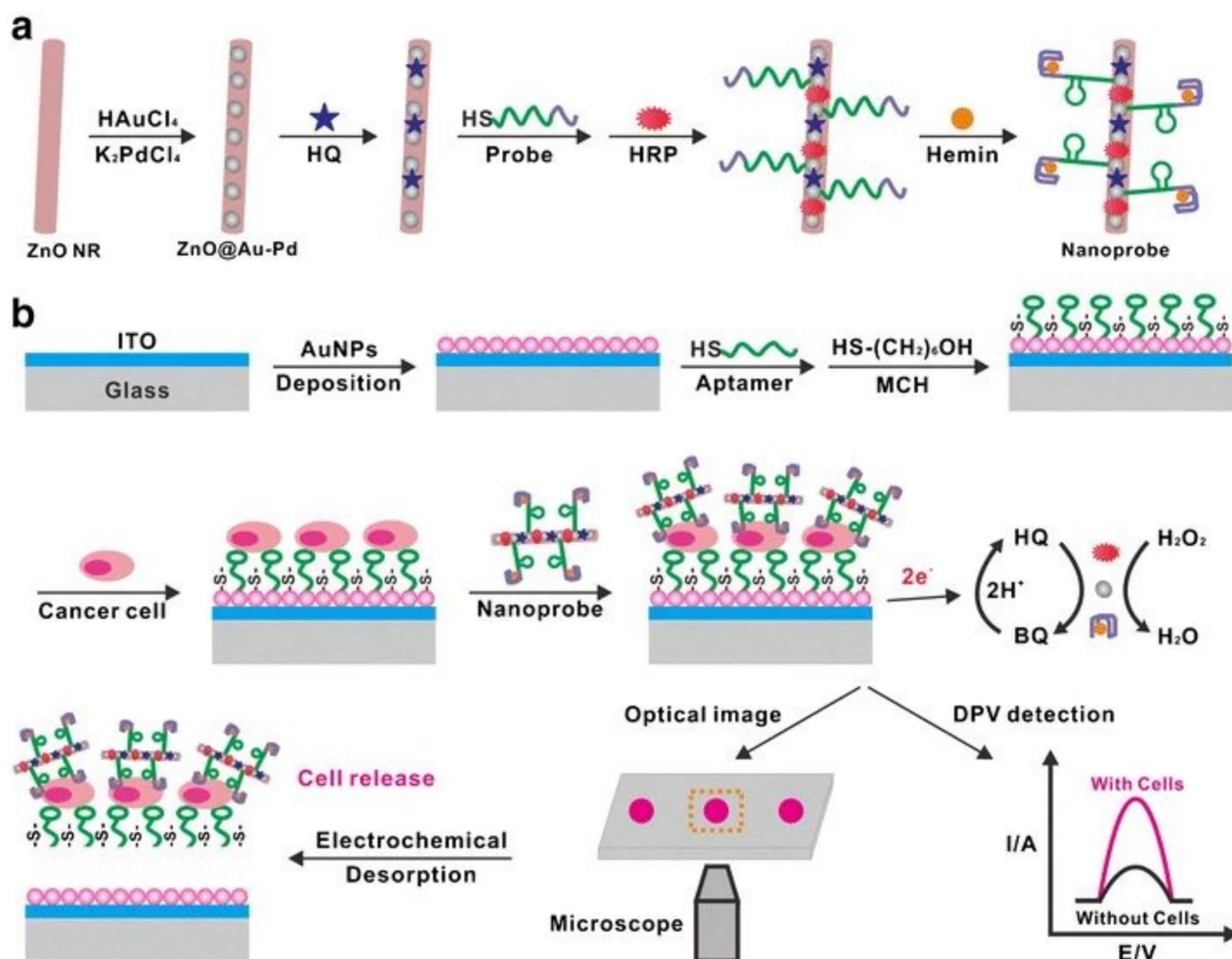

Fig. 8 **a** Scheme of palladium-aptamer hybrid electrochemical nanoprobe fabrication, **b** Scheme of electrochemical aptasensor assembly process. *AuNPs* gold nanoparticles, *DPV* differential pulse voltammetry, *HRP* differential pulse voltammetry, *HS* hot start aptamer, *ITO* indium tin oxide, *MCH* 6-mercapto-1-hexanol. Reproduced with permission from Sun et al. (2017) [149], ©Springer, 2017

nanostructure with more bases. The successful assembly of the sensor resulted in increased charge-transfer resistance. Among various proteins, only the HER2 protein exhibited signal changes, delineating its selectivity towards the HER2 target [150].

5.1.5 Aptameric Copper Nanosensors

Copper NPs have garnered significant interest for biomedical applications because of their unique properties, which include ease of synthesis, low toxicity, and excellent photophysical and spectral features [151]. They are especially noted for their fluorescence property, making them valuable in diagnostic applications [152], along with other unique features such as ease of synthesis, low toxicity, and excellent photophysical and spectral properties [153]. Zhang et al. developed an electrochemical aptamer-based biosensor for effective HER2 detection. In their approach, copper ions were introduced to partially substitute zirconium in a UiO-66 metal-organic framework with a ZIF-67-polydopamine nanocomposite, where single-stranded DNA aptamers specific to HER2 were immobilized. The aptasensor demonstrated an enhanced ability to detect the HER2 biomarker within 30 min, with a detection limit of 44.8 fg/mL and a range of 0.75–40 pg/mL [154]. Additionally, Yang et al. synthesized a fluorescent marker using double-stranded DNA-coupled copper NPs for detecting PDGF-BB, a protein implicated in tumor growth and progression as shown in Fig. 9. PDGF-BB is typically overexpressed in malignant cancer cells and is undetectable in normal cells. Their biosensor employed copper NPs coupled with an aptamer, with the DNA probe having two regions: one containing the aptamer and the other serving as a template for polymerases. The polymerization reaction did not initiate in the absence of PDGF-BB, resulting in low fluorescence. Native gel electrophoresis was utilized to verify the polymerization reaction, where the expected band of approximately 100 base pairs, corresponding to PDGF-BB, was absent in lane 4. The fluorescence intensity of the dsDNA-Cu NP complex increased upon selective binding to PDGF-BB, allowing it to act as a fluorescent marker for PDGF-BB detection [155]. Furthermore, Zhu et al. created poly(thymine)-templated copper NPs that were paired with a rolling circle amplification process for prostate cancer diagnosis. Aptamer-Au NPs were initially conjugated to form a sandwich-like structure for signal amplification, which subsequently triggered the rolling circle amplification reaction. Agarose gel electrophoresis revealed the presence of the rolling circle amplification product (~15,000 bp) and showed no bands for the control. Differential pulse stripping voltammetry studies indicated a redox peak from dissolved copper (Cu^{2+}) ions, correlating to the quantity of prostate-specific antigen (PSA) present. The analysis demonstrated that the current response increased with the deposition time up to 300 s, after which it reached saturation [156].

5.1.6 Aptameric Selenium Nanosensors

Selenium NPs have emerged as a promising agent for cancer diagnosis because of their unique optical, acoustic, thermal, and magnetic properties [152]. The multivalent nature of selenium allows for the synthesis of multi-functional NPs by conjugating with different ligands. These multi-functional NPs can bind with aptamers and capture target entities [157, 158]. Jalalian et al. combined 5TR1 aptamers, which are specific to NAS24 (an apoptosis induction agent), with selenium NPs for the targeted detection of cancer cells and the co-delivery of epirubicin. The study found that the aptamer-based system effectively targeted human breast carcinoma cells and murine colon carcinoma cells while sparing non-target hepatocellular carcinoma cells, demonstrating the system's potential as a sensor for the detection of specific cancer cells [159]. Similarly, Meng et al.

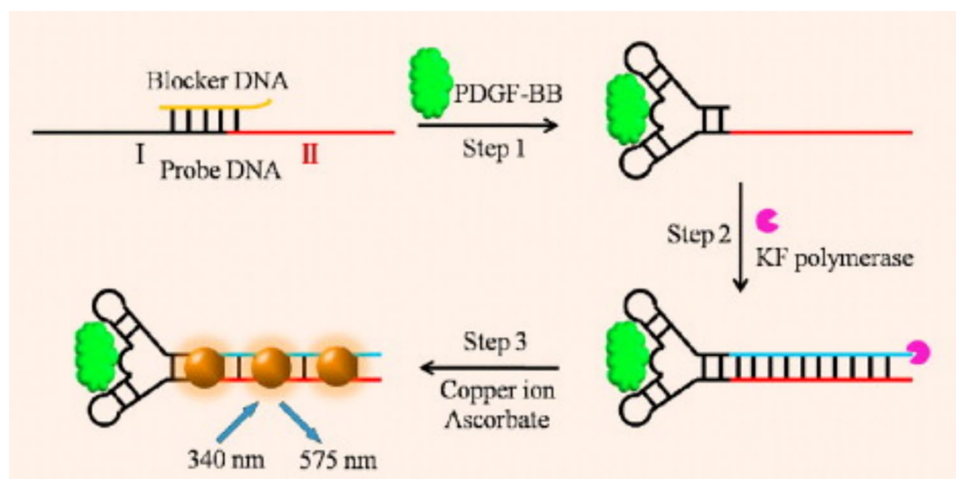

Fig. 9 Scheme of assay for an aptamer-copper nanoparticle-based sensor for platelet-derived growth factor-BB (PDGF-BB) dimer detection. *KF* Klenow fragment polA5. Reproduced with permission from Yang et al. (2014) [155], ©Elsevier, 2014

developed nucleolin-targeted cancer cell detection systems using aptamer-modified selenium NPs, given that nucleolin is overexpressed on the surface of many cancer cell types. The composition of the selenium NPs was confirmed by X-ray photoelectron spectroscopy, and dark-field microscopy images revealed the presence of green fluorescence. When the aptamer-selenium NP complex was incubated with HEP-2 cancer cells, the fluorescently labeled complex disrupted the specific small interfering RNA of nucleolin, reducing its binding efficiency [160, 161]. Moreover, Zhang et al. engineered an aptameric-cadmium selenide (CdSe) sensor using a layer-by-layer deposition method. A cationic polymer, polydiallyldimethylammonium chloride, was assembled onto an indium tin oxide electrode to form the sensor's base as shown in Fig. 10. The resulting six-layer deposition of CdSe/polydiallyldimethylammonium chloride showed good stability, and the photocurrent intensity increased with the presence of CdSe. After covalent bonding of the aptamer to CdSe, an enhancement in the photocurrent was observed. The impedance spectrum exhibited increased semicircle layers, indicating a reduction in the charge transfer rate. Upon exposure to cancer cells, the assembled layers became insulated, and the photoelectrochemical biosensor was able to detect the target with high selectivity and affinity [162].

5.2 Aptameric Metal Oxide Nanosensors

Metal oxide NPs, including those of copper (CuO), iron (FeO), zinc (ZnO), alumina (Al_2O_3), and titanium (TiO_2), have been integrated with aptamers for applications in cancer detection, paralleling developments with metal NPs. Recently, Xu et al. introduced an innovative electrochemical aptasensor combining metal-organic frameworks with bismuth copper oxide nanoflowers to detect HER2 effectively. This biosensor exploits target-specific complementary DNA aptamers in conjunction with metal-organic frameworks and hybrid metal-oxide nanostructures, achieving a remarkable detection limit of 0.049 pg/mL and a broad detection range of 0.001–20 ng/mL [163]. Wu et al. devised a method for preparing aptamer-templated CuO/Cu_2O NPs for breast cancer diagnostics. The synthesis involves the oxidation of Cu to CuO/Cu_2O NPs, followed by a hydrogen peroxide-mediated redox reaction that correlates peroxidase-like activity with a fluorescence output. The addition of thrombin to the CuO NPs stabilized the catalytic activity, leading to subdued fluorescence. The research also demonstrated that an aptamer

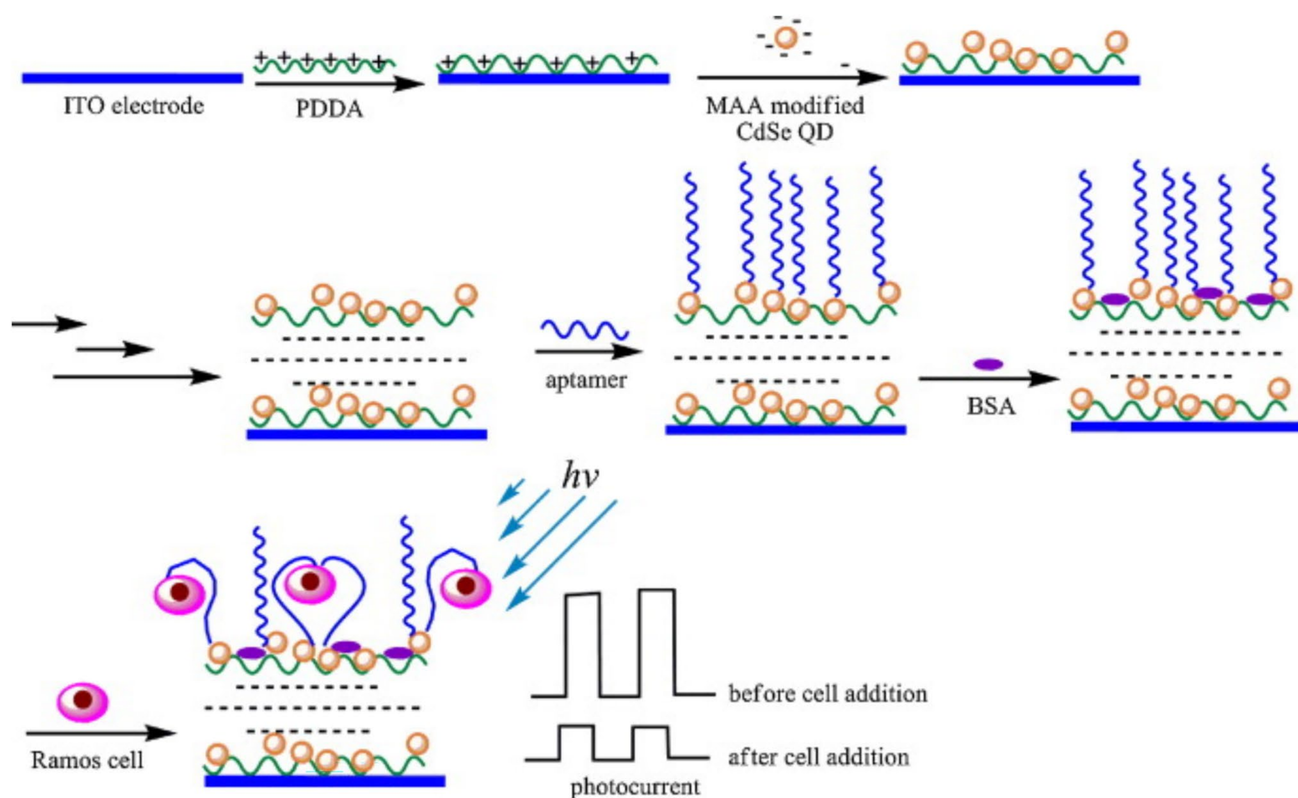

Fig. 10 Cadmium selenide-aptamer-based sensors for cancer cell detection. *BSA* bovine serum albumin, *CdSe* cadmium selenide, *ITO* indium tin oxide, *MAA* mercaptoacetic acid, *PDDA* polydiallyldimethylammonium chloride, *QD* quantum dot. Reproduced with permission from Zhang et al. (2011) [162], ©Elsevier, 2011

functionalized with MUC1 could effectively identify cancer cells, revealing a substantial decrease in fluorescence intensity after exposing a mixture of breast cancer cell lines to the aptamer-modified NPs [164]. In another innovative approach, Zhang et al. developed an aptamer-based sensor using magnetic iron oxide-silicon dioxide-avidin NPs for the precise detection of circulating tumor cells as shown in Fig. 11. The sensor employed single-stranded DNA aptamers fixed onto magnetic NPs, initiating a hybridization chain reaction with AND logic recognition to effectively determine the organ origin of circulating tumor cells [165]. Yu et al. took a different tack by coupling aptamers with prostate-specific membrane antigen and integrating them with thermally crosslinked superparamagnetic iron oxide NPs for prostate cancer detection and targeted drug delivery. Confocal laser scanning microscopy revealed that the aptamer-thermally crosslinked superparamagnetic iron oxide NP complexes selectively identified prostate cancer cells among various cell lines [166]. Wang et al. developed an aptamer specific to prostate-specific membrane antigen-TCL-SPION, which served dual purposes in prostate cancer detection and treatment. The NPs, coated with carboxylic acid and PEG, functioned as a magnetic resonance imaging contrast agent, where the PEGylation reduced cellular absorption and the carboxyl groups facilitated target molecule binding. The study affirmed the therapy suitability of TCL-SPION because of its low toxicity [167].

Erkmen et al. synthesized a sandwich-type electrochemical aptasensor for sensitive leptin detection via a voltammetric analysis. Given that leptin, secreted by adipocytes, is crucial for body metabolism and weight control, it may serve as a cancer biomarker. By immobilizing thiolated DNA aptamers onto Au NP-zinc oxide composites, the researchers achieved a detection limit of 0.0035 pg/mL and an impressive recovery rate in human plasma and serum [168]. Erkmen et al. also developed an impedimetric label-free aptasensor using Au-titanium dioxide NPs to detect leptin. Thiol-tethered DNA aptamers were anchored onto screen-printed electrodes modified with the NPs, yielding a detection limit of 0.312 pg/mL and a linear detection range

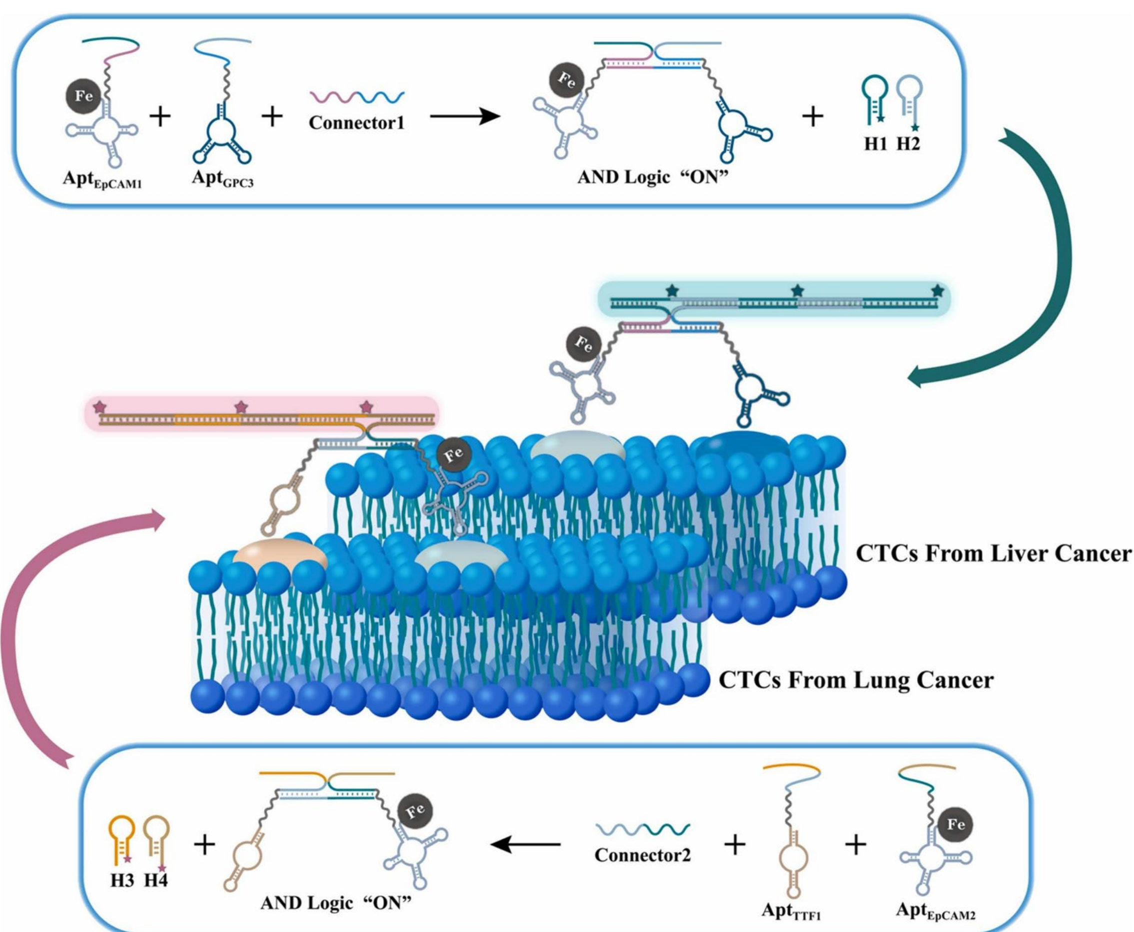

Fig. 11 Scheme of a magnetic iron oxide-aptamer-based sensor for the detection of lung circulating tumor cells (CTCs). Reproduced with permission from Zhang et al. (2023) [165], ©Elsevier, 2023

of 1–100 pg/mL, with high recovery percentages in biological samples [169]. Pla et al. demonstrated an alumina NP-aptamer-based sensor's effectiveness in diagnosing colorectal cancer using urine and blood samples. The sensor targets 8-oxo-7,8-dihydro-2′-deoxyguanosine, a molecule commonly overproduced in cancer cells, achieving a sensitivity of 95.83%, a specificity of 80%, a rapid detection time of approximately 60 min, and a detection limit of 1 nM [170].

5.3 Aptameric Carbon-Based Nanosensors

The conjugation of aptamers with carbon-based nanomaterials has been considered for sensor development because of their excellent mechanical and electrical properties, biocompatibility, stability, and high surface area [171]. The most commonly used carbon nanomaterials are single-walled nanotubes, multi-walled nanotubes, carbon quantum dots, reduced graphene oxide, and graphene [172]. Recently, Chen et al. utilized a novel aptamer-based sensor combined with multi-functional carbon nanotubes for effective lung cancer detection. The study showed that the aptamer specific to homocysteine, a sulfur-containing amino acid and potential lung cancer biomarker, can be immobilized on multi-functional iron oxide-multi-walled carbon nanotubes for cancer detection. The results highlighted that the aptasensor possesses a detection limit of 0.002 μmol/L with an excellent linear relationship between peak current and square-wave voltammetry and a target biomarker concentration detection range of 0.01–1 μmol/L [173]. Furthermore, Hao et al. prepared an aptameric graphene field-effect transistor for lung cancer diagnosis as shown in Fig. 12. In this study, oligonucleotide aptamers transferred electrons to graphene, resulting in a decreased Dirac point voltage. The introduction of interleukin-6 solution to the sensor led to a decrease in the V_{Dirac} due to the binding efficiency of the aptamer-interleukin-6 complex. The binding K_D was found to be 0.265 ± 0.100 nM, suggesting that the sensor has a high affinity toward the target [174]. Moreover, Gedi et al. conjugated an anti-cancer antigen 125 (CA125) aptamer with three-dimensional carbon nanotubes for the detection of CA125. They observed a colorimetric signal upon the aptamer's effective binding to CA125. The K_D value of the sensor was determined to be 166 nM, indicating a high binding affinity toward CA125. The aptamer was also labeled with 6-carboxy-fluorescein and incubated with ovarian cancer cells, which turned fluorescent upon binding, an essential feature for the detection of cancer cells. The detection limit was enhanced by the presence of carbon nanotubes, making this sandwich sensor highly sensitive compared with recombinant aptamers [175]. Additionally, Li et al. developed a mesoporous oxidized carbon nanosphere-based aptasensor for detecting mucin 1 protein, which is present on the surface of various cancer cells, including breast and prostate cancer. The aptamer was tagged with Cy3, and rapid fluorescent quenching was observed. The results indicated that the sensor had a higher detection limit in serum than other aptamer-based sensors. Confocal imaging studies demonstrated that the mesoporous oxidized carbon nanosphere/P0-Cy3 bound to MCF-7 cancer cells produced a strong fluorescence signal, while no fluorescence was detected in normal cells because of the competitive binding of OMCN to MCF-7 cells. The use of multiple detection methods confirmed that the OMCN/P0-Cy3 sensor has the highest detection limit and sensitivity [176].

5.4 Aptameric Polymer-Based Nanosensors

Polymers play a vital role in medical applications because of their unique properties, such as biocompatibility, high stability, cost effectiveness, and high affinity [177]. It has been shown that conjugating aptamers with polymers enhances performance and sensitivity [178]. In a recent study, Foroozandeh et al. detected the CA125 biomarker using a

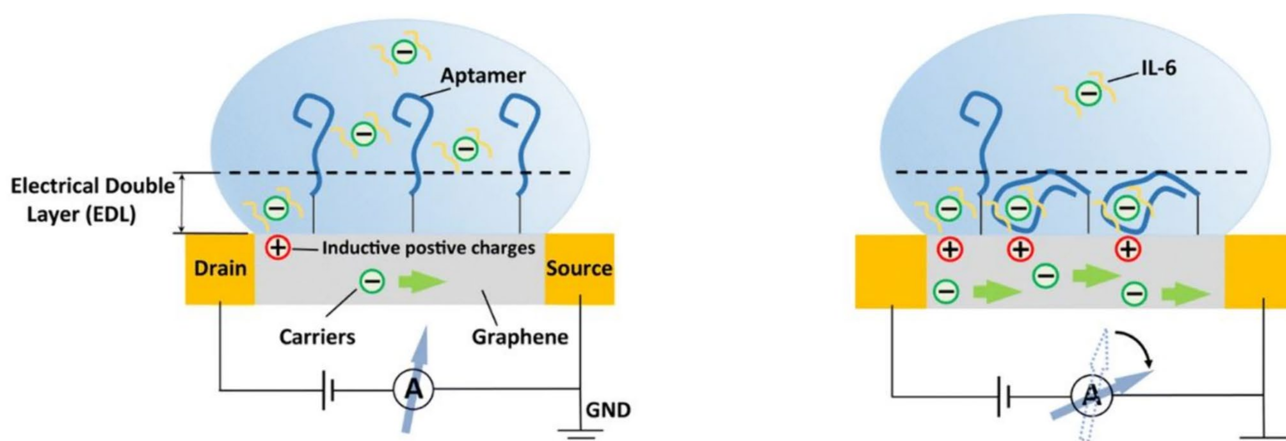

Fig. 12 Scheme of charge distribution in a graphene aptamer-based sensor for the detection of lung cancer cells. *GND* Ground, *IL-6* interleukin-6. Reproduced with permission from Hao et al. (2019) [174], ©Springer, 2019

complex graphitic-carbon nitride-magnetic iron oxide-polyaniline-Au electrode-based electrochemical aptasensor. The results demonstrated that the aptasensor, with a CA-125 specific DNA aptamer, had a linear range of 5–60 U/mL and a detection limit of 0.298 U/mL for the target antigen [179]. Similarly, Wang et al. conjugated a Cy3-labeled aptamer with a polydiacetylene liposome for MUC1 detection as displayed in Fig. 13. The gel retardation assay showed that the Cy3-aptamer and the Cy3-aptamer-PDA liposome appeared as bright and faint bands, respectively. Furthermore, the fluorescence of the Cy3-aptamer was quenched in the presence of liposomes following polymerization. Among the various proteins tested, only the MUC1 protein caused fluorescence spectral changes when bound to the Cy3-apt-PDA-liposome, indicating the system's selectivity for the target. Notably, the size of the PDA liposomes increased after binding with MUC1, enhancing selectivity toward the target [180]. Lyu et al. developed an afterglow semiconducting polyelectrolyte conjugated with an aptamer for cancer exosome detection. In their design, poly(*p*-phenylene vinylene) served as the sensor's backbone, while tetraphenyl porphyrin, a photosensitizer, was incorporated to amplify the afterglow signal. The study found that the afterglow and fluorescence signals were intensified by the efficient binding of the aptamer to the exosomes, and the signal recovery ratio increased with higher exosome concentrations. The detection limit for afterglow was lower than that for fluorescence in a phosphate-buffered saline medium. Recognition tests carried out on five types of exosomes, secreted by different cancer cells, showed that MCF-7 cells exosomes had elevated protein levels [181]. Apart from these polymers, block copolymer NPs and molecularly imprinted polymers were also combined

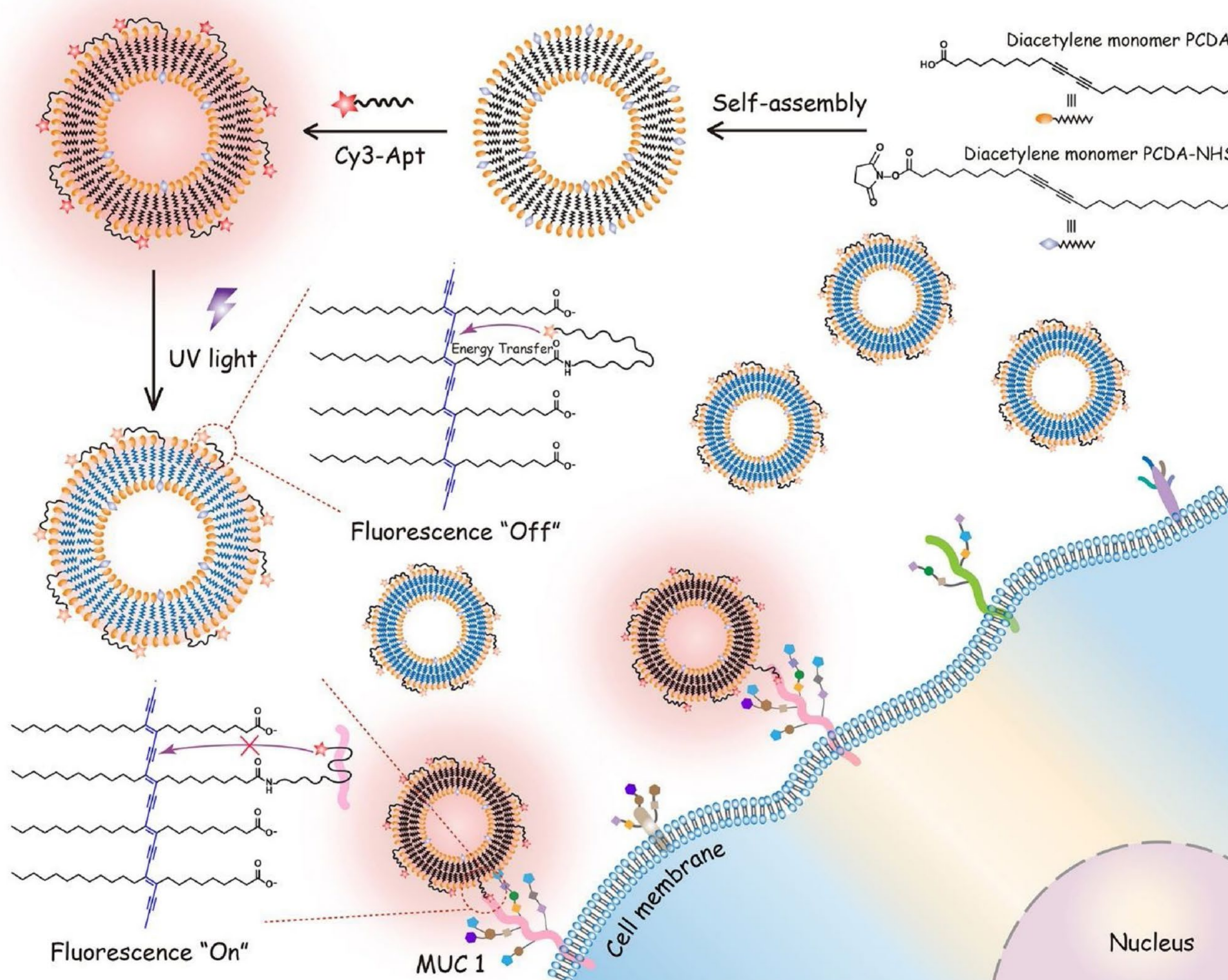

Fig. 13 Scheme of biosensor fabricated using aptamer and liposome for the targeted detection of cancer cells. PCDA-NHS (10, 12-pentacosadiynoic acid - N–Hydroxysuccinimide), *UV* ultraviolet. Reproduced with permission from Wang et al. (2020) [180], ©Elsevier, 2020

with aptamers for the effective, specific, and sensitive monitoring of cancer cells [182, 183].

5.5 Aptameric Nanocomposite-Based Hybrid Sensors

Nanocomposites have been combined with electrochemical aptasensors to increase signal production and decrease background noise in sensors [184]. These nanocomposites enable sensitive detection owing to the integrated properties of individual components [185]. They have functional groups suitable for the conjugation of aptamers [186]. Recently, Khoshsafar et al. demonstrated that an aptamer specific to tryptophan enantiomers, whose metabolism perturbation can lead to the immune escape of cancer cells [187], can be used with a nanocomposite as a potential biosensor. In this study, a biotin-L-tryptophan-sensitive aptamer was combined with a nanocomposite of palladium, copper, cobalt, and reduced graphene oxide, which was subsequently transformed into an immunochromatographic test strip. The novel sensor detected the target molecule using a screen-printed electrode with a linear detection range of 0.08–20 μM and a detection limit of 0.03 μM in blood plasma samples [188]. Furthermore, Wei et al. fabricated a paper-based sensor for detecting prostate cancer. Gold NP-reduced graphene oxide-thionine nanocomposites were coated onto the working electrode and immobilized with an aptamer. Thionine acted as an electrochemical mediator, transducing the biological recognition between the aptamer and PSA. The nanocomposite facilitated electron transfer, enhancing the detection of PSA. The current response decreased once the aptamer bound with the conductive nanocomposite electrode, and this decrease was amplified upon the conjugation of PSA with the aptamer. Differential pulse voltammetry results showed that the binding of prostate cancer cells led to a reduction in peak current, indicating a correlation with the concentration of PSA. The binding specificity of the aptasensor was confirmed in the presence of various antigens, yielding positive results [189]. Yazdanparast et al. developed a biocompatible nanocomposite for detecting human breast cancer cells. The sensor, a type of sandwich assay, comprised multi-wall carbon nanotubes and poly(glutamic acid) immobilized on a glassy carbon electrode. Silver NPs labeled with another aptamer were used to enhance selectivity and amplify the signal. The study confirmed that the binding of the aptamer with MCF-7 breast cancer cells decreased the peak current, as verified by cyclic voltammetry. Electrochemical impedance spectroscopy indicated an increase in charge transfer resistance after the MCF-7 cells were captured by the aptamer. The electrochemical measurements demonstrated that an increase in MCF-7 cell concentration resulted in a higher peak current. When three types of cancer cells were mixed and incubated with the sandwich sensor, the developed sensor detected MCF-7 cancer cells in human serum with high selectivity [190]. These studies, summarized in Table 1, show that combining nanocomposites with target-specific aptamers enhances the detection of target molecules compared with using NPs or nanocomposites alone. However, the potential toxicity of these nanocomposites and NPs in biosensors poses a significant environmental concern for the future [191]. Therefore, identifying alternative solutions to mitigate the environmental toxicity of NPs and nanocomposites is necessary.

6 Aptameric Nanocomposite-Based Biohybrid Sensors

The ideal solution to counteract the environmental toxicity of NPs and composites is the utilization of biohybrid particles of nano size, where at least one component is derived from biological sources, such as plant or microbial extracts [192, 193]. In some instances, NPs are encapsulated within biopolymers to mitigate their environmental impact before conjugating with aptamers for biosensor development [194]. Recently, de Valega Negrao et al. synthesized novel iron oxide NPs coated with a biodegradable block copolymer, subsequently functionalized with a target-specific aptamer for detecting HER2-positive breast cancer cells. The biodegradable block copolymer was synthesized using zwitterionic poly (2-methacryloyloxyethyl phosphorylcholine) and cationic poly (2-dimethylaminoethyl methacrylate) via the reversible addition-fragmentation chain transfer technique. Their findings indicated that the DNA aptamer-nanocomposite biohybrid was non-toxic within the cellular matrix and displayed outstanding recognition efficiency for HER2-amplified SKBR3 breast cancer cells [195]. Similarly, Mazloum-Ardakani et al. created a novel aptasensor by combining electro-synthesized carbon quantum dots with Au NPs biosynthesized using a *Saccharomyces cerevisiae* yeast extract. This biosensor, employing single-stranded DNA specific to the carcinoembryonic antigen, showed a linear detection range from 1 pg/mL to 0.001 g/mL and a detection limit of 0.26 pg/mL in human blood samples [196]. In a related study, Au NPs synthesized with *S. cerevisiae* were integrated with copper oxide-carbon dots and electrosynthesized conducting polymers to detect the carcinoembryonic antigen, achieving a detection limit of 0.19 pg/mL within the same linear range [197]. Apart from all these NP-aptamer hybrids, aptamers combined with several quantum dots are also gaining significant attention among researchers for the effective monitoring of cancer [198]. However, these quantum dots must be fabricated via a biosynthesis approach or encapsulated with biomolecules to include them as biohybrid biosensors. These examples underscore the potential of biosynthesized nanomaterials to maintain

Table 1 Aptamer-nanoparticle/nanocomposite-based sensor for cancer monitoring applications

Type of nanosensor	Aptamer	Nanomaterials	Biomarker	Target cancer	LOD	References
Electrochemical detection	Single-stranded DNA aptamer	Au	HER2	Breast cancer	5 ng/mL	[219]
Electrochemical immunosensor	3′-thiolated RNA aptamer	Au	HER2-positive breast cancer cells	Breast cancer	26 cells/mL	[131]
Fluorescence	Sgc8c aptamer	Au	CCRF-CEM cells	Leukemia	1160 cells/mL	[139]
Optical probe	Isoform of prion protein PrP^c aptamer	Ag	Prion protein	Bone marrow neuroblastoma cells	–	[135]
Fluorescence	MUC1-recognizing aptamer	Ag	Mucin-1	Breast cancer	0.05 nM	[137]
Fluorometric	Alpha-fetoprotein aptamer	Palladium	Alpha-fetoprotein	Hepatocellular carcinoma	1.4 ng/mL	[220]
Fluorescence	EpCAM and CD63 aptamer	Iron oxide quantum dots -Au	Cancer cell exosomes	Lung cancer and other types	–	[221]
Electrochemical	Thiolated TLS11 aptamer	Au-palladium core-shell	G-quadruplex/hemin	Liver hepatocellular carcinoma (HepG2) cells	15 cells/mL	[222]
Amperometric sensing	Sgc8c aptamer	Multi-walled carbon nanotubes, palladium	CCRF-CEM cells	Leukemic lymphoblast cancer cells	8 cells/mL	[148]
Electrochemical	Tetrahedral DNA nanostructure aptamer	DNA and manganese oxide/palladium@platinum nanoflower	HER2	Breast cancer	0.08 ng/mL	[150]
Fluorescence	PDGF-BB isoform aptamer	dsDNA copper	Platelet-derived growth factor	Human malignant tumors	4 nmol/L	[155]
Electrochemical	PSA-specific DNA aptamer	Au and copper	PSA	Prostate cancer	0.020 fg/mL	[156]
Bioimaging-based sensor	NCL-targeting aptamer	Selenium	Nucleolin	Human epidermoid cancer (Hep-2) and a few other types	–	[160]
Electrochemical	DNA aptamer	CdSe NPs	Oppositely charged macromolecules	Burkitt's lymphoma cells	84 cells/mL	[162]
Fluorescence	Mucin-1 binding DNA aptamer	CuO nanorods	Mucin-1 overexpressing tumor cells	Breast cancer	100 cells (mucin-1 cells)	[164]
MRI	Prostate-specific membrane antigen aptamer	SPIONs	Prostate cancer cells	Prostate cancer	–	[166]
Imaging	A10 RNA aptamer	SPIONs	PSMA-expressing PC3 cells	Prostate cancer	–	[167]
Field effect transistor	Interleukin-6 aptamer	Graphene	Interleukin-6	Lung cancer	139 fM	[174]
Imaging	Single-stranded DNA aptamer	Carbon nanotubes	Cancer antigen 125	Ovarian cancer cells	10 pg/mL	[175]
Fluorescence imaging	Cy3-labeled single-stranded DNA aptamer	Mesoporous carbon nanospheres	Mucin-1	Breast cancer, prostrate, tumor and many other malignant tumors	6.52 nmol/L (mucin-1) Cancer cells (8500 cells/mL)	[176]
Fluorescence	Cy3-labeled MUC1-binding aptamer	Liposomes	Mucin-1	Breast cancer	0.8 nM	[180]

Table 1 (continued)

Type of nanosensor	Aptamer	Nanomaterials	Biomarker	Target cancer	LOD	References
Optical	Black hole quencher-2-tagged CD63 aptamer	Semiconducting polyelectrolyte nanocomplexes	Cancer exosomes	Exosomes secreted from Hela (cervical cancer cells), chondrocytes (benign cells), MCF-7 (breast cancer cells), SKOV3 (ovarian cancer cells), and HepG2 (liver cancer cells)	–	[181]
Electrochemical	DNA aptamer	Graphene	PSA	Prostate cancer	10 pg mL^{-1}	[189]
Electrochemical	Mucin-1-binding DNA aptamer	Ag NPs	-	Breast cancer	25 cells	[190]
Electrochemical	Single-stranded DNA	Au@graphene sheets, cobalt-palladium binary NPs	Thrombin	Pulmonary metastasis	5 pg mL^{-1}	[223]
SERS	Single-stranded DNA	Ag NP trimers	Alpha-feto protein	Hepatocellular carcinoma, yolk sac tumor, germ cell tumor, gastric carcinomas	0.097 aM	[224]
Fluorescence resonance energy transfer	Covalently tagged amino group-modified single-stranded DNA aptamer	Upconversion phosphorus and carbon nanoparticles	Carcinoembryonic antigen	Lung cancer, breast cancer, rectal cancer	0.1 ng mL^{-1}	[225]
SERS	DNA aptamer	Ag NP pyramids	PSA, mucin-1, thrombin	Prostate cancer, pulmonary metastasis, breast cancer	0.96 aM (PSA), 9.2 aM (mucin-1), 85 aM (thrombin)	[226]
Fluorescence enhancement	DNA (sgc8c)	Ag nanocluster	CCRF-CEM cells	Human acute lymphoblastic leukemia, human Burkitt's lymphoma	150 CCRF-CEM cells	[138]
Colorimetry	Messenger DNA	Au NPs	HL-60 cells	Human leukemia	10–10^4 HL-60 cells	[227]
SERS	DNA	Ag-Au NPs pyramids	Vascular endothelial growth factor	Breast cancer, lung cancer, colorectal cancer	22.6 aM	[228]
Fluorescence sensor (Ag NPs)	DNA	Manganese-doped zinc sulfide quantum dots	Vascular endothelial growth factor-165	Breast cancer, lung cancer, colorectal cancer	0.08 nM	[229]
Field-effect transistor	Peptide	Single-walled carbon nanotube	Cathepsin E	Pancreatic cancer, gastric cancer	2.3 pM (PBS) and 0.23 nM (human serum)	[230]
Methylene blue-based signal amplification	DNA (sgc8c)	Au NPs	Protein tyrosine kinase-7	Lung cancer, gastric cancer, colon cancer, acute myeloid leukemia	372 fM	[231]
SERS	DNA	Au@Ag core-satellite nanostructures	Prostate-specific antigens	Prostate cancer	4.8 aM	[232]
Localized surface plasmon resonance	MUC-1 protein	Au nanorods	MCF-7 cells	Breast cancer	100 cells mL^{-1}	[233]

Table 1 (continued)

Type of nanosensor	Aptamer	Nanomaterials	Biomarker	Target cancer	LOD	References
Fluorescence	DNA	Mesoporous carbon nanospheres	Mucin-1, MCF-7 cells	Breast cancer and a few others	6.52 nmol/L (mucin-1), 8500 cells/mL	[176]
Fluorescence resonance energy transfer	DNA	Streptavidin@ Ag NPs	Human platelet-derived growth factor-BB	Breast cancer	0.8 ng/mL	[234]
Fluorescence	Peptide	Polydiacetylene liposomes	Mucin-1	Breast cancer and a few others	0.8 nM	[180]
SERS	DNA	Au nanorods core-Ag NPs	Mucin-1	Breast cancer	4.3 aM	[235]
Electrochemical	OPN aptamer and complementary DNA probe	Au NPs	Osteopontin	Hepatocellular carcinoma	10.7 ng mL^{-1}	[236]
Electrochemical	Oligonucleotide	Polyethyleneimine-coated Au nanoparticles	Alpha-fetoprotein	-	9.5 pg/mL	[134]
Dual fluorescence	$PL5_{truc}$ aptamer	Au nanoparticles-silver nanoprobes in core-satellite structure	Periostin	Serum-spiked condition	463.3 pM	[136]
Electrochemical	DNA	Palladium nanoparticles	HER2	Breast cancer	8 pg/mL	[147]
Electrochemical	ssDNA	ZIF-67-polydopamine nanocomposite	HER2	Breast cancer	44.8 fg/mL	[154]
Diagnosis	5TR1 aptamer	Selenium nanoparticles	NAS24	Human breast carcinoma and murine colon carcinoma cells	–	[159]
Electrochemical	cDNA	Bismuth copper oxide nanoflower-metal organic framework	HER2	-	0.049 pg/mL	[163]
Electrochemical	Thiolated DNA aptamers	Au-zinc oxide nanoparticles	Leptin	Cancer detection using human plasma and serum	0.0035 pg/mL	[168]
Square-wave voltammetry	DNA aptamer	Iron oxide multi-walled carbon nanotubes	Homocysteine	Lung cancer	0.002 µmol/L	[237]
Electrochemical	CA-125-specific DNA aptamer	Graphitic-carbon nitride-magnetic iron oxide-polyaniline-Au electrode	Antigen-125	Cancer	0.298 U/mL	[179]
Immunochromatographic test strip	Biotin-L-tryptophan-sensitive aptamer	Palladium-copper-cobalt-reduced graphene oxide nanocomposite	Tryptophan enantiomers	Cancer in blood plasma	0.03 µM	[188]

Ag silver, *Au* gold, *cDNA* complementary DNA, *CdSe* cadmium selenide, *dsDNA* double-stranded DNA, *HER2* human epidermal growth factor receptor 2, *LOD* limit of detection, *MRI* magnetic resonance imaging, *NCL* nucleolin, *NPs* nanoparticles, *PBS* phosphate-buffered saline, *PSA* prostate-specific antigen, *PSMA* prostate-specific membrane antigen, *SERS* surface-enhanced Raman spectroscopy, *ssDNA* single-stranded DNA

the cancer-detecting efficacy of aptamers while reducing or eliminating toxicity to humans and the environment.

7 Limitations, Future Perspective, and Conclusion

Diagnosis of cancer biomarkers using aptamer-conjugated nanostructured materials is based on different modes of detection, such as surface plasmon resonance, colorimetry, surface-enhanced Raman scattering, and imaging approaches [199]. The assay performance of an aptamer-functionalized nanosensor, i.e., its sensitivity and specificity, depends on the properties of the nanomaterials (size, shape, and concentration) and the aptamers (secondary structure, density, and valency) [200]. It is important to validate the performance of aptamer-based nanosensors in both pure and clinical samples, such as urine, serum, and other biological fluids, as results may vary [201]. A major challenge for these aptamer-based nanosensors is the background interference caused by non-target substances present in clinical samples, which limits their analytical performance [202]. It is imperative to systematically evaluate the sensitivity of these sensors to target molecules in different clinical sample types to determine their robustness [203]. Therefore, the standardization of the diagnostic approach for detecting cancer cells or biomarkers using nano-aptasensors should be conducted to ensure accurate diagnostic results that are comparable with existing conventional methods [204]. Washed and non-washed biosensing platforms have been developed for the diagnosis of cancer; however, these washing procedures may also affect the performance of the sensors [205]. The sensor's ability to process multiple cancer biomarkers in biological samples should also be explored [206].

It is noteworthy that aptamers, especially RNA aptamers, are prone to rapid degradation in biological media owing to their biomolecular interaction [24]. The swift degradation in blood within minutes is a major concern to consider RNA aptamers for medical applications [207]. Thus, the stability of aptamers can be improved by formulating them with NPs or biomaterials. Aptamers have been combined with NPs as hybrids for improving their stability [116]. In addition, there are several reports that indicate the excretion of aptamers via renal filtration from the bloodstream due to their low molecular weight. Aptamer conjugation with polyethylene glycol or polymeric NPs increases their circulation time in the bloodstream [208]. Furthermore, limitation in controlling the duration of an aptamer's action in a biosensor set-up [209], interruption while binding with intracellular targets [210], aptamer generation using unpurified target protein [211], a high probability of cross-reactivity [212], and issues with automation of aptamer synthesis [213] are additional challenges. Advanced analytical, computational, and material characterization approaches provide opportunities to address these challenges.

The nanomaterials used in sensor fabrication must be precisely controlled, optimized, and reproducible [214]. Moreover, the conjugation of aptamers to nanomaterials is facilitated by surface modifiers, which affect the overall stability of the nanocomposite and the matrix [215]. The design of nucleic acid-based nanosensors for in vivo applications has faced several shortcomings, such as lack of stability, biocompatibility, high cytotoxicity, and resistance to nuclease activity [216]. Thus, hybrid nanostructures have been developed that provide intracellular stability and protect nucleic acids from degradation [217]. In contrast to nanomaterials, molecular beacons designed for this purpose are unable to penetrate the cell membrane [218]. The sustainability of nano-aptamer-based diagnostic tools hinges on cost effectiveness, which facilitates the clinical translation and large-scale commercialization of the product in the future.

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