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Materials-Functionalized Point-of-Care Testing Devices for Pathogen Detection

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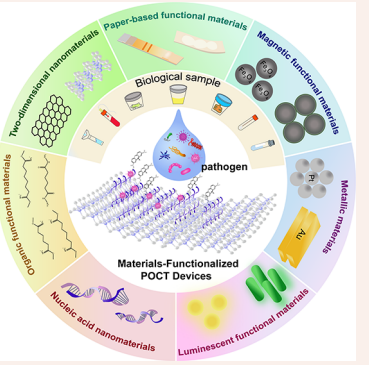
CONSPECTUS: Pathogen infection can lead to deterioration of physical fitness, organ function decline, and even death, and the continuous interhuman transmissions contribute to the epidemic outbreak. The rapid and sensitive detection of pathogens in clinical samples at scale thus becomes critical to infectious disease screening and containing outbreaks. Traditional detection methods, including microbial culture and polymerase chain reaction (PCR) technologies, involve bulky instrumentation in centralized laboratories, professional technicians, and a lengthy assay time, hence severely hampering the suppression of infection chains and disease treatment. Advanced diagnostic technologies capable of rapidly identifying pathogens are therefore ideal for prompting infection diagnosis and precision medicine. Point-of-care testing (POCT) devices, usually consisting of recognition elements and signal transduction units, offer a promising alternative as they can detect pathogens specifically and give qualitative results within a short time. By overcoming the issues of time-consuming growth culture and complex sample treatment, POCT devices can remarkably expedite the sample-to-result time of infection diagnosis with high sensitivity, thus allowing clinicians to quickly make decisions. Recent years have seen major progress in the development of functional materials that show unique physical and chemical properties to facilitate the performance enhancement of POCT devices, including inorganic nanomaterials, organic polymers, biomaterials, and the like. By contributing to the biorecognition and transduction of biological binding events into electrical and optical readout, functional materials at the interfaces between POCT sensors and the biological samples enable measurements with higher sensitivity and selectivity and faster responses. Hence, the development of high-performance functional materials is expected to increase the microbial detection efficiency of POCT devices by simplifying sample handling and improving the accuracy, thereby aiding in the on-site and real-time detection of pathogens and the large-scale screening of infectious diseases. In this Account, to clarify the potential of POCT devices coupled with functional materials in the rapid diagnosis of infectious diseases, we summarized the applications of materials-engineering-based POCT devices for human pathogen detection in terms of the types of functional materials, such as magnetic materials, metallic materials, luminescent materials, functional nucleic acids, and so forth. Based on our previous studies, we highlighted the abilities of functional materials-assisted POCT devices to detect pathogens in multiple actual biological samples, including urine, saliva, blood, stool, and so on. These applications provide substantial benefits for pathogen diagnostics with regard to fast response, high sensitivity, ease of use, portability, and low cost. Finally, the challenges and future directions of functional materials for POCT devices aimed at clinical pathogen detection are also briefly summarized.



1. INTRODUCTION

Microbial pathogens residing in the environment have remained an important global problem in public health.[1] Lately, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 700 million infections and 6 million deaths worldwide.[2] It was also reported that *Mycobacterium tuberculosis* infection led to 1.6 million deaths in 2021.[3] The *Helicobacter pylori* infection has been proven to account for peptic ulcer.[4] The infected patients often have subtle symptoms in the initial stage of the disease due to the low microbial burden in the body.[5] However, the pathogens are still pathogenic and increase their pathogenicity during disease latency, thereby delaying the treatment.[6] Therefore, rapid identification of pathogens from the body and timely diagnosis are essential for breaking chains of transmission and protecting health.[7]

The accurate detection of microbial pathogens in human biosamples plays a pivotal role in the diagnosis and treatment of infectious diseases.[8] Conventional analysis methods involve quantitative reverse transcription polymerase chain reaction (RT-qPCR) and laboratory culture of infectious agents.[9] However, these techniques are time-consuming and require supporting laboratory infrastructures along with technicians,

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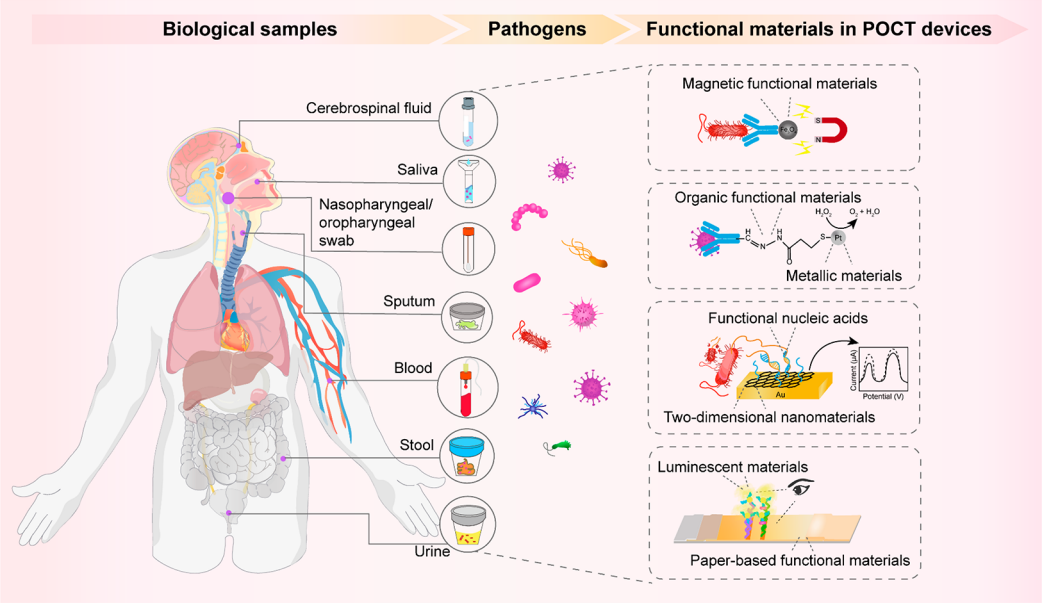

Figure 1. Overview of materials-functionalized POCT devices for pathogen detection in various biological samples from humans.

greatly restricting the large-scale detection of pathogens.[10] To overcome these issues, point-of-care testing (POCT) devices have been recently developed.[11] By integrating molecular recognition elements and signal transduction modules, the POCT devices can sensitively and rapidly translate microbial signals into readable electrical or optical signals.[12] POCT devices offer advantages including ease of use, real-time detection, high sensitivity, and low cost, thus facilitating large-scale detection or home testing.[13] The functional materials at interfaces between POCT devices and biological samples, including inorganic nanomaterials, organic polymers, and biomaterials, are critical for improving the analytical performance of POCT devices.[14,15] The functional materials can provide higher sensitivity and specificity, streamline the sample handling, or serve as supporting substrates for POCT devices.[15] Hence, the development of functional materials for POCT devices has real-world implications for the fast and large-scale detection of pathogens.[16]

Heretofore, the pathogen detection mechanisms of POCT devices and the applications of nanomaterials in pathogen detection have been extensively reviewed, whereas a few reviews focus on materials engineering in POCT devices for pathogen detection, including functional nucleic acid materials, paper-based functional materials, and organic functional materials.[17−19] Moreover, the application potential of different functional materials in clinical samples is rarely emphasized. To illustrate the POCT-systems-enabled microbial analysis of biological samples, this Account reviewed the recent advances in materials engineering of POCT devices for pathogen diagnostics. It starts by introducing the developed functional materials in POCT devices for pathogen testing according to our previous work. Then, the applications of POCT devices in clinical biospecimens, like blood, saliva, and urine, are summarized (Figure 1). Finally, current challenges and future prospects of functional materials-assisted POCT devices for microbial analysis are proposed.

2. FUNCTIONAL MATERIALS IN PATHOGEN DETECTION

The POCT devices mainly consist of a recognition element and signal transduction element. Recognition elements and transduction elements are responsible for the specific recognition of pathogens and signal conversion, respectively. Functional materials exhibit great potential in improving the performance of recognition elements or transduction elements. This section presents several functional materials that are involved in the performance enhancement of POCT devices.

2.1. Magnetic Materials

Low microbial load is an important cause of false-negative results. Therefore, the enrichment and concentration procedures are necessary for pathogen detection in clinical samples. To get rid of the dependence on the centrifuge, immunomagnetic capture was applied to rapid enrichment of pathogens. Our research group used the magnetic bead−antibody complex to enrich *Escherichia coli* and *Staphylococcus aureus* in urine, with luminescent nanoparticles simultaneously binding to the pathogens (Figure 2a).[20] Carboxyl-modified Fe_3O_4 nanoparticles were functionalized with antibodies against *E. coli* and *S. aureus*. Then, the pathogens and luminescent nanoparticles were separated from urine under a magnetic field. The urinary tract infections were confirmed by the luminescence intensity after resuspension. Our group also explored the aptamer-enabled immunomagnetic capture in rapid *E. coli* and *S. aureus* detection (Figure 2b).[21] We developed capture complexes made of mesoporous TiO_2-coated magnetic nanoparticles that were functionalized with the aptamers targeting *E. coli* and *S. aureus*. The mesoporous TiO_2 has a large pore size and high surface area to increase the effective area for anchoring aptamers and improve the pathogen capture efficiency. By combination of the magnetic materials with mesoporous TiO_2, the enrichment and separation of pathogens can be more effective. The bacteria were isolated after the aptamer binding and the application of a magnetic field. The results indicate that most of the bacteria were isolated from blood samples within 2 h.

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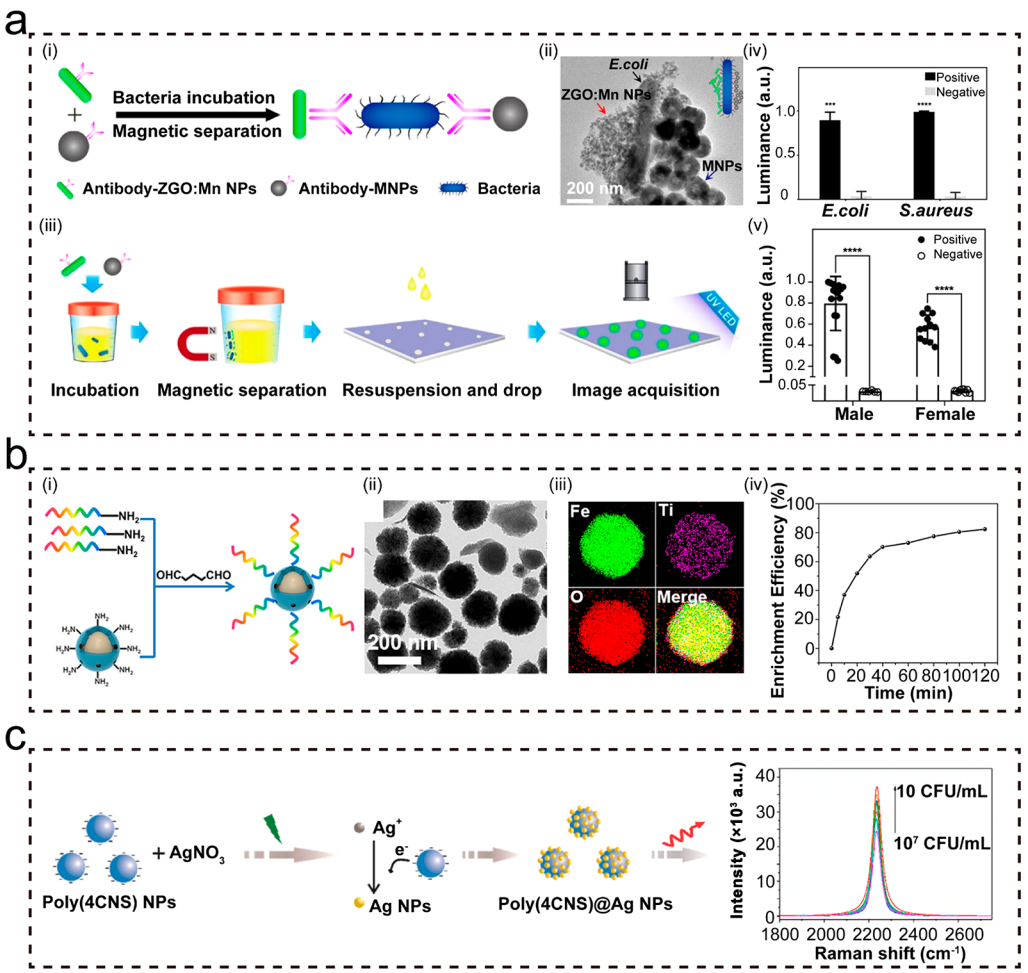

Figure 2. Magnetic materials and metallic materials for pathogen detection using POCT devices. (a) The magnetic materials for bacteria detection in urine. (i) The antibody-modified Fe_3O_4 magnetic nanoparticles that can specifically enrich *E. coli* and *S. aureus* in urine. (ii) Transmission electron microscopy (TEM) image of *E. coli* attached by Zn_2GeO_4:Mn nanoparticles (ZGO:Mn NPs) and magnetic nanoparticles (MNPs). Scale bar, 200 nm. (iii) Luminescent nanomaterials and magnetic-bead-assisted biochip. (iv) Normalized luminance values of samples with or without *E. coli* and *S. aureus*. (v) Normalized luminance values of samples collected from healthy or infected volunteers. Reproduced with permission from ref 20. Copyright 2021 American Chemical Society. (b) The synthesis and characterization of the aptamer/magnetic materials capture platform. (i) Preparation of TiO_2-coated magnetic nanoparticles functionalized with an aptamer (Apt-Fe_3O_4@mTiO_2). (ii) TEM image of Apt-Fe_3O_4@mTiO_2. Scale bar, 200 nm. (iii) Elemental mapping images of the Apt-Fe_3O_4@mTiO_2. (iv) Relationship between enrichment efficiency for *S. aureus* in the blood and incubation time. Reproduced with permission from ref 21. Copyright 2016 American Chemical Society. (c) Raman signal enhancement by the photoreduction of silver ions on the surface of poly(4-cyanostyrene) nanoparticles (poly(4CNS)@Ag NPs). Reproduced with permission from ref 22. Copyright 2022 Elsevier.

2.2. Metallic Materials

Metallic materials have attracted great interest for their superior physical and chemical properties and convenience for micromachining. Noble metal nanoparticles-enabled surface-enhanced Raman spectroscopy (SERS) assays can quantify specific pathogenic bacteria at low concentrations. However, their time-consuming pretreatment and detection procedures as well as poor reproducibility hamper the wide applications of SERS in POCT devices. To facilitate the rapid quantification of target pathogens, our group synthesized the SERS tag by integrating poly(4-cyanostyrene) nanoparticles and Ag^+, which can be photoreduced into Ag nanoparticles surrounding the negatively charged poly(4-cyanostyrene) nanoparticles under laser irradiation, thus enhancing the Raman signals (Figure 2c).[22] As the concentrations of *E. coli* and *S. aureus* increased, more Ag^+ was adsorbed on bacteria, thereby leading to less Ag^+ in the supernatant and a weakened Raman intensity. The whole assays can be performed within 40 min and detect at least ~10 cells of bacteria mixture. In addition, microfluidic technology can be used to prevent nonspecific adsorption in sample pretreatment. Kamińska et al. used the SERS immunoassay to develop a microfluidic system for virus identification.[23] The microfluidic chip integrated with a SERS-active substrate based on Au−Ag-coated GaN was applied to the detection of the hepatitis B virus antigen (HBsAg) in human blood plasma. This system was strategically designed by using basic fuchsin (FC) and antibodies, giving strong SERS enhancement and highly specific chemisorption on the Au nanoflower. The LOD for HBsAg was estimated to be 0.01 IU/mL.

Colorimetric biosensors translate recognition signals into distinct color changes that can be easily observed by the naked eye. However, naked-eye detection with limited capacity for microbiological diagnostic testing will affect the accuracy of results. In contrast, noble metal nanomaterials with intrinsic catalytic properties can elicit gas bubble formation, leading to distinct visual patterns that can qualitatively detect the target pathogens. Draz and co-workers synthesized platinum nanoparticles to label the hepatitis B virus (HBV), hepatitis C virus

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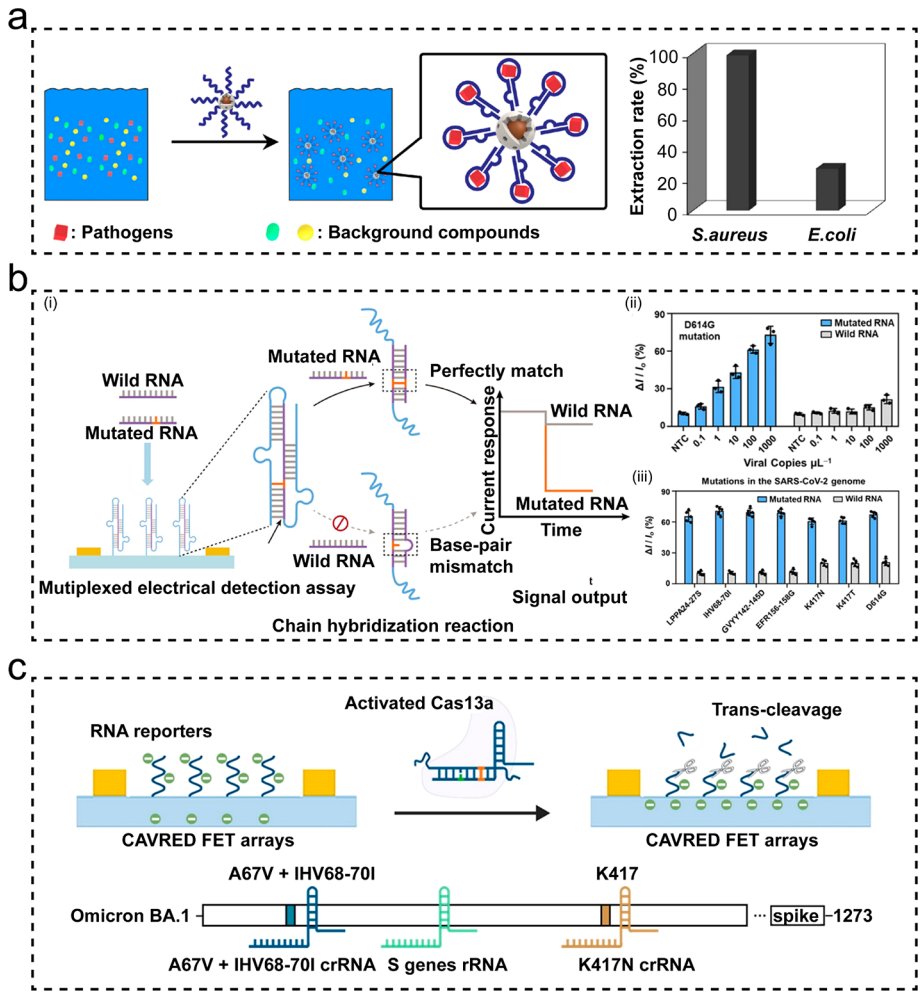

Figure 3. Functional nucleic acids for pathogen detection using POCT devices. (a) Schematic of aptamer-based adsorbents for selective pathogen extraction (left) and the extraction efficiencies in selectivity tests (right). Reproduced with permission from ref 25. Copyright 2017 Springer Nature. (b) The structure of the PNprobe and detection of SARS-CoV-2 RNA mutations. (i) Schematic of PNprobe-functionalized FET biosensor. (ii and iii) Current responses of PNprobe-functionalized FET biosensors to (ii) the SARS-CoV-2 D614G mutation and (iii) seven mutations. Reproduced with permission from ref 27. Copyright 2023 American Chemical Society. (c) The activation of Cas12a by target changing the surface charge density of the FET (top) and the mutations on the S gene of the Omicron variant (bottom). Reproduced with permission from ref 28. Copyright 2023 John Wiley and Sons.

(HCV), and Zika virus (ZIKV).[24] The platinum nanoparticles generate gas bubbles in the presence of hydrogen peroxide, which create distinct visual patterns and allow sensitive virus detection with the aid of machine learning algorithms.

2.3. Functional Nucleic Acid Nanomaterials

Functional nucleic acid nanomaterials provide promising strategies for pathogen-specific testing with merits such as programmable structure, high affinity, low cost, and ease of modification. By leveraging the high affinity of aptamers toward target pathogens, our group reported an efficient strategy for extraction of *S. aureus*, which is realized by aptamer-functionalized core−shell magnetic nanoparticles (Apt-SA-MNPs) (Figure 3a).[25] Apt-SA-MNPs extracted 99.80% of *S. aureus*, while only small amounts of *E. coli* were captured in the assays, demonstrating the specific targeting of *S. aureus* by aptamers. We also reported other aptamer-based platforms in fast pathogen capture and detection.[21,26]

Nucleic acids can also be designed as three-dimensional structures or nucleic acid probes to selectively respond to pathogens. Electrochemical biosensors hold great promise in pathogen detection due to their extremely low detection limit, ease of microfabrication, and rapid response. However, the instability of the probe on the interface of the electrode and nonspecific adsorption of proteins on the interface can greatly impact the transport properties of electrochemical biosensors. Functional nucleic acid nanomaterials could be advantageous as a probe molecule modified on the electrode interface, underlying specific and reproducible detection of pathogens. We reported a paperclip-shaped nucleic acid probe (PNprobe) to functionalize a field effect transistor (FET) biosensor (Figure 3b).[27] Its unique three-stem structure helps stabilize the probe, which, in turn, amplifies the thermodynamic stability difference between variant RNAs. The probe immobilized on the FET interface could recognize and combine with target viral RNA with negative charges, leading to a change of charge density on the FET biosensing interface. The electrical responses for variants increased in a viral concentration-dependent manner, whereas that for the wild type virus remained stable.

Additionally, clustered regularly interspaced short palindromic repeat (CRISPR) technology can be utilized to detect microbial nucleic acids with high sensitivity. We proposed a CRISPR-based amplification-free viral RNA detection platform,

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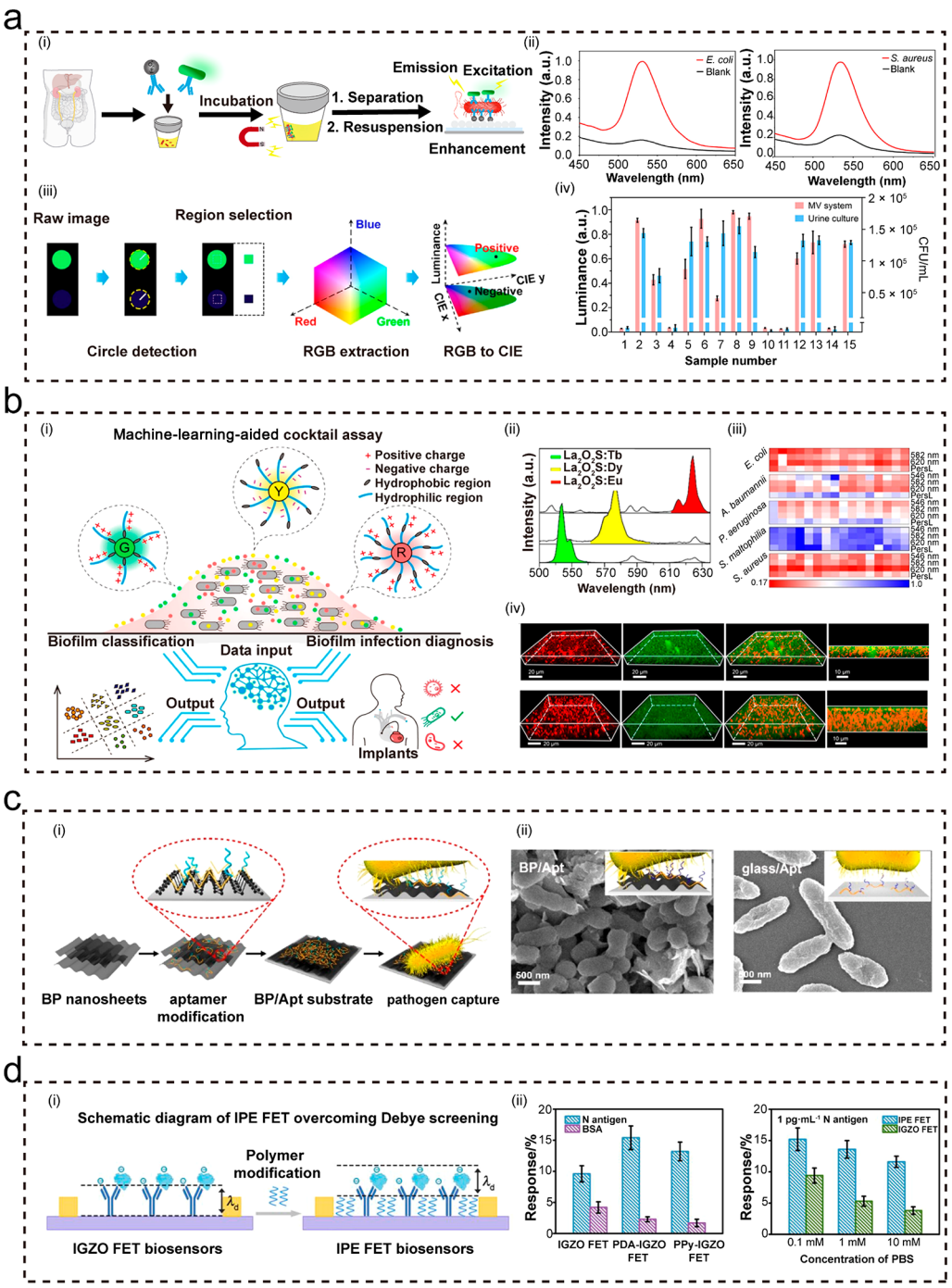

Figure 4. Luminescent materials, two-dimensional nanomaterials, and organic functional materials for pathogen detection using POCT devices. (a) The machine vision (MV)-based diagnostic system with luminescent materials for bacteria detection in urine. (i) ZGO:Mn luminescent nanomaterials that quantified *E. coli* and *S. aureus* in urine samples. (ii) Luminescence spectra of *E. coli*, *S. aureus*, and a blank sample labeled by antibody-modified ZGO:Mn NPs. (iii) Workflow of Python algorithm for immunoluminescence image analysis. (iv) Diagnostic results obtained by urine culture and the MV-based detection system. Reproduced with permission from ref 20. Copyright 2021 American Chemical Society. (b) The machine-learning-aided cocktail assay to profile biofilms. (i) Lanthanide-doped luminescence nanoparticles for biofilm identification. (ii) Photoluminescence spectra of lanthanide-doped nanoparticles. (iii) Heat map of the 16 samples for each biofilm. (iv) 3D images showing the distributions of the Tb-dextran nanoprobes (green channel) in the *S. aureus* (red channel, top) and *E. coli* (red channel, bottom) biofilms, respectively. Scale bar, 20 μm (three images on left) and 10 μm (right). Reproduced with permission from ref 30. Copyright 2022 American Chemical Society. (c) The aptamer-functionalized black phosphorus nanosheets for capture and detection of *E. coli* and *S. aureus*. (i) Substrate preparation and bacteria capture. (ii) Representative scanning electron microscopy (SEM) images of *E. coli* captured on the black phosphorus/aptamer substrate and the glass/aptamer surface. Scale bar, 500 nm. Reproduced with permission from ref 26. Copyright 2020 American Chemical Society. (d) Fabrication and characterization of an interfacial polymer-engineered (IPE) FET biosensor. (i) Depiction of the polymer modification layer to overcome the Debye screening effect. (ii) Comparison of the current responses of FET biosensors for BSA and the SARS-CoV-2 N antigen with and without polymer modification. Reproduced with permission from ref 35. Copyright 2023 John Wiley and Sons.

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which can discriminate mutant against wild RNA of the SARS-CoV-2 virus at single-nucleotide resolution (Figure 3c).[28] The *trans*-cleavage of Cas13a was alternatively activated by mutant-specific crRNA that can specifically recognize the target sequences of the SARS-CoV-2 virus. The detection array exhibited distinct current responses upon the addition of various variants. Reprogrammed with CRISPR RNAs (crRNAs), the CRISPR technology can provide a platform for specific RNA sensing.[29] Integrated POCT devices based on CRISPR−Cas systems are expected to reshape the diagnosis of infectious diseases.

2.4. Luminescent Materials

An optical signal is a readily measurable and discernible visible signal. Fluorescent biosensors exhibit high sensitivity and are therefore widely applied in pathogen detection. Specific recognition elements impart selectivity to fluorescent biosensors, while fluorophores are modified for signal transduction. Compared to fluorescent dyes, luminescent nanomaterials with a high quantum yield and high stability provide reliable signal transduction for fluorescent biosensors. For example, Zn_2GeO_4:Mn nanoparticles exhibit merits such as ease of synthesis, excellent stability and biocompatibility, and strong luminescence intensity. Our group synthesized Zn_2GeO_4:Mn fluorescent nanoparticles to detect both bacteria of *S. aureus* and *E. coli* in urine (Figure 4a).[20] Carboxyl-group-modified Zn_2GeO_4:Mn nanoparticles were functionalized with antibodies against bacteria, so as to form immunocomplexes with bacteria and magnetic beads. The quantification of bacteria can be achieved by detecting the luminescence signals of Zn_2GeO_4:Mn nanoparticles at 535 nm. After combining immunoluminescence strategy with a photonic crystal (PC)-based signal amplification biochip, the luminescence intensity increased by more than 4 times. The luminescence intensity increased in proportion to the concentration of target bacteria, whereas other bacteria exert little effect on the signals.

By taking advantage of multiplexed measurements and machine learning algorithms, our group recently reported lanthanide nanoparticles for the specific detection of bacteria in biofilms (Figure 4b).[30] The lanthanide nanoprobes with different emission wavelengths were synthesized by replacing the hosts and dopants, followed by surface modifications with different groups. Electrostatic and hydrophobic−hydrophobic interactions determined the binding of the lanthanide nanoparticles to biofilms, as demonstrated by the 3D images obtained by confocal microscopy. Then, the luminescence intensity at different wavelengths was used to discriminate the different bacteria. Different luminescence signal patterns were obtained across different biofilms, which exhibit good classification performance in the machine learning model.

Carbon dots nanomaterials possess prominent properties such as high fluorescence stability and excellent biocompatibility. Robby et al. described the design of the $CsWO_3$−FCD nanohybrids, which were prepared using fluorescent carbon dots (FCDs) and near-infrared (NIR)-responsive cesium tungsten oxide ($CsWO_3$).[31] The LOD was 70 CFU·mL^{-1} for *E. coli* and 131 CFU·mL^{-1} for *S. aureus* using this FCDs-based luminescent method.

2.5. Two-Dimensional Nanomaterials

Two-dimensional nanomaterials with high electrical conductivity are critical for enhancing the electrical performance of POCT devices and can also serve as substrates for the ligation of various recognition molecules. Afsahi et al. employed graphene as the base material for the FET platform and demonstrated the sensitive and specific detection of ZIKV.[32] The two-dimensional nanomaterials with engineered surface structure could also serve as a capture substrate of target pathogens. Our group developed a light-responsive device containing aptamer-functionalized black phosphorus nanosheets (Figure 4c), which can detect small amounts of *E. coli* and *S. aureus* in blood.[26] The black phosphorus nanosheets were functionalized with amino groups for conjugating aptamers. The unique wrinkled architectures of black phosphorus and the specificity of the aptamer help the effective enrichment of *E. coli* and *S. aureus* in blood. Notably, the structure of the aptamer modified on the black phosphorus can be changed under near-infrared irradiation, thereby realizing the release of the captured pathogen.

Recently, the digital polymerase chain reaction (dPCR) technique, which initiates thermal cycling after splitting the samples into nanoliter or picoliter droplets, can surpass traditional PCR technology in precise and efficient gene readout. However, dPCR machines are still relying on sophisticated thermocycling modules.[33] Two-dimensional carbon nanomaterials with excellent photothermal effects, such as reduced graphene oxide (rGO), can be integrated into dPCR machines to simplify the thermocycling module. For example, Kim et al. demonstrated a dPCR platform for bacterial discrimination, which consists of hydrogel matrixes containing photothermal nanomaterials rGO and primers. rGO enables ultrafast real-time PCR within 5 min and multiplex assays of bacteria in a single reaction.[34]

2.6. Organic Functional Materials

Organic functional materials can be tailored to produce interactions with pathogens as they contain abundant chemical groups, and their structures can be precisely designed. Interfacial polymer engineering can be employed to enhance the interaction between biosensors and target pathogens, thus realizing the enrichment and rapid detection of pathogens. To eliminate the Debye screening effect of body fluids, our group introduced the polymer layer at the electrode interface of FET biosensors to shorten the distance between pathogens and the electrode.[35] Polydopamine and polypyrrole were functionalized on the electrode surface with solution polymerization and electrodeposition, as demonstrated in Figure 4d. In comparison with the bare electrode, polydopamine- or polypyrrole-modified FET biosensors exhibited higher current responses to the target SARS-CoV-2 N proteins, and this trend was more remarkable when biosensors were exposed to antigens with higher concentrations.

2.7. Paper-Based Functional Materials

Although microfluidic chips exhibit superiority in rapid processing and microbial extraction of biological samples, their high cost limits their large-scale applications in resource-limited settings. Of note, paper is an ideal POCT platform with the characteristics of low cost, ease of process, and incineration, which prevents further infection after diagnosis. Xu et al. developed a capillary-flow platform fabricated by wax printing for the rapid malaria diagnosis.[36] This paper-based platform is not only low cost but can also integrate loop-mediated isothermal amplification (LAMP) reactions and a portable fluorimeter to become a multiplexing detection system. An additional remarkable advantage of paper-based POCT devices is that samples can be readily disposed by incineration, which lowers the risk for disease transmission. As one of the most widely used POCT devices, the lateral-flow test strip exhibits

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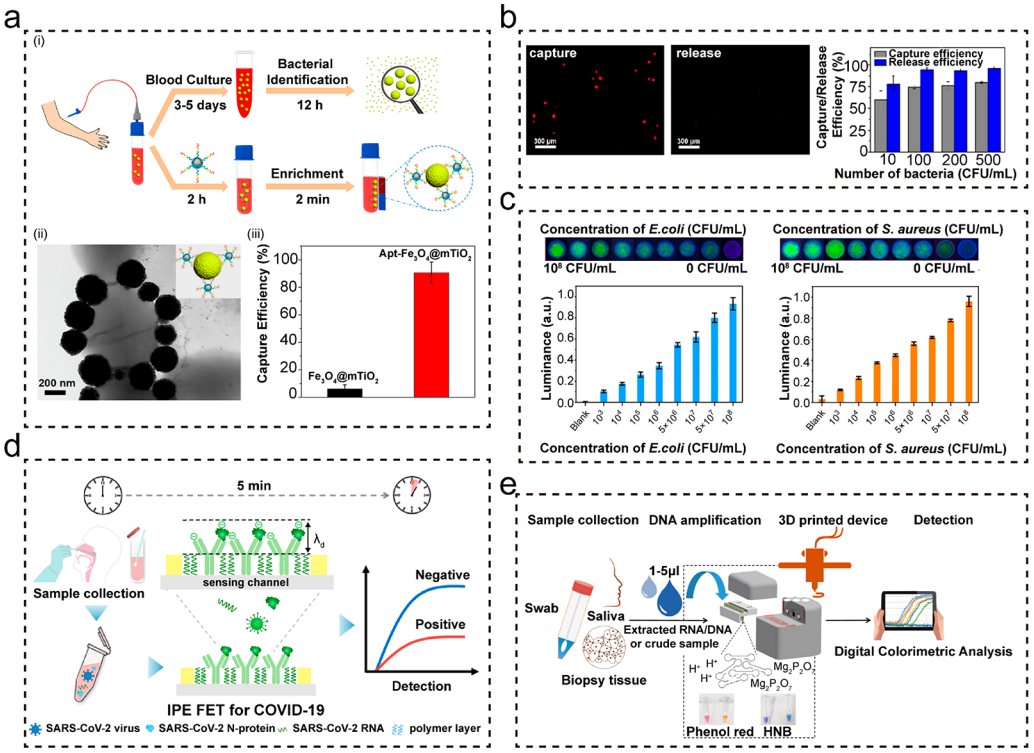

Figure 5. The applications of functional materials-assisted POCT devices in pathogen identification in blood, urine, saliva, and respiratory tract samples. (a) Aptamers/magnetic materials complex to identify pathogens in human blood. (i) Schematic of Apt-Fe_3O_4@$mTiO_2$ nanoparticles capturing and identifying pathogens in the blood. (ii) TEM image and the binding model of *S. aureus* conjugated with Apt-Fe_3O_4@$mTiO_2$. (iii) Capture efficiency of unfunctionalized Fe_3O_4@$mTiO_2$ and Apt-Fe_3O_4@$mTiO_2$. Reproduced with permission from ref 21. Copyright 2016 American Chemical Society. (b) Fluorescence images of *E. coli* captured and released on the black phosphorus/aptamer substrate (left) and the capture and release efficiencies of the black phosphorus/aptamer substrate (right). Scale bar, 300 μm. Reproduced with permission from ref 26. Copyright 2020 American Chemical Society. (c) Normalized luminance values of samples of *E. coli* or *S. aureus* at different concentrations in urine. Reproduced with permission from ref 20. Copyright 2021 American Chemical Society. (d) Polymer-engineered FET biosensor for the efficient detection of the SARS-CoV-2 N antigen in saliva. Reproduced with permission from ref 35. Copyright 2023 John Wiley and Sons. (e) Schematic of respiratory tract samples testing for COVID-19 diagnosis by the qcLAMP device. Reproduced with permission from ref 41. Copyright 2022 the authors.

tremendous advantages in the rapid detection of a variety of pathogens and has been commercially used. Its sensitivity can be further enhanced by other functional nanomaterials. For example, plasmonically active antibody-conjugated fluorescent gold nanorods were introduced into the test strip to harness plasmon-enhanced fluorescence.[37]

3. APPLICATIONS OF MATERIALS-FUNCTIONALIZED POCT DEVICES IN CLINICAL PATHOGEN DETECTION

Body fluids have been characterized by abundance, accessibility, and display of disease-related physicochemical information. In this section, the capabilities of POCT devices based on materials engineering to detect pathogens in complex biological samples are discussed according to our previous work.

3.1. Blood

Blood is one of the most common clinical diagnostic samples, potentially providing polymicrobial information during the early phase of the illness. Traditional diagnostic tools for pathogens in blood are represented by blood culture, while limited sensitivity in the case of exposure to antimicrobials and risk of contamination confine its application in pathogen detection. Notably, direct detection of pathogens employing unprocessed whole blood samples is more favorable by reducing the testing time and avoiding complicated sample processing. To this end, our group proposed the aptamer−magnetic bead complexes to specifically isolate the pathogens from clinical whole blood samples (Figure 5a).[21] The mesoporous Fe_3O_4@$mTiO_2$ nanoparticles were functionalized with *S. aureus* and *E. coli*-specific aptamers. Due to the high affinity of aptamer toward target, the bacterium was surrounded by the aptamer-conjugated complexes, then the bacteria could be isolated from blood samples with high efficiency.

The screening of small amounts of pathogens and the downstream analysis of pathogens in blood play pivotal roles in cancer concurrent infection diseases diagnosis. To achieve this goal, our group employed aptamer-functionalized black phosphorus nanosheets as the substrate to enrich bacteria in blood (Figure 5b).[26] The combination of aptamers and black phosphorus led to the highest capture efficiency. Of note, the near-infrared irradiation reconstructed the structures of aptamers, thus realizing the reversible release of captured *E. coli* and *S. aureus* from blood. We further performed genetic analysis for the bacteria and demonstrated their resistance to antibiotics, which is instrumental in pathogen behavior monitoring and cancer therapy.

In spite of the many merits for blood samples, puncturing the skin, known as the invasive nature of blood sample collection, makes the patient feel painful and anxious. By developing microneedle patches and other painless assays, the POCT device can facilitate the detection of pathogens in blood. For example, Blicharz et al. designed a high-velocity insertion mechanism in

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Acc. Mater. Res. XXXX, XXX, XXX−XXX

an arrays of solid microneedles device for painless and automated capillary blood collection.[38] This microneedle device received premarket clearance by the US Food and Drug Administration.

3.2. Urine

Urine is the liquid byproduct of metabolism extracted from the bloodstream by the kidney. The microbial content of urine samples is closely associated with urinary infection. The current gold standard method for identifying pathogens in urine in clinical laboratories is urine cultivation. However, culture-based assays have drawbacks, such as long turnaround times and uncultivatable pathogens.

The POCT devices based on optical sensors were widely applied to diagnostics in urinary tract infection by the naked eye. Machine vision with robust computing algorithms and signal transduction of fluorescent materials can offer quantitative and reliable results for urine infection testing. Our group used a digital single-lens reflex camera to capture luminescence images and utilized algorithms for image processing (Figure 5c).[20] The carboxyl-modified magnetic nanoparticles and luminescent Zn_2GeO_4:Mn nanoparticles were functionalized with antibodies against *S. aureus* and *E. coli* to form an immunosandwich complex. By amplifying the optical signal with a PC-assisted biochip and using the machine vision algorithm, the image resolution is much better than the naked-eye detection.

Physicians routinely prescribe broad-spectrum antimicrobial drugs for an unknown urinary tract infection in resource-limited settings, thus leading to antimicrobial resistance. Therefore, rapid antibiotic susceptibility testing (AST) is essential for precise antibiotic therapy along with pathogen detection. Michael et al. proposed a hand-held POCT device that enabled the on-site detection of urinary tract infections using undiluted urine, and this device was also used to perform AST within 120 min.[11] The operation processes include introducing an antibiotic-treated urine sample into the device, after which viable bacterial cells cause changes in the color of the formazan dye. The reduction in signal intensity suggests that bacteria are susceptible to antibiotic drugs.

3.3. Saliva

Saliva, as one of the most important body fluids in the body, contains nonexocrine components such as microbes.[39] Saliva has received attention for the diagnosis of infectious diseases due to its high viral load. Saliva collection is noninvasive and has an important role in clinical diagnosis. FET biosensors are label-free and easy to manufacture, making them good candidates for pathogen screening in saliva samples. Our group fixed the SARS-CoV-2 N antigen on an FET channel surface deposited by In_2O_3, Ga_2O_3, and ZnO, then functionalized the channel surface with polydopamine and polypyrrol, thereby shortening the distance between the target N antigen and the sensing interface.[35] The LOD for SARS-CoV-2 detection in untreated saliva was as low as 4.6 fg mL^{-1} within 5 min (Figure 5d).

Identifying pathogens from untreated saliva samples is more favorable for the one-step detection of pathogens. Ricotta et al. detected ZIKV in human saliva samples using a chip-based potentiometric sensor without any sample manipulation.[40] They prepared the alkanethiol (11-mercapto-1-undecanol) self-assembled layer on the chips, thus creating imprinted cavities that only match the dimensions of ZIKV. The results demonstrated that the engineered layer has the capability to selectively detect ZIKV with LOD < 10^{-1} PFU mL^{-1} in 20 min.

3.4. Respiratory Samples

Common clinical respiratory samples can be divided into upper respiratory tract samples, such as nasopharyngeal and oropharyngeal (NP/OP) swabs samples, and lower respiratory tract samples, including sputum. The respiratory samples can trap inhaled pathogens and are therefore important in respiratory infections diagnosis. The clinical upper respiratory samples collected by swabs are easy to possess. Both sensitivity and specificity can be improved, and the processing procedures of NP/OP swabs samples can be simplified by using the LAMP technique. Papadakis and co-workers proposed a real-time quantitative colorimetric LAMP (qcLAMP) device that embedded a mini-camera and used phenol red and hydroxy naphthol blue for better discrimination for RGB sensors in approximately 30 min (Figure 5e).[41]

Sputum samples are coughed up from the lower respiratory tract, and sputum collection is noninvasive and independent of sampling skills. Hence, sputum samples are very suitable for POCT devices. Jaroenram's group developed a rapid and sensitive method for *M. tuberculosis* (*Mtb*) detection in sputum samples, which is based on the LAMP reaction and lateral flow dipstick (LFD).[42] In one reaction, the designed probe allows the simultaneous completion of cohybridization and amplification of *Mtb* DNA in a total assay time of approximately 70 min.

3.5. Other Samples

Since stool samples are less invasive and costly than colonoscopy and gastroscopes, they are an excellent source to identify many pathogens associated with gastrointestinal disorders. Ali et al. used wax printing to fabricate the paper-based indicator containing three zones interconnected by a channel, where the middle sensor zone assembled the DNAzyme−urease beads that can specifically bind to the crude extracellular mixture of *H. pylori*, thus activating the DNAzyme cleavage reaction and releasing the cleavage fragment containing urease (Figure 6a).[43] The freed urease reached the right detection zone containing urea and phenol red, generating a distinct color change that can provide results in several minutes.

The cerebrospinal fluid (CSF) is rich in nutrients and signaling molecules that are vital for brain function and can be used for clinical diagnosis of both bacterial and viral meningitis and central nervous system infections. Microfluidic chips combined with fluorescent dyes can enable efficient meningitis detection. Tian et al. fabricated a multifunctional microfluidic module using polydimethylsiloxane (PDMS), which can be used as an auxiliary method for early diagnosis of cryptococcal meningitis (Figure 6b).[44] The CSF samples were injected into the module to effectively capture and enrich *Cryptococcus* in the CSF, followed by on-chip nucleic acid extraction.

There are major privacy concerns associated with the collection process of the clinical samples for diagnosing diseases such as clinical vaginal and cervical swab samples for gynecologic conditions. Therefore, POCT devices have advantages in self-testing for these diseases. Yin and co-workers proposed a convenient and reliable nucleic acid quantification device for HPV detection in clinical vaginal swab samples, which is based on the metal ion indicator eriochrome black T (EBT) and the LAMP assay to produce hue value changes that can be directly quantified by a smartphone (Figure 6c).[45]

Serving as an exchange medium between blood plasma and cells, interstitial fluid (ISF) contains a variety of molecular biomarkers that originated from cells and surrounding blood capillaries. However, the utility of ISF in pathogen detection is

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Acc. Mater. Res. XXXX, XXX, XXX−XXX

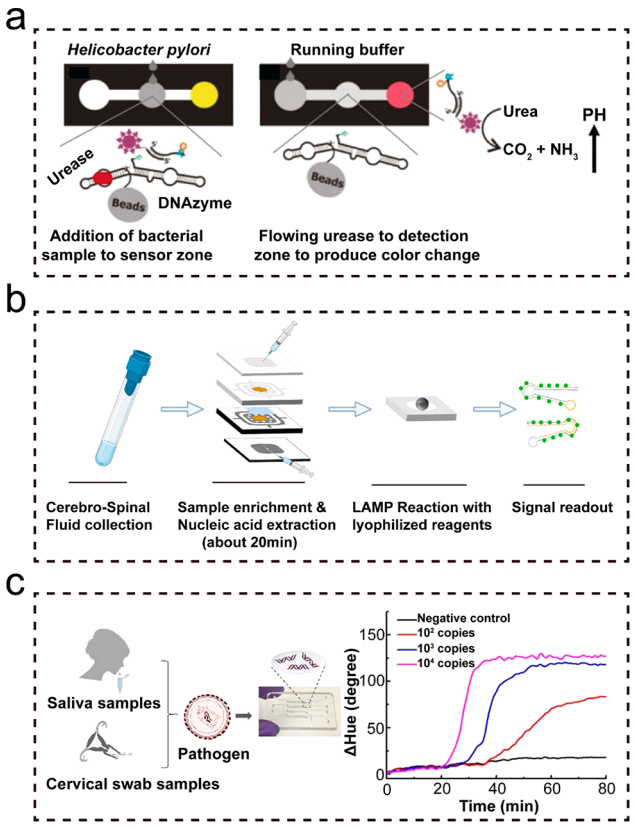

Figure 6. The materials-functionalized POCT devices for infectious disease diagnosis using human stool, cerebrospinal fluid, and vaginal swab samples. (a) *H. pylori* detection in human stool samples by colorimetric paper sensor. Reproduced with permission from ref 43. Copyright 2019 John Wiley and Sons. (b) The process of detecting *Cryptococcus* in CSF samples on a microfluidic module. Reproduced with permission from ref 44. Copyright 2022 Elsevier. (c) The hue-based microfluidic chip containing four independent LAMP reactors for real-time HPV detection in vaginal swab samples. Reproduced with permission from ref 45. Copyright 2020 the authors.

limited because the efficient extraction of specific biomarkers in ISF remains challenging. In view of this, Yang et al. combined the advantages of microneedles consisting of micrometer-scale needle arrays with iontophoresis to improve the extraction efficiency in ISF and developed a label-free, enzyme-free, minimally invasive engineered wearable POCT system.[46] This system can detect the Epstein−Barr virus from ISF within 10 min.

Cells release exosomes that transfer their compositions to neighboring cells to communicate with each other. Exosomes are cell-derived vesicles that offer the ability to enrich specific components about infection and can be retrieved in many body fluids, such as blood, urine, and saliva.[47] During infection by pathogenic bacteria, exosomes play a critical role in antigen presentation. However, the utility of exosomes has far been limited by the fact that biological sample composition is complex, requiring isolation or lysis of exosomes from a heterogeneous background. To address these issues, Qian et al. designed a paper-based sensor cartridge to detect influenza A virus (IAV) RNA and exosome mRNA.[48] The sensor cartridge included a lysis chamber with membrane paper, a channel composed of cellulose paper strips, and three paper-based reaction chambers. This sensor achieved quantitative analysis of target nucleic acids and exosomes within 1 h, with an LOD of 10^6 exosomes/mL.

4. CONCLUSION AND PERSPECTIVE

As pathogen infection induces diseases and can spell great disaster for humans, the rapid detection of pathogens in biological samples is essential to the fight against infectious diseases. In comparison with specialized equipment in laboratory settings, POCT devices with advantages of high sensitivity, low cost, and rapid response can be widely applied to infectious disease screening in resource-poor settings. By virtue of the outstanding physical or chemical properties, functional materials are advantageous for sample pretreatment, pathogen sensing, and signal readouts in POCT devices.[49] Despite the fact that functional materials for performance enhancement of POCT devices are becoming more attractive, current research still presents several problems as mentioned below.

First, the sensitivity of existing POCT devices is still insufficient to identify pathogens with ultralow concentrations in actual samples. In the early stages of disease development, the low pathogen load in biological samples usually leads to false-negative results in testing. For example, the viral loads in the majority of patients infected with monkeypox virus (MPXV) were low in blood (Ct 32 ± 8) and urine (31 ± 1) within 14 days, hence resulting in MPXV-negative results.[50] Most POCT devices involve immobilized biorecognition elements, such as antibodies, to detect target pathogens. However, when the volume of the biological sample is small, there remains an obstacle to generate a significant signal output. Also, nonspecific adsorption of biomolecules on the electrode surface can give rise to high background baselines and affect the reliability of electrochemical methods. Moreover, the clinical samples containing complex components require pretreatment by well-trained personnel, thus limiting the sensitivity of the POCT devices. In the future, the materials for specific enrichment and concentration of pathogens are urgently needed, such as mesoporous nanomaterials and aptamers or antibody-conjugated two-dimensional materials. In addition, high-performance carbon nanomaterials and black phosphorus nanomaterials are promising candidates to amplify the electrical response caused by antigen binding. Carbon nanomaterials have excellent electrical conductivity and stability. Black phosphorus nanomaterials show high carrier mobility, a large on−off current ratio, and a wide band gap range. These merits can greatly enhance the electrical performance of the POCT devices. Also, the unique surface structures of these materials suggest a strong interaction with biomolecules.

Second, existing POCT devices in practice remain dependent on cumbersome peripherals to provide the functionality extension, thus limiting their portability. Most POCT devices for pathogen detection are used under laboratory conditions with controlled reaction conditions. Meanwhile, sample pretreatment, analyte sensing, and signal readouts are separated from each other and entail various instruments, respectively. Therefore, better portability and usability are still challenges for the applications of functional materials in bedside and home testing. Integrating sample pretreatment and signal transduction in a single unit and getting rid of the dependence on peripheral devices, such as fluorometers, heating blocks, and magnetic racks, will advance the development of portable POCT devices.

Also, the reliance on antibodies elevates the cost of pathogen detection and limits the sensitivity of POCT devices due to the instability of antibodies. Additionally, coupling antibodies to

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Acc. Mater. Res. XXXX, XXX, XXX−XXX

functional materials as well as long-time exposure at ambient temperature may also reduce antibody activity. For example, FET sensors need to be stored under dry and cold conditions, so as to maintain the conformation and activity of antibodies at the electrode interface. Ensuring an extended shelf life of the device is therefore a critical issue for practical applications. Innovative molecular recognition strategies are promising for sensitivity and stability elevation. For example, aptamers rival antibodies in the specificity and affinity, and their production costs are relatively low. Aptamers can also be functionalized with various chemical groups or nanomaterials, thereby offering more functionalities and a rapid response. Although aptamers are promising candidates for pathogen detection, some challenges still remain. For example, aptamers exhibit cross-binding to nontarget molecules in actual complex samples. Moreover, the availability of aptamers against many pathogens is still insufficient due to the limited screening efficiency. In view of this, artificial bases can be introduced into nucleic acid libraries to improve the efficiency of aptamer screening and to develop aptamers with stronger specificity.[51]

Overall, the materials engineering in POCT devices for pathogen diagnostics helps improve the efficiency and accuracy in infectious disease diagnosis, which requires collaborations among multiple disciplines, including microelectronics, materials, and biology. Future design of high-performance functional materials will promote the applications of POCT devices in clinical pathogen detection and disease diagnosis. We envision that functional materials-assisted POCT devices will be positioned to be the first line of defense in the battle against infectious diseases.

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