Biomaterials Science

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d0bm02164d

A comprehensive review on the applications of nano-biosensor-based approaches for non-communicable and communicable disease detection

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The outstretched applications of biosensors in diverse domains has become the reason for their attraction for scientific communities. Because they are analytical devices, they can detect both quantitative and qualitative biological components through the generation of detectable signals. In the recent past, biosensors witnessed significant changes and developments in their design as well as features. Nanotechnology has revolutionized sensing phenomena by increasing biodiagnostic capacity in terms of specificity, size, and cost, resulting in exceptional sensitivity and flexibility. The steep increase of non-communicable diseases across the world has emerged as a matter of concern. In parallel, the abrupt outbreak of communicable diseases poses a serious threat to mankind. For decreasing the morbidity and mortality associated with various communicable and non-communicable diseases, early detection and subsequent treatment are indispensable. Detection of different biological markers generates quantifiable signals that can be electrochemical, mass-based, optical, thermal, or piezoelectric. Speculating on the incumbent applicability and versatility of nano-biosensors in large disciplines, this review highlights different types of biosensors along with their components and detection mechanisms. Moreover, it deals with the current advancements made in biosensors and the applications of nano-biosensors in detection of various non-communicable and communicable diseases, as well as future prospects of nano-biosensors for diagnostics.

Received 21st December 2020,
Accepted 19th February 2021

DOI: 10.1039/d0bm02164d

rsc.li/biomaterials-science

Introduction

Diagnosis is fundamental towards improving the effectiveness of treatments.[1] There are two prospects of diagnosis: one is to confirm the disease and the second is to investigate the susceptibility of a person as part of an age-related group for various diseases. Globally, about 1 in 6 deaths are due to late-stage cancer detection and inaccessible diagnosis.[2] Communicable diseases with their infectious etiology cause around 4 million deaths each year globally. Though the non-communicable diseases (NCD) are not infectious or communicable, they have emerged as a principal cause of illness and death worldwide, contributing to 71% of all deaths.[3] These figures indicate that a high mortality rate is more associated with NCD than communicable diseases globally.[4] Communicable diseases are contagious but proper precautions and sanitation can prevent their transmission and prevent people acquiring infections while NCD are triggered by unhealthy lifestyle as well as aging includ-

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ing all physiological, environmental, genetic, and behavioral factors.[5,6]

However, whether the disease is communicable or not, the treatment and recuperation entirely depend on its early and effective diagnosis. Microscopic techniques, immunosorbent methods (ELISA), and immunofluorescence, though proved to be clinically significant, tend to display certain limitations such as lower sensitivity, cumbersome nature, low specificity, imprecise results, and high cost.[7] To surmount the mentioned drawbacks quick, effective, biocompatible and high-throughput diagnostic techniques are unmet clinical requirements. In recent decades, the identification and detection of biological markers associated with communicable and NCD have been accomplished by various sensing techniques.[8] These techniques include high-conductivity electrodes that can perceive or trace electro-active biomolecules found in the body that are specific for the disease condition and generate a strong signal.[9] All these mentioned features exist in a sensing device christened a biosensor. Therefore, the implementation of biosensors could be an advantageous approach for the prominent detection of biological markers. Moreover, recent developments in biosensors have brought evolutionary changes in biomedical research, healthcare clinics, agriculture, food processing, and many other fields.[10]

Presently, biosensors are categorized broadly based on either the biological element, including an antibody, enzyme, or nucleic acid, or on the transducing element like electrochemical, acoustic, optical, and calorimetric.[11,12] Despite being effective, biosensors entail certain limitations like poor selectivity, charged particle interference and manipulation, lack of surface architecture, and susceptibility to environmental interference.[9,13,14] However, these limitations could be effectually eliminated through amalgamating biosensors with nanotechnology and this concept has gained great importance over the last several decades. The primary concept of nanotechnology deals with the implementation of nanoparticles (NPs), with a structural dimension of less than 100 nm, in manipulating materials at the molecular as well as atomic level.[15] This provides NPs with a permissible size to interact with subcellular structures, including cell organelles or biological macromolecules, thereby enabling their ready incorporation into biological systems.[16,17] The large surface area of these NPs works as a potent transducer, and thereby integrating these nanomaterials (NM) along with electrical systems could give rise to smart nanoelectromechanical devices (NEMS) which are proactive in their electrical transduction mechanisms.[18] It further increases the sensitivity to several magnitudes, provides a high specific surface and hence provides high immobilization.

Bio-functional NM have been proved to produce a collective impact among biocompatibility, conductivity, and catalytic activities to hasten the signal processing, but also provide augmented recognition events by elevated loading of signal tags, that resulted in increased sensitivity and unambiguous biosensing.[19,20] The performance of nano-based biochemical sensors is outstanding in terms of linearity, response time, selectivity, sensitivity, stability, and reproducibility compared to the traditional biosensors. This emerging approach is critically useful in the biomedical sector and clinical diagnosis. Therefore, the current review presents the historical hierarchy of biosensors, their components, and types, as well as the recent advancements made in the development of biosensors and NP-based biosensors. The role and detailed applicability of nanoparticle-based biosensors in disease diagnosis of various NCD (cancer, metabolic, neurological, and neonatal disorders) and communicable diseases (viral, bacterial, fungal, and parasitic infections) are also described. The review presents some of the commercialized nanoparticle-based biosensors. Lastly, with this prospect, the current review highlights the trending, novel, and innovative investigations accompanying nano biosensors like *in vitro* detection and *in vivo* imaging of DNA methylation,[21] histone acetyltransferase detection,[22] development of biosensors with engineered molecular manipulators, and application of smart technologies[23,24] that can revolutionize the biomedical sector as a whole.

Types of biosensor and their components

Biosensors have numerous beneficial applications in several domains such as medical sciences, agricultural science, environmental science, as well as management sciences.[25–28] As a result of these benefits and applications, researchers are now utilizing several types of biosensors which are been employed in diverse areas of human endeavors.[29–31] As reported by Turner *et al.*,[32] the first/initial discovery of the biosensor which was chemical/glucose-based was by Leland Clark Jnr (popularly known as the Clark electrode or biosensor), and was used for detecting the quantity of oxygen (O_2) circulating in the blood.[33] Nevertheless, it was in the year 1962 that Clark and Lyons designed the first known biosensor that quantifies glucose in biological samples, which employed the approach of electrochemical recognition of hydrogen peroxide (H_2O_2) or oxygen (O_2) employing a measured glucose ($C_6H_{12}O_6$) oxidase electrode (Fig. 1). Biosensors first came to public attention in the mid-1970s, and they have since grown tremendously in terms of capabilities and the use of biosensor machinery with progressive tendencies. There are various biosensor mechanisms developed for several viable drives encompassing electrochemistry, nanotechnology, and bioelectronics.[25,28,34,35]

Undoubtedly, the present modern-day biosensor mechanisms have prevalent benefits, which offer extra precision, sensitivity, and rapid, perceptible, and multiplicative outcomes when compared to preceding chemical/glucose-based biosensors.[25] The sensing/detecting mechanisms of biosensors comprise immunosensors (antibodies), enzymes, microbes, organic organelles, and tissue-specific macromolecules. The transduction approaches are centered on the physiochemical distinction ensuing from sensing/detecting mechanisms.

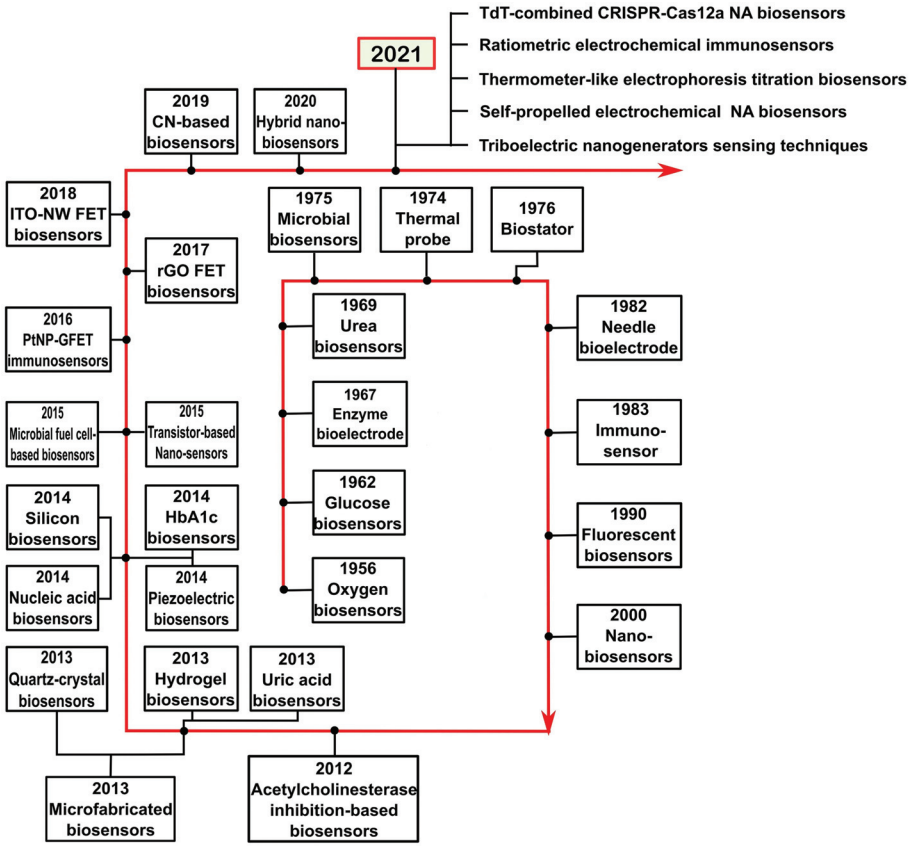

Fig. 1 Timeline of advancements in biosensors. FET-field-electric transistor, GFET-graphene FET, PtNPs-platinum nanoparticles, rGO-reduced graphene oxide, ITO-NW-indium–tin oxide nanowires, CN-carbon nanotubes, TdT-terminal deoxynucleotidyl transferase. Figure concept is obtained from previously published articles.[205–210]

Consequently, different transducer biosensor mechanisms could be electrochemical, piezoelectric, optical, and calorimetric.[36] Accordingly, some of the most important categories of piezoelectric transducer biosensor mechanisms are ultrasonic and acoustic; those of the electrochemical transducer biosensor mechanisms are conductometric, amperometric, and potentiometric; while the optical transducer biosensor mechanisms are chemiluminence, absorbance, and fluorescence.[27,37,38]

Biosensors operate on the cell signaling principle and as stated earlier the foremost components of a functional biosensor include an element of biorecognition, a biotransducer, and electronic parameters that could integrate a microprocessor, amplifier, and display/monitor.[19] The biorecognition or sensing component is a bioreceptor that is intended to detect or act on a specific analyte (the target substance) whose related feature are to be identified or measured.[20] The transducer receives input from the bioreceptor and, depending on the transducer employed, a signal is relayed to the signal processor. The signal output amplitude is proportional to an analyte's concentration.[39] The signal is then amplified by the electronic device and processed.

Considering an amperometric sensor, the bioreceptor comprises a deactivated enzyme or specific bio-material and the said deactivated bio-material is maintained in close connection with the transducer. The analyte reacts with the biomaterial. In this way, a new analyte may be formed which in effect gives the calculable electronic response. Sometimes, the analyte is transferred to a system that can be attached to heat, gas, or electron/hydrogen ion discharge. In this, the transducer could regulate the mechanism linked, then translate it to electrical signals that could be altered and computed.[27,39,40] Biosensors could be distinguished by way of the transduction sensing strategy employed in their construction. Common families are: electrochemical, calorimetric and optical. In some cases, one family may dovetail into another in which case there may not be very clear boundaries of distinction.[29,30,39,40]

The components of a biosensor are instrumental to its operation. First, every biosensor is designed to perform specific functions. The way and manner in which a biosensor operates are dependent on the bioreceptor (enzyme, DNA, phage, antibody, *etc.*) and the sensing strategy (the workings of the transducer).[19,20,30,41] The transducer's electrical signal is always small and overlays a fairly high baseline. Usually, the processing of the signal requires the deduction of a baseline location signal, collected from a similar transducer without a covering of any biocatalyst. The biosensor reaction's comparatively slow character significantly eases the issue of electrical

noise filtration. The direct output is an analog signal at this point. However, the signal may be digitized and relayed to the microprocessor unit where the information is processed, guided by preferred units, and exported to a data store.[42] A biosensor can work inside or outside a living organism; however, the target characteristic parameter to which the device is applied to detect/measure often emanates from the living organism or ecosystem. Illustratively, the foremost components of a functional biosensor with processor and display capabilities are shown in Fig. 2.

Biosensors are more progressive in terms of selectivity and sensitivity compared with any other former existing diagnostic device. Some of the momentous benefits of biosensors include fast and continuous measurement, condensed use of reagents, eradication of calibration and re-calibration, high precision, quick response time, and ability to measure non-polar molecules that other traditional devices cannot estimate.[27] The utilization of biosensors has accomplished some substantial benefits in several domains such as biomedical sciences, pharmacology, environmental sciences, agricultural science (food protection and processing), management sciences, *etc*. The discovery of biosensors has resulted in the evolution of precise and dominant diagnostic mechanisms through biological sensing machinery.[26,28] The different kinds of biosensors have variations in their applications and machinery.

Hence, Fig. 3 shows some of the types of biosensors such as electrochemical biosensors, optical biosensors, microbial biosensors, photoelectrochemical biosensors, calorimetric biosensors, mass-based biosensors, and their subtypes of biosensors. Electrochemical biosensors are a class of biosensors that operate using an electrochemical transducer and can be classified into amperometric, potentiometric, conductometric, and impedimetric sensors,[30,43] while optical biosensors are devices that contain a biorecognition sensing constituent combined with an optical transducer system.[44] Fluorescent, luminescent, colorimetric, interferometric, surface plasmon resonance and optic fiber are the primary types of optical biosensor. A microbial biosensor on the other hand is a device with a biomolecule (a component of a microorganism) integrated transducer that generates a measurable signal indicating the analyte concentration.[45] Photoelectrochemical biosensors exploit the process where photon to electric exchange occurs from charge separation and concurrent charge transfer after absorption of photons during illumination.[46] Calorimetric biosensors explore the process of estimating the amount of heat released or absorbed during a chemical reaction.[30] In principle, mass-based biosensors operate based on the piezoelectric properties of the sensors, so binding events and their simultaneous mass increase at the sensor surface are measurable by a change in the oscillation of the surface acoustic wave.[47]

Application of nanotechnology in designing biosensors

The use of NMs in the design and development of biosensors enhances their performance because properties at the nanoscale are different from those of the bulk form of a material.[48] Among the NMs that are used the following can be mentioned:

Noble metal nanoparticles

These types of structures exhibit unique electric, photonic and catalytic properties like local surface plasmon resonance, surface-enhanced Raman scattering,[49] and surface-enhanced fluorescence[50] as well as good stability and biocompatibility. Different nanoparticle shapes have been used, for instance, spheres,[51] nanorods,[52] nanocages,[53] and nanoclusters.[54] They

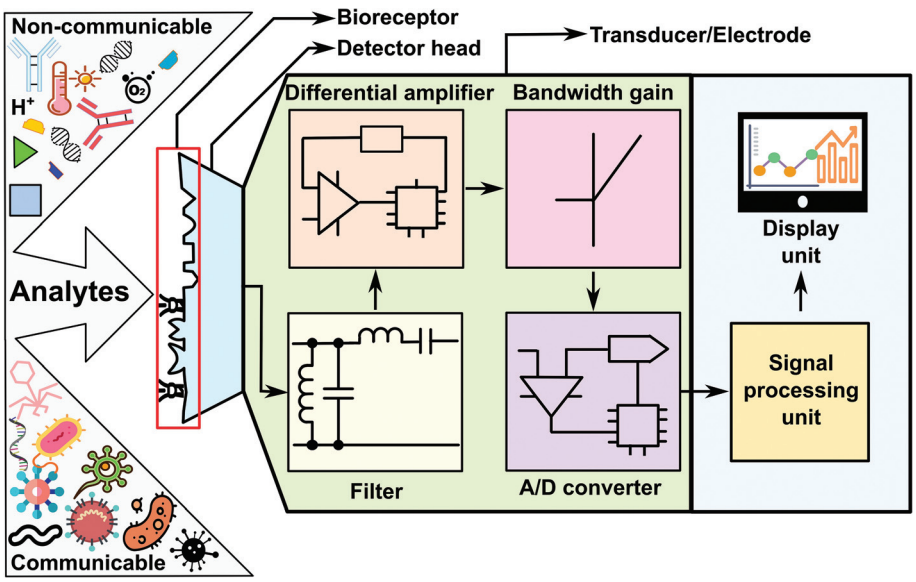

Fig. 2 Block prototype of a functional biosensor.

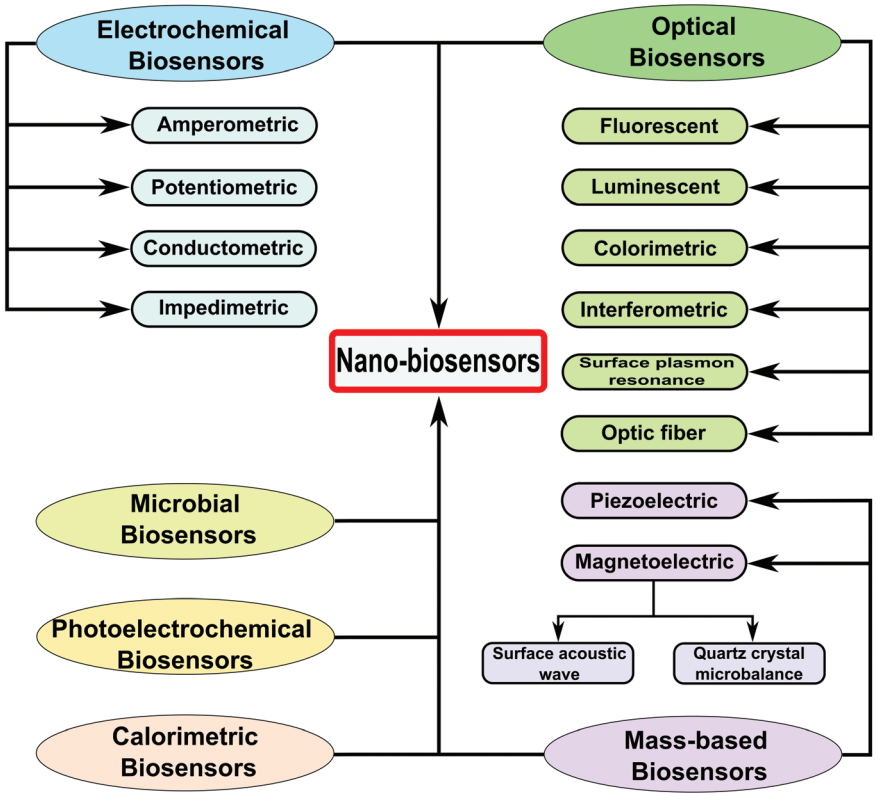

Fig. 3 Some of the foremost types and subtypes of biosensors.

have been widely investigated for their usage in electrochemical, optical, chemiluminescent, photoelectrochemical, colorimetric, and piezoelectric biosensing.[55]

Magnetic nanoparticles

These NMs are constituted by magnetic elements, such as iron,[56] nickel,[57] cobalt,[58] chromium,[59] manganese,[60] gadolinium[61] and their chemical compounds. Magnetic nanoparticles are superparamagnetic due to their nanoscale size.[62] Other features they exhibit are extra anisotropy contributions, high saturation field, high field irreversibility, or shifted loops after field cooling. Such properties originate from narrow and finite-size effects and surface effects that influence the magnetic behavior of the individual NPs.[63] They are incorporated into electrochemical, piezoelectric, optical, and magnetic field biosensors.[64]

Quantum dots (QDs)

They are semiconducting nanocrystals derived from atoms belonging to groups II–VI, III–V, or IV–VI of the periodic table. They possess size-tunable optical properties such as emission spectrum, which leads to the detection of different targets.[65,66] They are a good alternative to fluorescent protein and organic fluorophores.

Carbon-based NMs

They are synthetic carbon allotropes, for instance, carbon nanotubes (CNTs), crystalline diamond, and diamond-like carbon. Each structure possesses its own characteristics. The most common carbon nanostructures used in biosensors are carbon nanotubes, which display low mass density, high flexibility, and large aspect ratio, which result in excellent mechanical, thermal, and electrical properties.[67] There is also graphene, with outstanding barrier, optical, electronic, mechanical, thermal, and chemical properties like high surface area, high Young's modulus, high electron mobility, transmittance, superior thermal conductivity, chemical stability, and a high level of transparency.[68] They are highly used in electrochemical and electrochemiluminescence biosensors.[69–71]

Other NMs

Other NMs more than the aforementioned ones have been taken into account, like chitosan, which is a cationic biopolymer that has been studied in electrochemical and voltammetric biosensing, and is usually reported as a part of a composite system.[72–74] In the biosensor domain nanostructures like dendrimers are used as linkers[75] as well as for non-covalent and covalent binding of enzymes.[76]

Application of nanotechnology in biosensor development

Advanced NMs are currently being engineered, along with their ingenious features and advantages for biosensor mecha-

nisms, as nanotechnology advances.[77] Based on the sensing approach applied in the fabrication, about seven foremost types are known; the additional one that makes it eight is the nano biosensor which is based on NPs. As illustrated in Fig. 3, nano biosensors may well be a hybrid and could apply the sensing approaches applied in other foremost types. The alliance of polymer-based NPs with different types of biosensor has presently improved the efficacy of the abovementioned applications.[25,28,78–80] Moreover, scientific advancement has been of great assistance in the development of microbial biosensors utilizing biological or organic synthesis approaches that are now contributing to energy and environmental management, monitoring, and sustainability.[25,28,81]

The use of NPs such as gold, silver, carbon, titanium-based, and silicon-built bio-fabrication has produced innovative procedures for biomedical disease detection.[82] Also, the coating/covering of polymers on these NPs brought enormous advancements in contact-built electrochemical sensing. The foremost benefits of these electrochemical sensors include sensitivity and specificity with real-time detection. Despite restrictions such as a narrow or limited temperature range, a short or limited shelf time, and cross-sensitivity to other gases, the low cost of such electrochemical sensors makes them more affordable.[28]

Non-communicable diseases

A disease that is not contagious can be regarded as an NCD.[83] For example, heart and stroke disorders, cancer, chronic respiratory obstruction conditions, diabetes, *etc*. are some of the examples of NCDs. These diseases influence people of all regions and nations and are linked to older age groups. Recent reports state that around 15 million NCD-related deaths are recorded between 30 and 69 years of age and more than 85 percent of such mortalities are reported in low- and medium-income countries.[84] These mortalities can be controlled through an effective, early, and accurate diagnostic process. These requirements can be met with the advancement in the field of nano biosensors, designed for detecting specific biomarkers for the disease type which supports further precise treatment of the patients.[85] Therefore in the sections below applications of nano biosensors are briefly discussed in some of the most debilitating NCDs like cancer, metabolic disorders, neurological disorders, and neonatal disorders (Table 1).

Cancer

Cancer is defined as an abnormal group of cells that has lost its cell cycle arresting mechanism and hence shows uncontrolled cell proliferation and division[86] (Fig. 4). The cell acquired this type of fate because of specific genetic and epigenetic defects in its nuclear DNA, along with certain types of physical, chemical, and biological factors that are also responsible. The proliferation of the cell leads to the formation of a tumor mass which imbalances the homeostasis of the body.[87] As the cancer progresses, it rapidly breaks down the basal membrane of the primary tissue layer and travels through a blood vessel or lymphatic vessel to develop secondary new tumors in other parts of the body, thus making it untreatable.[88] The traditional techniques used for diagnosing cancer *via* CT scan (computed tomography) and biopsy are cost-deficit and often tedious approaches with a high chance of a false report. The other techniques used for cancer detection such as magnetic resonance imaging (MRI), cancer protein assay, ultrasonography, RI (radionuclide imaging), fluorescence, and MACS (magnetic-activated cell sorting) depend on the proficiency and evaluative suggestions of well-skilled/trained personnel.[89]

Although these techniques are highly efficient still they lack specificity and sensitivity. Determining the signatures of the cancerous or the abnormal cells with the help of NM-based biosensors would be a plausible approach for the early detection of cancer.[90] Potential advantages of nano-biosensors over conventional cancer diagnosis techniques, specifically speed, portability, elevated sensitivity, unambiguousness, simplicity, and miniaturization are vastly appreciated.[91] Identification of heterogeneous types of cancer based on their specific biomarkers would be an efficient and specific way to detect the type of cancer. A biomarker is a molecule whose expression pattern gets altered in response to pathophysiological conditions.[92] For example, there is overexpression of specific kinds of proteins by the cancer cells, either present on their surface or released into the blood,[93] thereby facilitating the diagnosis. Some of these advancements in the field of nano-biosensors in cancer diagnosis are described below (Fig. 5).

Nano-biosensors in cancer cell proliferation associated angiogenesis detection

When it comes to cancer cell proliferation, angiogenesis plays a very critical role in the progression of cancer because solid tumors need the supply of blood for their survival and metabolism which helps them to proliferate.[94] Cancer cells release some of the blood vessel-inducing factors that can stimulate the formation of new ones from the existing blood vessels and these types of molecules are known as angiogenic factors.[94] $VEGF_{165}$ is one of the potential angiogenic factors and is one of the promising biomarkers in a different type of cancer diagnosis. Clinical monitoring of the expression level of $VEGF_{165}$ is one of the most important strategies in the cancer treatment plan. To improve the conventional technique of $VEGF_{165}$ detection Moghadam and Rahaie[95] made a bivalent aptamer–Cu nanocluster nano biosensor for the sensitive detection of $VEGF_{165}$. Thus, in the presence of $VEGF_{165}$, the nanostructure undergoes self-aggregation and shows fluorescent emission which quantifies the level of $VEGF_{165}$. The sensor has a limit of detection around 12 pm which showed high rate sensitivity.

Nano-biosensors in colorectal cancer detection

Mutation and inactivation of the *APC* (adenomatous polyposis coli) gene are highly associated with colorectal cancer because

Table 1 Nano-based biosensor for detection of non-communicable diseases

Biomarkers	Disease types	Techniques used in biosensor	Nanoparticles/biological elements used	Limit of detection	Ref.
Cancer					
miRNA-182	Lung cancer	Electrochemical	MoS_2 (molybdenum disulfide)/Ti_3C_2 nanohybrids and modified glassy carbon electrode (GCE)	0.43 fM	228
miR-106a and let-7a	Gastric cancer (GC)	Electrochemical	AuNP and CdSe (cadmium selenide) @CdS (cadmium sulphide) quantum dots-contained magnetic nanocomposites polythiophene/ reduced graphene oxide-modified carbon electrodes	0.02 fM for let-7a and 0.06 fM for miR-106a	229
CXCL5	Colorectal cancer cells CXCL5	Electrochemical impedance spectroscopy (EIS) and voltammetry	Chemokine receptor 2 (CXCR2) attached to conducting polymer-AuNP film	0.078 ± 0.004 ng mL^{-1}	230
miR-199a-5p	Triple-negative breast cancer (TNBC)	Electrochemical	Glassy carbon electrode (GCE) with graphene oxide (GO) and Au nanoroad (AuNR)	4.5 fM	231
HER-2	Breast cancer	Electrochemical	AuNP-grafted functionalized graphene and nanostructured polyaniline (PANI)	2 cells per mL	232
miR-155	Breast cancer	Electrochemical	GO and AuNR	0.6 fM	233
BRCA1	Breast cancer	Cyclic voltammetry	ssDNA probe (BRCA1)/PANHS (polycyclic aromatic nitrogen heterocycles)/MWCNT/GCE	3×10^{-18} mol L^{-1}	234
MUC1	Human non-small-cell lung cancer cells	Amperometric	MUC1 (mucin) aptamer probe and benzoic acid (TTBA) on AuNPs	8 cells per mL	235
MAGE A2	Lung cancer	Electrochemical	Graphite/CNT (carbon nanotubes)–chitosan/Ag (silver)/Ab (antibody)	5.0 fg mL^{-1}	236
CpG islands of adenomatous polyposis coli (APC)	Colorectal cancer	Fluorescence	Fe_3O_4 (ferrosoferric oxide)/Au (gold) core/shell nanoparticles	3.1×10^{-16} M	237
Metabolic disorders					
Uric acid (UA)	Neuropapillitis, neurodegenerative diseases, sclerosis, and aplastic anemia	Electrochemical	Gold/cobalt (Au/Co) bimetallic nanoparticles (NPs) decorated hollow nanoporous carbon framework (Au/Co@HNCF)	0.023 μM	238
Glucose	Diabetes	Electrochemical	Copper (Cu)-nanoflower decorated AuNPs–GO nanofiber (NF)	0.018 μM	118
Vaspin	Type 2 diabetes	Fluorescence	Upconverting nanoparticles (UCNPs)	39 pg mL^{-1}	239
Ascorbic acid (AA), dopamine (DA), uric acid (UA) and acetaminophen (AC)	Scurvy, neurodisorders	Electrochemical	CeO_2 (cerium oxide) nanoparticle-decorated CNTs	3.1 nM for AA, 2.6 nM for DA, 2.4 nM for UA and 4.4 nM for AC	240
Vitamin D3	Rickets, and cardiovascular diseases	Electrochemical	CuNPs (copper nanoparticles)-NiNPs (nickel nanoparticle) @reduced-fullerene-C60 on GCE	0.0025 μM	241
Leptin	Non-alcoholic fatty liver (NAFLD)	Electrochemical	A BSA (bovine serum albumin)/anti-leptin/Glu (glutaraldehyde)/Cys (cysteamine)/AuNPs/PG (porous graphene)–BP (black phosphorus)/ GCE immunosensor was used	0.036 pg mL^{-1}	242
Glucose	Diabetes	Electrochemical	Carbon quantum dots (CQDs)/ AuNPs and glucose oxidase (GOx) enzyme	17 μM	243
3-Hydroxybutyrate (3-HB)	Hyperketonemia and diabetic ketoacidosis (DKA)	Amperometric	Immobilization of the enzyme 3-hydroxybutyrate dehydrogenase onto a screen-printed carbon electrode modified with rGO and thionine (THI)	1.0 μM	244
Glucose	Diabetes	Amperometric	Glucose oxidase immobilized on rGO–Fe_3O_4	0.1 μM	245
Creatinine	Chronic kidney disease, cardiovascular disorder, and type-2 diabetes	Amperometric	Immobilization of NPs of creatininase, creatinase, and sarcosine oxidase onto glassy carbon electrode	0.01 μM	246
Neurological disorders					
Thioflavin T (ThT)	Neurological disorder	Fluorescence	ZnO NFs grown over nano-silver thin film coated glass slide	1.388 mg mL^{-1}	247

Table 1 *(Contd.)*

Biomarkers	Disease types	Techniques used in biosensor	Nanoparticles/biological elements used	Limit of detection	Ref.
Survival motor neuron (SMN) protein	Spinal muscular atrophy	Voltammetric	Carbon nanofiber-modified screen printed electrodes	0.75 pg mL^{-1}	248
miR-195	Parkinson's disease	Electrochemical	Exfoliated GO and AuNWs were used to modify the surface of the screen-printed carbon electrode	2.9 fM	249
APOe4	Alzheimer's disease	Fluorescence and electrochemical	Curcumin–graphene quantum dot platform coated on the transparent indium–tin–oxide electrode	0.48 pg mL^{-1}	250
Amyloid-β	Alzheimer's disease	Fluorescence	Sheet-like structures of GQDs (graphene quantum dots)	Dependent on the fluorescence intensity	251
miR-145	Multiple sclerosis	Fluorescence	Silver nanoclusters and hairpin oligonucleotide probes, MB1 and MB2	0.1 nM	252
α-1 antitrypsin	Alzheimer's disease	Voltammetry	Carbon nanotubes and silver nanoparticles functionalized with alkaline phosphatase labeled antibodies	0.01 pmol L^{-1}	253
Acetylcholine	Alzheimer's disease	Voltammetry	Highly porous gold electrode functionalized with acetylcholinesterase (AChE)	10 μmol L^{-1}	254
Amyloid-β	Alzheimer's disease	Electrochemical	Screen-printed electrode carbon electrodes	0.1 ng mL^{-1}	255
Neonatal disorders					
C-reactive protein (CRP)	Sepsis	Electrochemical	Magnetic rGO (reduced graphene oxide)/Ni (nickel)/PtNPs (platinum nanoparticles) micromotors biofunctionalization on the outer layer using carbon black (CB), reduced graphene oxide (rGO), multi-walled carbon nanotubes (MWCNTs) and anti-CRP	0.80 μg mL^{-1}	256
Thyroid stimulating hormone (TSH)	Thyroid dysfunctioning	Electrochemical	Screen printed carbon electrode, anti-TSH antibody, and amino-coated gold nanoparticles	0.001 μIU mL^{-1}	257
Bilirubin (BR)	Jaundice	Voltammetric	Reduced graphene oxide (rGO)–poly styrene sulfonate (PSS) coated upon glassy carbon electrode	2.0 μM	258

of the changes in the *APC* gene which synthesize truncated gene products, thus triggering Wnt signal pathways and deregulating other cellular processes.[96] Darestani-Farahani *et al.*[97] developed a DNA nano biosensor having a sensitive fluorescent property that determines the DNA sequence of the *APC* gene, which is a well-known tumor suppressor gene. The molecular mechanism of the nano biosensor can be reflected by the phenomenon of DNA hybridization to its complementary sequence. To increase the sensitivity of the nano biosensor, a fluorophore was conjugated on AuNPs (gold nanoparticles). The fabricated DNA nano biosensor displayed a fluorescence emission at 477 nm with an excitation wavelength of 360 nm. The additions of the ssDNA target showed enhanced emission and the limit of detection was found to be 1.3×10^{-11} mol L^{-1}.

Nano-biosensors in prostate cancer detection

Cancer types like prostate cancer have also been found to be a lethal disease and to be a significant cause of death in men between the ages of 55 and 80. The androgen receptor (AR) is the primary driver of malignancy in most prostate cancers.[98] AR signals may function in the genesis of this disease to cause the rearrangement of AR-regulated genes, such as *TMPRSS2* (transmembrane protease serine 2) and transcription factors such as *ERG* (ETS-related gene), in turn preventing terminal differentiation and promoting intrusive cancer production and metastatic dissemination by-products such as fusion genes now regulated by AR.[99] Owing to the incidence of prostate cancer in men the demand for novel biomarkers like prostate-specific antigen (PSA) has been raised for precise diagnosis.[100] To avoid false results, highly sensitive nanobiosensors that have been developed so far include an electrochemical-based nano biosensor that was designed by Yazdani *et al.*[101] which was fabricated with a synthetic protein receptor to emulate PSA-specific antibody function with the highest specific affinity. The Freundlich isotherm fitting studies displayed increased affinity for the imprinted PSA of the synthesized receptor film and the detection limit for PSA was recorded to be 2.0 pg mL^{-1}.

Nano-biosensors in lung cancer detection

Likewise, lung cancer also has a significant influence on human health and quality of life for all cancers. Worldwide, over 1.76 million people are suffering from lung cancer, which is responsible for nearly 25% of all deaths from cancer.[102]

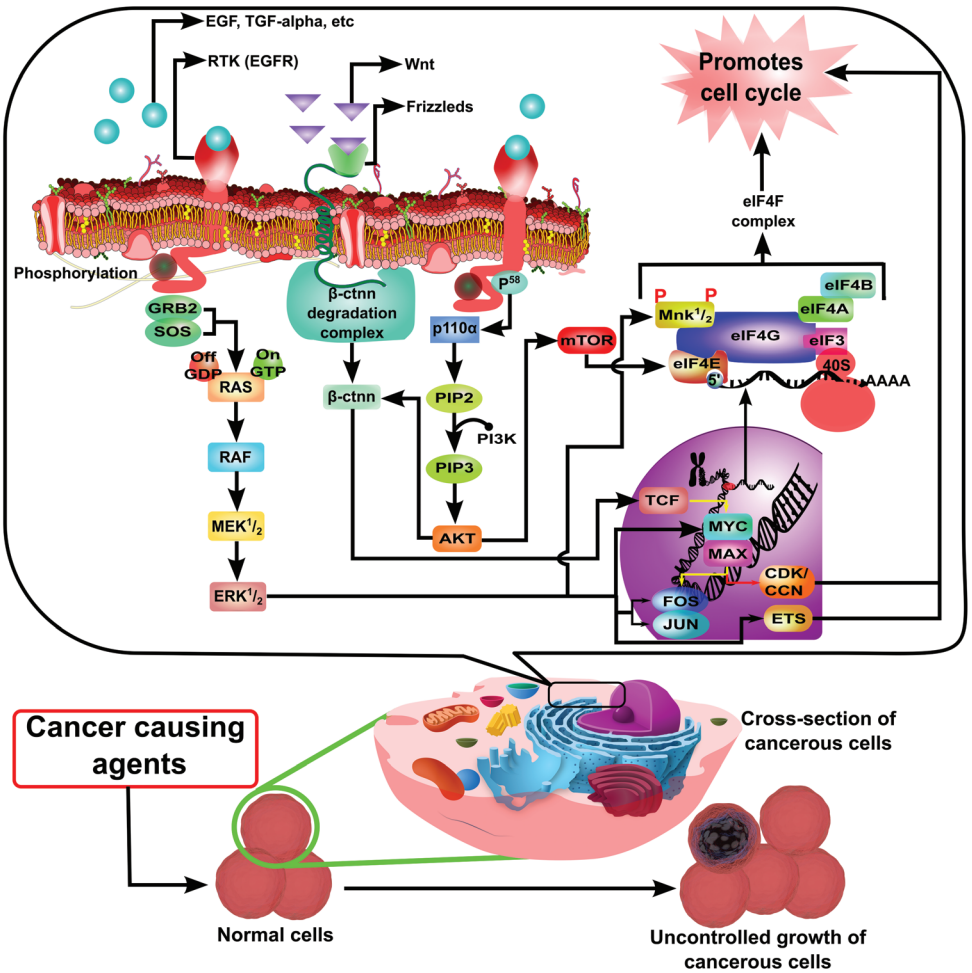

Fig. 4 Cancer-inducing agents promote cell growth and development of cancerous cells *via* the activation of several pathways such as the RAS/RAF/MEK/ERK, Wnt signaling, and AKT pathways. These pathways activate numerous transcription factors that directly or indirectly promote cancer cell growth and development. EGF-epidermal growth factor, TGF-α-transforming growth factor-alpha, RTK-receptor tyrosine kinase, EGFR-epidermal growth factor receptor, GRB2-growth factor receptor-bound protein 2, SoS-Son of Sevenless, RAS-rat sarcoma, RAF-rapidly accelerated fibrosarcoma, MEK-mitogen-activated protein kinase, ERK-extracellular signal-regulated kinase, β-ctnn-beta-catenin, PIP2-phosphatidylinositol biphosphate, PIP3-phosphatidylinositol-3,4,5-triphosphate, Akt-protein kinase B (PKB), mTOR-mammalian target of rapamycin, Mnk1/2-MAPK-interacting kinase 1 and 2, eIF4E-eukaryotic translation initiation factor 4E, eIF4G-eukaryotic translation initiation factor 4G, eIF4B-eukaryotic translation initiation factor 4B, eIF4A-eukaryotic translation initiation factor 4A, eIF-eukaryotic translation initiation factor, TCF-T-cell factor/lymphoid enhancer-binding factor, MYC-avian myelocytomatosis virus oncogene cellular homolog, MAX-Myc-associated factor X. Terminal deoxynucleotidyl transferase. Figure concept is obtained from previously published articles.[211–214]

During the early stages, lung cancer appears naturally to spread or metastasize, resulting in a serious life-threatening condition that cannot easily be treated. Lung cancer can attack any organ in the body, particularly the suprarenal glands, liver, brain, and bones. Nevertheless, it appears that 90 to 95% of lung cancers are caused by the epithelial cell lining. Therefore, bronchogenic cancer is often referred to as lung cancer.[103]

On the other hand, difficulties in early-stage tumor diagnosis with invasive approaches such as sputum cytology, bronchoscopy, and needle biopsy are common but are associated with sampling difficulty and resolution error.[104] Developing trustworthy and responsive detection NM-based sensors is a basic requirement for the accurate detection of lung cancer biomarkers. Recently, cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1) was used as a potent biomarker in non-small cell lung cancer diagnosis.[105] Later for precise detection of CYFRA21-1 tumor marker in serum, Zeng *et al.*[106] devised a label-free electrochemical immune-based sensor. In brief, 3D-graphene along with AuNPs (3D-G@Au) was modified to improve the conductivity of the immunosensor on a glassy carbon electrode (GCE) surface. Anti-CYFRA21-1 was captured and added to the GCE by cross-connecting chitosan (CS), glutaraldehyde (GA), and anti-CYFRA21-1. This nano-based sensor was used for detecting CYFRA21-1 under optimized conditions and had a broad linear range of detection, starting from 0.25–800 ng mL^{-1} to as low as 100 pg mL^{-1}.

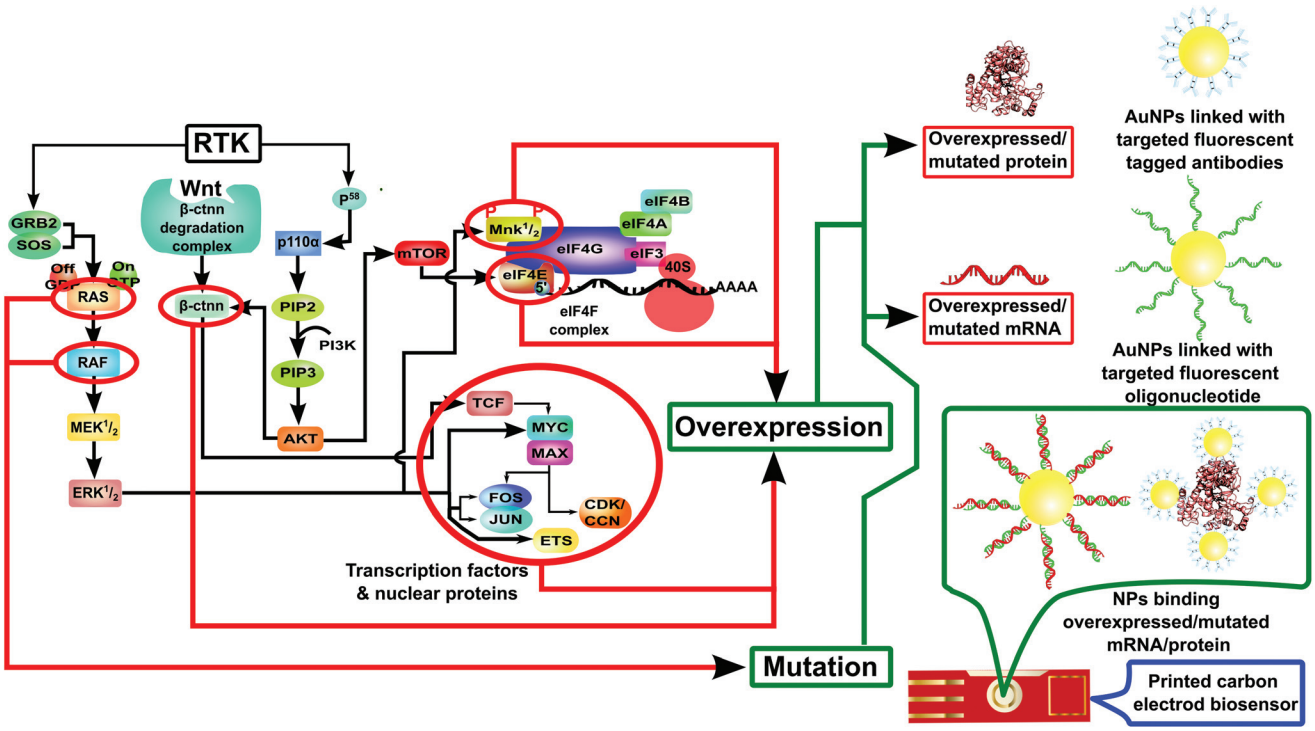

Fig. 5 Mutation in cell signaling modulators such as RAS and RAF genes, and overexpression of various transcription factors and proteins such as β-ctnn, Mnk1/2, eIF4E, *etc.* can possibly be detected *via* a nano-based biosensor. EGF-epidermal growth factor, TGF-α-transforming growth factor-alpha, RTK-receptor tyrosine kinase, EGFR-epidermal growth factor receptor, GRB2-growth factor receptor-bound protein 2, SoS-Son of Sevenless, RAS-rat sarcoma, RAF-rapidly accelerated fibrosarcoma, MEK-mitogen-activated protein kinase, ERK-extracellular signal-regulated kinase, β-ctnn-beta-catenin, PIP2-phosphatidylinositol biphosphate, PIP3-phosphatidylinositol-3,4,5-triphosphate, Akt-protein kinase B (PKB), mTOR-mammalian target of rapamycin, Mnk1/2-MAPK-interacting kinase 1 and 2, eIF4E-eukaryotic translation initiation factor 4E, eIF4G-eukaryotic translation initiation factor 4G, eIF4B-eukaryotic translation initiation factor 4B, eIF4A-eukaryotic translation initiation factor 4A, eIF-eukaryotic translation initiation factor, TCF-T-cell factor/lymphoid enhancer-binding factor, MYC-avian myelocytomatosis virus oncogene cellular homolog, MAX-Myc-associated factor X. Terminal deoxynucleotidyl transferase. Figure concept is obtained from previously published articles.[211,212,213,215]

Metabolic disorders

Metabolism is the biochemical catabolic and anabolic processes of generating energy from the food an organism consumes.[107] Chemicals in the digestive system break down the food components into sugars and acids, the fuel for your body. A metabolic disorder occurs when irregular chemical reactions perturb this mechanism in the body.[108] When this happens, the body has too many or too few of the diverse substances that it needs to maintain homeostasis. There are various groupings of illnesses, some that affect amino acid breakdown, and others that affect carbohydrate breakdown, or lipids, resulting in malfunctioning cellular and sub-cellular organelles.[109] If other organs, such as your liver or pancreas, fail to function normally, the body may develop metabolic disorders like diabetes, obesity, fatty liver, *etc.* In the past, there has been considerable effort to establish appropriate techniques for evaluating the type of disorder in the patient but there has been lack of sensitivity and accuracy which until now has remained a challenging task.[110] The advancement in the field of nanotechnology opens several doors to solve the lacuna associated with conventional diagnostic techniques with the help of nano biosensors.[111,112] In the present sub-topic, some of the advancement in the field of nanobiosensors for the diagnosis of metabolic disorders is described (Fig. 6).

Nano-biosensors in diabetes detection

Diabetes is a common metabolic disorder that occurs due to the absence of enough insulin from the pancreas or the ineffectiveness of the body to properly utilize the insulin which is a blood sugar-regulated hormone.[113] The common effect of uncontrolled diabetes is hyperglycemia or raised blood sugar. It leads over time to serious damage to many of your body systems, particularly nerves and blood vessels.[114] According to the WHO (World Health Organization), diabetes existed in 2014 in 8.5% of adults 18 years old and older. The primary cause of 1.6 million deaths in 2016 was diabetes, and 2.2 million more deaths were caused by high blood glucose in 2012.[115] Blindness, organ failure, heart attacks and strokes are significant effects of diabetes.[116] Diabetes can be treated with proper diet, physical activity, medication, and routine monitoring to prevent complications. Insulin is an essential part of the glucose cycle and is of high importance for diagnosis and diabetes management.[117] To determine the level of glucose in the body fluids Baek along with his group members developed an electrochemical biosensor.[118] To develop this they fabricated a

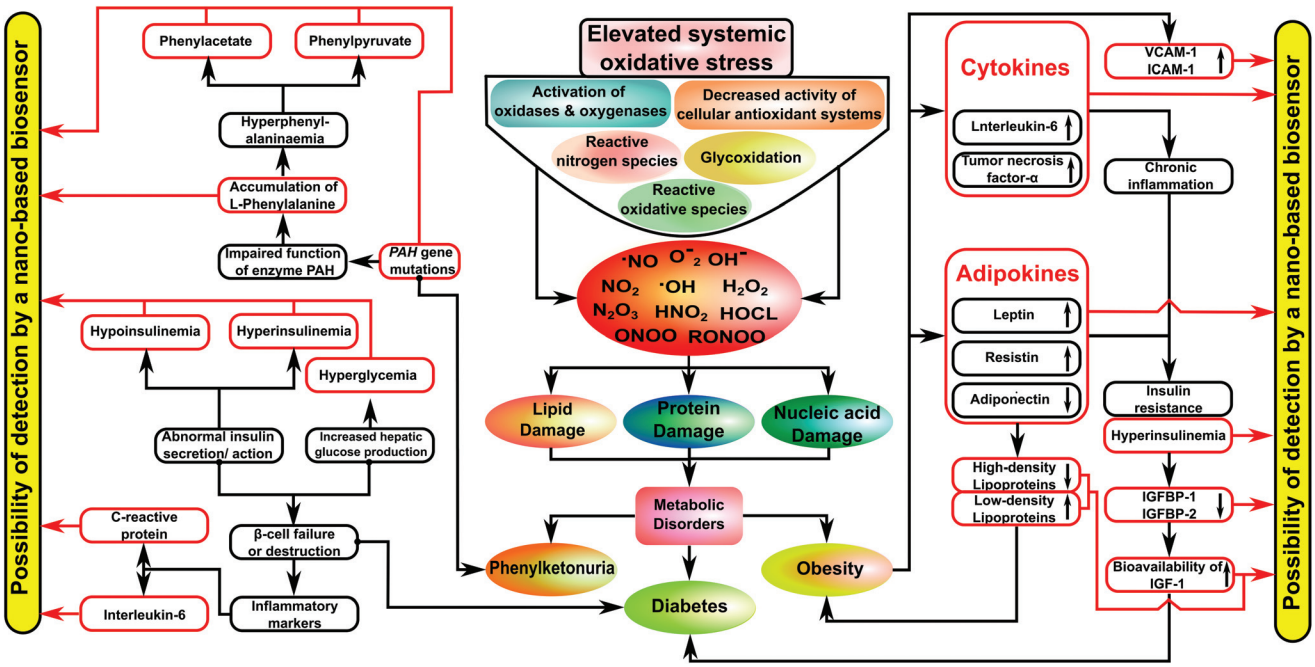

Fig. 6 Elevated systemic oxidative stress can induce activation of oxidases and oxygenase, reactive oxidative species, reactive nitrogen species, and glycoxidation, and decrease activity of cellular antioxidant systems, which results in the induction of various metabolic disorders like phenylketonuria, diabetes, and obesity. The figure highlights some biochemical molecules, proteins, inflammatory markers in red-colored rectangular boxes which can be detected by a nano-based biosensor. PAH gene-phenylalanine hydroxylase gene, VCAM1-vascular cell adhesion molecule 1, ICAM1-intercellular adhesion molecule 1, IGFBP-1-insulin-like growth factor-binding protein-1, IGFBP-2-insulin-like growth factor-binding protein-2, IGF-1-insulin-like growth factor-1. Terminal deoxynucleotidyl transferase. Figure concept is obtained from previously published articles.[26,216–219]

copper (Cu)-nanoflower with AuNPs, graphene oxide (GO), and nanofiber (NF). The Cu nanoflower was conjugated with glucose oxidase (GOx) and horseradish peroxidase (HRP). This nano biosensor showed excellent catalytic action converting glucose to gluconic acid which was detected as the end product by the sensor (minimum 0.018 μM). Their findings suggested that nano-bio hybrid materials can be applied to track glucose levels in biofluids.

Nano-biosensors in obesity detection

Similarly, the excessive accumulation of fat or adipose tissue in the body that impairs health by combining it with the risk of diabetes mellitus, cardiovascular disease, hypertension, and hyperlipidemia is obesity.[119] It is a significant disease in public health that has slowly intensified over the last 50 years. Obesity has a multifactorial etiology and is a chronic disorder. Obesity is the product of an imbalance between a normal consumption of energy and an excessive increase in mass. The epidemic of obesity is multifactorial, caused by various causes, including biology, culture, and community.[120] Cholesterol forms the main building blocks of biological membranes and is used for the preparation of fatty acids in the tissues. In the clinical diagnosis of obesity, the determination of cholesterol levels is very important. Alagappan *et al.*[121] made an electrochemical biosensor by immobilizing cholesterol oxidase enzyme conjugated with AuNPs functionalized with a multi-walled carbon nanotube (MWCNT)–polypyrrole (PPy) nanocomposite modified electrode. Cyclic voltammetry determination showed a reduction in current with increasing cholesterol concentration, the change arising because of the competing action of the Triton X100 surfactant which was used for the preparation of the cholesterol solution. The detection limit of the nano biosensor was found to be 10.12 μA mM^{-1} cm^{-2} and 0.1×10^{-3} M respectively.

Nano-biosensors in phenylketonuria detection

Another type of metabolic disorder, phenylketonuria (PKU), affects newborn children, and this disease is mainly associated with DNA mutation.[122] PKU is a rare inborn autosomal recessive disorder due to variants in genes encoding phenylalanine hydroxylase (PAH) in phenylalanine (Phe) metabolism. PAH usually transforms Phe into tyrosine (Tyr), which includes tetrahydrobiopterin (BH4), molecular oxygen, and iron as a cofactor.[123] The lack of PAH allows Phe to build up in the blood and brain. Untreated PKU can cause many neurological disorders like autism, seizures, developmental problems, aberrant behavior, *etc.*[124] An accurate diagnosis followed by precise medication treatment can increase the survivability of the patients. Sm *et al.*[125] developed a nano biosensor by coating AuNPs on a reduced graphene oxide sheet upon a printed carbon electrode that accurately detects PKU. The unique single-stranded DNA alkanethiol probes were connected to the AuNP surface using a self-assembly technique and Oracet blue was used as an intercalating electrochemical mark. The detection level ranges from 80–1200 fM and the detection limit was found to be 21.3 fM.

Neurological disorders

All disorders caused by brain or nervous system dysfunction, causing physical and/or psychological symptoms, are characterized by the term "neurological disorder". Neurological disorders are the second leading cause of disability around the world with 276 million DALYs, and annually 80% of these are in countries of low- and middle-income.[126,127] There is no standard examination to offer a definitive diagnosis for most neurological conditions. Tests like MRI (magnetic resonance imaging), EMG (electromyography), and EEG (electroencephalography) are carried out in conjugation with the collection of a complete medical history and multiple neurological exams. Conventional biochemical studies include immunosorbent assays (for example, ELISA, for Alzheimer's amyloid-β peptides) and enzymatic assays (for example, hexosaminidase A Tay–Sachs assay). The use of PCR (for example, allele-specific Tay–Sachs PCR) or RT-PCR (for example, retroviral detection) is determined using standard genetic tests. The drawbacks of traditional immunoassays include low precision, time, and scientific automation[128] (Fig. 7).

Nano-biosensors in Alzheimer's disease detection

Metabolism, proteome, and genome-based biological markers used in biosensors for the detection of neurological diseases are easy, sensitive, and accurate.[129] Moreover, many neurological conditions can be detected by measuring a single enzyme activity or genomic factor.[130] For example, Alzheimer's disease (AD) is a type of serious neurological disorder that causes brain cells to die (Fig. 7). The progression of this disease is associated with the accumulation of an insoluble protein known as amyloid-β (Aβ) that forms plaques in the brain tissues.[131] Additionally, abnormal protein deposits form tau tangles in the brain and form amyloid plaques which block neural connections, leading to the gradual destruction of healthy neurons.[132] During the first cycle, the damage initially tends to occur in the hippocampus and the entorhinal cortex. Furthermore, the increased destruction of neurons initiates piecemeal shrinkage of additional areas of the brain. Finally, towards the end of AD, the damage becomes extensive and the brain tissue diminishes considerably.[131]

The possibility of treatment options would increase if the disease were diagnosed at an earlier stage. Due to the existence of the above-stated limitations associated with the conventional diagnosis process, biosensors are preferred for immediate and accurate detection. Especially, the use of nano biosensors for enhanced signal amplification appears to be more favorable as compared to conventional biosensors. Nanostructures are more commonly used materials for the designing of nano biosensors as they elevate the surface area for greater absorption of bioanalytics followed by immobilization of the bio-recognition elements. Considering the advantage of associated NMs Negahdary and Heli[133] designed an electrochemical peptide-based nano biosensor by conjugating highly specific

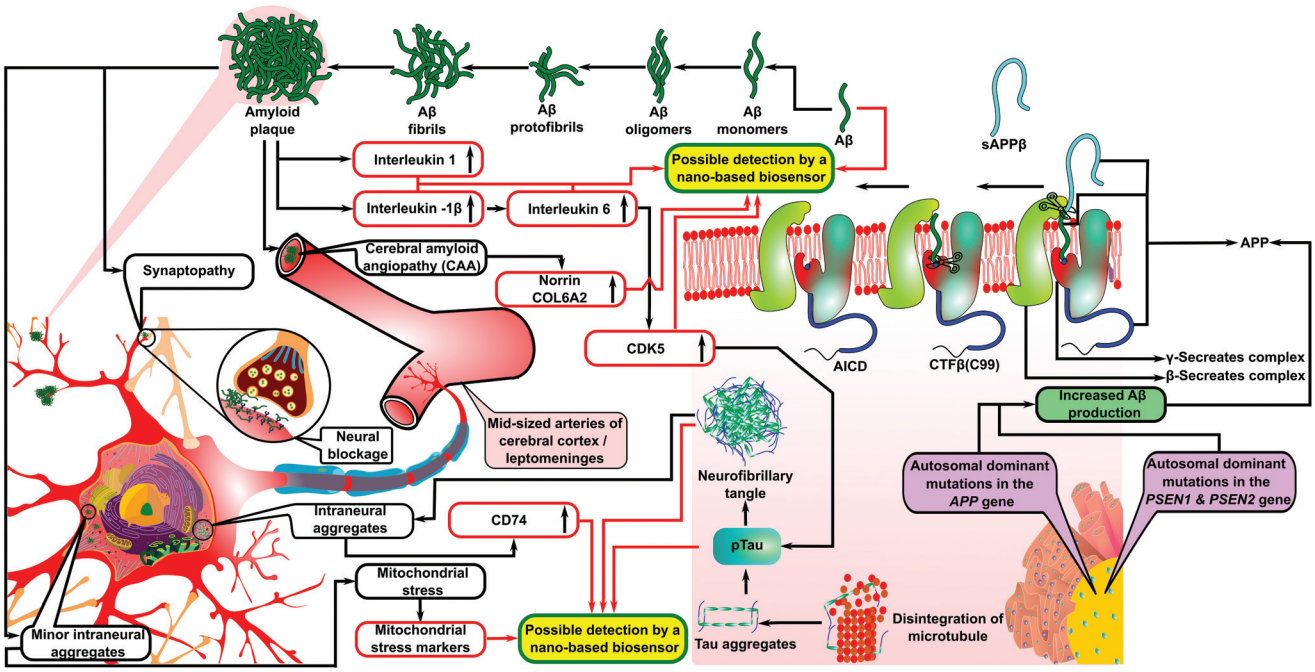

Fig. 7 Pathophysiology of Alzheimer's disease, emphasizing cerebral amyloid angiopathy (CAA), beta-amyloid plaque formation, neurofibrillary tangle formation, intraneural aggregations both of neurofibrillary tangles and β-amyloid, and associated protein markers, neuroinflammatory markers and mitochondrial stress markers, possibly can also be detected by nano-based biosensors. Aβ-amyloid-beta, APP-amyloid precursor protein, CTFβ-carboxyl-terminal fragment-beta, COL6A2-collagen, type VI, alpha 2, presenilin-1, presenilin-2, pTau-hyperphosphorylated tau, CD74-cluster of differentiation 74, CDK5-cyclin-dependent kinase-5. Terminal deoxynucleotidyl transferase. Figure concept is obtained from previously published articles.[220–227]

peptide sequence on the surface of a microporous Au nanostructure *via* the thiol group of its cysteine residue, and this showed strong affinity towards $A\beta_{(1-42)}$. To quantify the concentration of $A\beta_{(1-42)}$ in clinical samples a ferrocyanide/ferricyanide redox couple was used as a redox marker, where the detection limit was around 0.2 pg mL^{-1}.

Nano-biosensors in Parkinson's disease detection

Similarly, Parkinson's disease (PD) is also a type of neurodegenerative condition with motor symptoms such as akinesia (loss or impairment) of voluntary motion, bradykinesia (slow motion), tremors, rigidity, and unstable posture followed by hallucinations and depression.[134,135] About 1% of people above the age of 60 and 0.3% of general populations suffered from this type of neurological disorder.[136] Loss of dopaminergic neurons in the substantia nigra (SN) pars compacta (SNpc) along with the deposition of misfolded α-synuclein protein (mainly found in intra-cytoplasmic inclusions called Lewy bodies (LBs)) are the major hallmark of pathogenesis.[137] A large proportion of the dopaminergic neurons has been already lost in the SNpc when patients are first diagnosed and neurodegeneration extends to other regions of the central nervous system.[138] Presently available therapies give strong motor symptom management yet neurodegeneration development, disease evolution, and growing impairment are not prevented at the later stage.[139] The variability in response to dopaminergic medication, clinical heterogeneity followed by the overlapping of the symptomatology makes the diagnostic process very critical.[140] To improve the diagnostic process nano biosensors against a particular biomarker have been designed for efficient detection. The principal protein involved in PD is alpha-synuclein, a 14 kDa peptide that was found to be aggregated into Lewy bodies in PD patients. Lately, Karaboğa and Sezgintürk[141] designed an electrochemical nano biosensor for determining the amount of alpha-synuclein in the cerebrospinal fluid, and the detection limit of this was 0.135 pg mL^{-1}. Overall, the developed nano biosensor possessed greater reproducibility potency and long storage stability.

Neonatal disorders

The deterioration of a newborn's body's natural state, organs, and abnormal activity includes neonatal disorders.[142] In the future treatment process for better infant survival, early diagnosis of these diseases plays a vital role. A plausible device for fast and accurate detection is the use of nanobiosensors. This section briefly discusses some of the common conditions of the disorders, such as iron deficiency anemia (IDA) and jaundice that are associated with neonates.

Nano-biosensors in iron deficiency anemia detection

During an early stage of the lifespan, the diet has a significant effect on the quality of health. Micronutrients are considered vital for the development of the brain, stable growth, and a strong immune system.[143] Micronutrient deficiency like ID refers to a state of substantially low iron content in the body in healthy red blood cells. The core function of iron in the body is the carrying of oxygen in the blood. Iron deficiency can cause IDA if not diagnosed and treated early. Anemia is a condition in which the levels of hemoglobin (Hb) are less than average and inadequate to satisfy a person's physiologic needs due to the presence of lower red blood cells (RBC).[144] It reduces the work activity of children, and impairs cognitive growth and behavioral development in newborns.[145] ID affects children's cognitive growth from infancy to puberty and is associated with increased morbidity levels. However, ID in children is often not recognizable at the neonatal stage. So, the development of a nano biosensor for its accurate diagnosis is the need of the hour. To solve this problem Oshin *et al.*[146] developed a graphene-based field-effect transistor (GFET) biosensor conjugated with anti-ferritin antibodies for the detection of ferritin protein in the serum. The limit of detection was found to be 10 fM. This indicates the enormous potentiality of the GFET nano biosensor for the detection of ferritin.

Nano-biosensors in bilirubin detection

Bilirubin (BR) is a tetra-pyrrolled pathogenic yellow pigment and a byproduct of normal red blood cell breakdown.[147] Free bilirubin is plasma-toxic and can cause hepatical or biliary disease, and besides, can cause persistent brain damage or death due to a higher concentration of free bilirubin in the blood.[148] If untreated, higher concentrations of BR cause jaundice and are associated with hepatitis followed by hemolysis, and an elevated level of free BR can cause brain damage, hearing loss, and in extreme conditions death.[149] In a newborn child an unconjugated BR level of more than 340 μM L^{-1} within the first week of life is commonly regarded as harmful and even life-threatening.[150] Consequently, the accurate measurement of the free bilirubin is of great clinical importance given the diagnostic value of BR and the development of a cheap analytical method for its detection. This is where the nano biosensors come into play. To tackle this Thangamuthu and group members developed an electrochemical nano biosensor to detect the concentration of BR.[151] They functionalized screen-printed carbon electrodes (SPEs) with MWCNT and graphene for selective measurement of BR within a range around 0.3 ± 0.022 μM. Viability of blood serum samples is validated by measuring BR and selectivity is assured by the use of an ionic Nafion membrane to inhibit popular interfering biologic substrates.

Communicable diseases

Despite the advancements in technology, mankind is still facing the greatest threat because of communicable diseases. Diseases such as dengue, Zika, and Ebola continue to attack communities and even diseases that were thought to be eradicated are re-emerging.[152] Communicable diseases in humans are transmitted through either direct contact or some media

such as vectors, contaminated food and water, body fluids, and air.[153] Severe communicable diseases such as HIV, tuberculosis, Zika virus disease, dengue, and chikungunya still prevail and continue to ravage humans. In 2016, a total of 5168 noncongenital ZIKAV disease cases were reported in the United States, by the same year 36.7 million people had been infected with HIV, around 2 million people die of tuberculosis yearly and dengue is a severe life-threatening disease that is slowly prevailing in developing countries.[152] Prevention and early diagnosis and treatment are the most suitable ways to save lives and stop the spread of such diseases (Table 2).

Viral infection detection

Viral infectious disease outbreaks have become the main concern of today's world. Over the last few decades, viral disease outbreaks have become more and more prevalent including Zika virus, influenza virus, human immunodeficiency virus, dengue virus, Ebola, and hepatitis virus, and currently, the world is facing the COVID-19 pandemic.[154–156] A 120 nm virus has brought the world to its knees. Such viruses are genetically stable and spread very rapidly, thus posing a threat to public health.[19] Since its appearance in December 2019 in Wuhan (China), COVID-19 became a global pandemic in less than four months. The rapid spread of the virus has left millions infected and dead in a very short time. Significant and fast propagation of COVID-19 is due to airborne and contact routes of transmission as well as through aerosols; its long incubation period and most importantly lack of research are some reasons for COVID-19 becoming a pandemic.

Early detection and treatment are essential to contain the virus. Currently, RT-PCR is being used to diagnose patients infected with COVID-19.[157] PCR requires about 3 to 4 hours, special equipment, trained professionals, requires extra kits for RNA extraction which is a very sensitive procedure and thus may create issues such as longer assay time sophisticated procedures.[158] To overcome the abovementioned issues an immense research focus is being driven towards the development of alternative rapid methods of viral detection. Considering clinical point-of-care (POC) purposes, the detection of pathogenic viruses accurately and rapidly is inevitable. Keeping this in mind a combination of PCR and lateral flow assay (LFA) technology, graphene-based field-effect transistors (FET),[159] conventional LFAs based on CRISPR (clustered regularly interspaced short palindromic repeats) assays,[160] and optical biosensors in combination with localized surface plasmon resonance and plasmonic photothermal effect has been developed.[161]

In the last two decades, various promising approaches have been explored to utilize the surface and interfacial properties of several nanostructures towards the development of a biosensor for rapid and point-of-care detection of viral infections.[162] Seo *et al.*[159] developed a field-effect transistor (FET)-based biosensing device for the detection of COVID-19 in clinical samples. The abovementioned biosensor can detect viral spike protein at 1 fg ml^{-1} in PBS and 100 fg ml^{-1} in clinical samples. Also, the FET sensor was successful in detecting SARS-CoV-2 in clinical samples and culture medium. This device does not require any labeling or sample pretreatment. Another device consisting of a dual-functional plasmonic biosensor that combines localized surface plasmon resonance (LSPR) sensing transduction and the plasmonic photothermal (PPT) effect provides an alternative method for the clinical diagnosis of COVID-19. The device uses two-dimensional gold nanoislands (AuNIs) which are functionalized with complementary DNA receptors. These can accurately detect specific sequences from SARS-CoV-2 through nucleic acid hybridization. The abovementioned biosensor displays high sensitivity toward selected SARS-CoV-2 sequences, is able to detect concentrations as low as 0.22 pM and allows accurate detection of the specific target in a mixture of multiple genes.[161] A DNA biosensor was designed for the detection of hepatitis B virus (HBV) using tin-doped WO_3/In_2O_3 nanowires. This nano biosensor could detect the targeted DNA at much lower concentrations in a label-free approach. The mentioned biosensor is very sensitive and accurately detects concentrations of DNA in the range of 0.1 pM to 10 μM (ref. 163) (Fig. 8).

Bacterial infection detection

Major pathogens that adversely affect human health worldwide are food-borne microorganisms. They cause human diseases on consumption of food, mostly animal products contaminated with pathogens or their toxins. Two-thirds of food-borne diseases in humans are caused by bacteria worldwide, with a higher proportion in developing countries.[164] The three types of diseases caused by food-borne microbes are intoxication, infection, and toxic infections.[165] Intoxication occurs when food poisoning is caused by the toxins the pathogen produces. Infection happens when contaminated food is ingested and toxic infections occur when pathogens growing inside the human intestine produces toxins. *Salmonella* species, *S. aureus*, *L. monocytogenes*, *E. coli*, and *Campylobacter* species are the main bacterial zoonotic pathogens responsible for food-borne bacterial diseases in humans around the world.[164] There is also a substantial amount of clinical and preclinical data suggesting a bacterial influence in pancreatic cancer, resistance to therapy, and its progression.[166] There are several pieces of evidence suggesting a vital role of bacteria in various cancers such as colorectal, lung, hepatocellular, and esophageal carcinoma.[167]

An important bacterial role has also been observed in cardiovascular disease, autoimmune pancreatitis, and obesity.[168] *Helicobacter pylorus* is one such Gram-negative bacterium, which is known as a risk factor for gastric carcinoma, mucosa-associated lymphoid tissue lymphoma, and gastric carcinoma. The liver of patients with cholangiocarcinoma and hepatocellular carcinoma showed *H. pylori*.[169] Cells contain a second messenger signaling network that aids in adapting to changing environmental conditions. Cyclic di-GMP is a second messenger molecule present in bacteria that coordinates

Table 2 Nano-based biosensor for communicable disease detection

Biomarkers	Disease types	Techniques used in biosensor	Nanoparticles/ biological elements used	Limit of detection	Ref.
Viral infections					
Antibodies against COVID-19	SARS-CoV-2	Multiplexed grating-coupled fluorescent plasmonics	Au-coated nanoscale	1 : 1600 dilution	259
Dengue viral RNA	Dengue virus	Electrochemical monitoring	Methylene-blue conjugated AuNPs	100 fM	260
S spike glycoproteins	SARS-CoV-2	Electrochemical monitoring	Graphene oxide (GO) and gold nanostars	1.68×10^{-22} μg mL^{-1}	261
Peptide nucleic acid	Influenza A viruses (H1 to H16 subtypes)	Visual colorimetric assay	AuNPs	2.3 ng	262
DENV proteins	Dengue viral disease	ELISA-plate spectrophotometers	Gold nanorods	1 pg	263
SARS-CoV-2 spike protein	SARS-CoV-2	Field-effect transistor (FET)-based biosensor	Graphene sheets	LOD: 2.42×10^2 copies per mL	159
Complementary sequences of RdRp-COVID, ORF1ab-COVID, and E genes of SARS-CoV-2	SARS-CoV-2	PPT effect and LSPR sensing transduction	Two-dimensional gold nanoislands (AuNIs)	0.22 pM	161
HBV DNA	Hepatitis B	Electrochemical impedance spectra (EIS)	Tin-doped WO_3/ In_2O_3 nanowires	0.1 pM to 10 μM	163
Virus nucleic acid	Closely related Zika and dengue viruses	Fluorometric detection	Graphene oxide	2.1×10^6–5.1×10^8 FFU per mL	264
Dengue viral DNA	Dengue viral disease	Sandwich hybridization strategy of DNAs	AuNPs	1×10^{-29} M	265
Sialyloligosaccharide receptor-mimic peptide	Influenza A virus	Optimized peptide termination	Boron-doped diamond electrode	5–10 pfu per sample	266
HCVcoreAg	Hepatitis C	Change of buffer pH from acidic to neutral	Silicon-on-insulator (SOI) nanowire	0.3 pg mL^{-1}	267
Concanavalin A lectin	Dengue type 2, Zika, chikungunya, and yellow fever	Cyclic voltammetry and impedance spectroscopy	Zinc oxide nanoparticles	0.0421 pfu mL^{-1} for ZIKV, 0.0437 pfu mL^{-1} for YFV, 0.062 pfu mL^{-1} for CHIKV, and 0.0382 pfu mL^{-1} for DENV	268
L-Lysine levels	HIV	Amperometric biosensor	L-Lysine oxidase nanoparticles (LOxNPs) and graphene oxide nanoparticles (GrONPs)	0.01 μM	269
Non-specific proteins	MERS-CoV and HCoV	Electrochemiluminescence	Au NPs	0.4 and 1.0 pg mL^{-1} for HCoV and MERS-CoV, respectively	270
Hepatitis B virus gene	Hepatitis B	Electrochemical monitoring	AMT–AuNP–PGEs	0.86 μg mL^{-1}.	271
Viral DNA	HPV-18	Fluorescence assay	Ti_3C_2 nanosheets	100 pM	272
HIV-1 gene	AIDS	Electrochemiluminescence nanosensor	Europium sulfide nanocrystals (EsNCs)	3.0 fM to 0.3 nM	273
Envelope protein antibody (Zev-Abs)	Zika-virus	Electrochemical immunosensor	Interdigitated micro-electrode of gold (IDE-Au)	10 pM	274
Virus oligonucleotide	MERS-CoV	Colorimetric assay	Citrate anion-stabilized AgNPs	1.53 nM	275
Virus oligonucleotide	Human papillomavirus	Colorimetric assay	Citrate anion-stabilized AgNPs	1.03 nM	
Surface receptor	Influenza A	Chromatographic assay	Carbon nanoparticles	350 TCID50 per mL (*i.e.*, the 50% tissue culture infectious dose)	276
JEV *via* recognition cavities	Japanese encephalitis virus	Fluorescent detection	Magnetic silicon microspheres	2.5–45 nM	277
	Influenza A (H1N1) A (H3N2)	Paper-based immunoassay	AuNPs	2.7×10^3 to 2.7×10^4 plaque-forming units per assay	278
Antibody specific to influenza virus	Influenza A (H7N9)	Electrochemical sensor	Graphene oxide, multi-walled carbon nanotube	0.81 pg mL^{-1}	279

Table 2 *(Contd.)*

Biomarkers	Disease types	Techniques used in biosensor	Nanoparticles/ biological elements used	Limit of detection	Ref.
Antibody specific to viral infection	Influenza A and B	Immunoassay	Europium nanoparticle	10^1 to 10^3 EID50 per mL	280
Specific mouse α-A NP mAbs	Influenza A (H1N1)	Fluorescence immunoassay	Magnetic nanoparticle ($MnFe_2O_4$)	0.007 HAU	281
	Influenza A (H3N2)	Field-effect transistor biosensor	Silicon nanowire, magnetic nanoparticle	29 viruses per μL	282
DNA-based detection	Influenza A (H5N1)	DNA–based microarray assay (scanomatric detection)	AuNPs with silver staining method	102 fM per assay (PCR fragments) 103 TCID50 per assay (viral RNA)	283
Bacterial infections					
Bacterial target DNA	*S. aureus*	Targeted DNA was quantified in spectrophotometry at 260 nm. Sensitivity of this method was studied with PCR and gel agarose electrophoresis	MNP-TiO_2-AP-SMCC	230 CFU mL^{-1}	284
Electrostatic interaction of cell wall and concomitant inhibition of peroxidase activity of CS-MNPs	Gram-negative *Escherichia coli* or the Gram-positive *Staphylococcus aureus*	Colorimetric assay	Chitosan-coated iron oxide magnetic nanoparticles (CS-MNPs)	104 CFU mL^{-1} by the naked eye and 102 CFU mL^{-1} by spectrophotometry within 10 min	285
Anti-*E. coli* O157 antibody	*E. coli* O157	Cyclic voltammetry and electrochemical impedance spectroscopy	AuNPs	15 CFU mL^{-1}	172
Anti-E. coli antibody	*E. coli*	Chemiresistive biosensor	AuNPs	12 cfu mL^{-1}	286
Biofilm	*Staphylococcus epidermidis*	Electrochemical sensing	Magnesium zinc oxide (MZO) nanostructure	A drain current change of ~80% after ~200 min of *S. epidermidis* bacteria culturing	173
Bacterial peptides	*Listeria monocytogenes* and *Staphylococcus aureus*	Electrochemical biosensor	Au NPs	3 CFU mL^{-1} for *Staphylococcus aureus* and 9 CFU mL^{-1} for *Listeria monocytogenes*	171
Bacteria's target DNA	Foodborne bacteria including *Escherichia coli* O157:H7, *Vibrio parahaemolyticus*, *Salmonella*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Shigella*, *etc*.	Amplified microcantilever array biosensor	Au NPs	0.005–0.040 fM or (1–9 cells per mL)	287
Receptor-binding protein of bacteria	*Escherichia coli*, *Pseudomonas aeruginosa* and *Vibrio cholerae*	Colorimetric assay	AuNPs	The limit of detection (~100 cells)	288
Mycobacterium tuberculosis Oligonucleotide	*Mycobacterium tuberculosis* (MTB)	Colorimetric assay	Citrate anion-stabilized (AgNPs)	1.27 nM	275
Fungal infections					
Fungal spores	*Aspergillus Niger*	Colorimetric assay	Peptide-modified AuNPs	50 spores	289
Concanavalin A (ConA) and wheat germ agglutinin (WGA) lectins	*Candida* spp.	Impedimetric biosensor	Lectin-modified AuNPs	10^2 to 10^6 CFU mL^{-1}	176
Protein biomarkers	*Aspergillus fumigatus* Allergen Asp f 1	Colorimetric assay	Magneto-nanosensor biochip	~100 pg mL^{-1}	290
Parasitic infections					
Antibody as receptor	Malaria	Electrochemical biosensor	Platinum nanoparticles (Pt NPs)	8.0 ng mL^{-1}	291
pLDH	Malaria	EIS: electrochemical impedance spectroscopy	Glassy carbon electrode	0.5 fM	179
β-Hematin	*P. berghei*, *P. falciparum*	Electrochemical nanosensor	Au–CuO	3.60–4.8 mM 0.65–1.35 mM	292
Bilharzia antibody	Bilharzia disease	Electrochemical nano-biosensor	Nano-strip with immobilized gold nanoparticles	8.3887×10^{-2} ng mL^{-1}	293

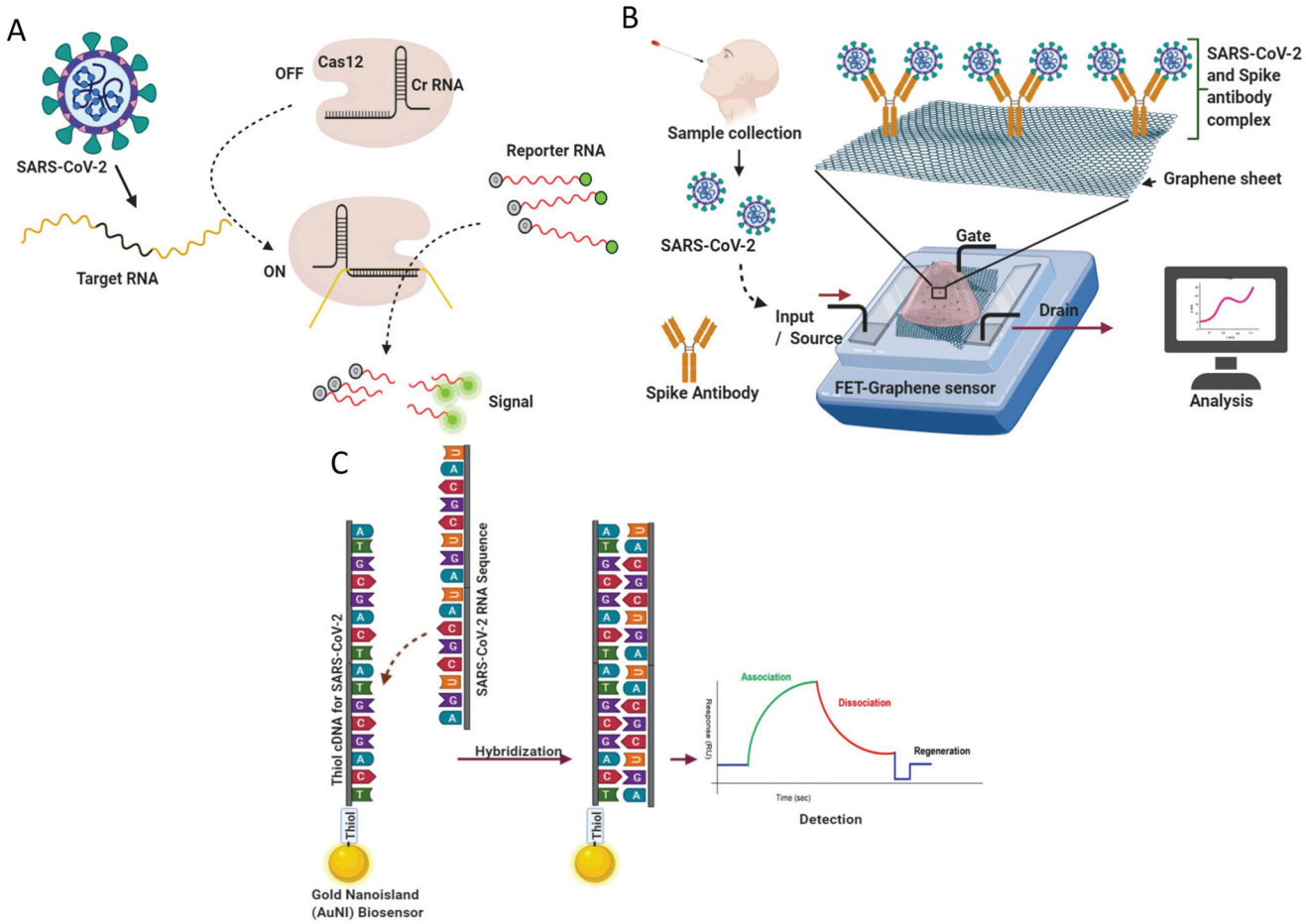

Fig. 8 Biosensors for diagnosis of viral infections. (A) In CRISPR-based COVID-19 diagnosis, the Cas12/CRISPR-RNA complex gets activated after the recognition of the target gene of SARS-CoV-2 and cleaves the labeled reporter RNAs, and generates signals. (B) Schematic diagram of COVID-19 diagnosis using an FET-graphene sensor. SARS-CoV-2 spike antibody is conjugated onto the graphene sheet which binds selectively with the spike protein of SARS-CoV-2 virus and results in signals. (C) Localized surface plasmon resonance (LSPR) based detection of COVID-19. Selected RNA sequences from SARS-CoV-2 get hybridized with complementary DNA receptors functionalized on two-dimensional gold nanoislands (AuNIs), and the change in response units is recorded.

several processes such as virulence, motility, and biofilm formation as well as helping in the infection of mammalian host cells. Dippel *et al.*[170] were the first to generate a ratiometric chemiluminescent biosensor scaffold that selectively identifies c-di-GMP. These biosensor scaffolds have a significantly high sensitivity of K_D < 300 pM and can generate cyclic di-GMP images in tissues. The sensitivity of this biosensor is comparable to LC-MS/MS. *Listeria monocytogenes* and *Staphylococcus aureus* are the two most significant foodborne pathogens. They can be detected by a new electrochemical biosensor composed of an array of AuNP-modified SPEs. These electrodes consist of magnetic NPs bound to specific peptides and immobilized through a streptavidin–biotin interaction. Detection was achieved in 1 minute, by utilizing the activity of bacterial proteases on the specific peptide. The sensitivity of this biosensor was significantly higher; it was 3 CFU ml^{-1} for *Staphylococcus aureus* and 9 CFU ml^{-1} for *L. monocytogenes*.[171] *E. coli* O157 can be detected using SPEs which are modified with AuNPs. This biosensor uses immobilized anti-*E. coli* O157 antibodies by –NHS cross-linking. The time of detection of this biosensor was found to be 30 minutes. This nano-based biosensor is a successful portable diagnostics tool for quick and label-free detection of *E. coli*.[172]

Early detection of biofilms formation is very necessary because biofilms, once formed, show significant antibiotic resistance, unlike the free-floating bacteria. This makes the treatment of bacterial infections much more difficult. Thus, to detect biofilm formation of *Staphylococcus epidermidis* early, a biosensor consisting of an actuator made of magnesium zinc oxide (MZO) dual-gate thin-film transistor (DGTFT) and an MZO nanostructure array coated conducting pad as the extended sensing gate was constructed. An *in vitro* culture of *S. epidermidis* was done on the nanostructure modified sensing pad and the occurrence of charge transfer between the MZO nanostructure and the microbial cells during the initial stages of bacterial adhesion was detected by the DGTFT. The results show that approximately 80% of the current change was achieved after culturing the bacteria for about

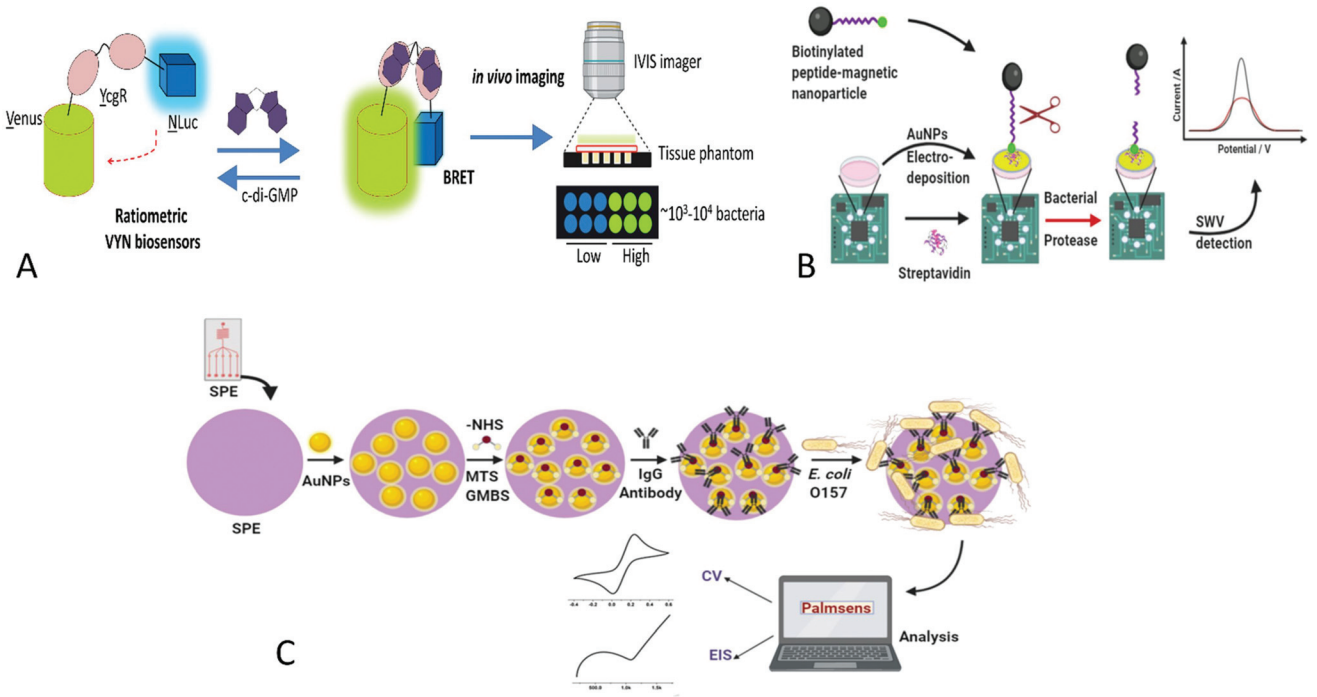

Fig. 9 Biosensors for diagnosis of bacterial infections. (A). Ratiometric Venus-YcgR-NLuc (VYN) biosensors for bacterial infection. Binding of cyclic di-GMP (c-di-GMP) from the bacteria to the VYN biosensor gives bioluminescence resonance energy transfer (BRET) which can generate cyclic di-GMP images in tissues. (B) Schematic diagrams of the multiplexed electrochemical array biosensor, in which gold nanoparticles (AuNPs), are electrodeposited on the array chip followed by cross-linking of streptavidin over it; then biotinylated peptide-magnetic nanoparticles are fabricated over a streptavidin cross-linked gold nanoparticle (AuNP) deposited array chip. The presence of bacterial proteases cleaves the peptide at the specific site and releases magnetic nanoparticles which are detected by square wave voltammetry. (C) Generation of the electrochemical biosensor using AuNP-modified carbon screen-printed electrodes (SPEs) with immobilized anti-*E. coli* O157 antibodies by –NHS cross-linking for detection of *E. coli* O157 bacteria.

200 minutes. Tiny bacterial colonies that just started to form at 200 minutes were observed by a crystal violet staining-based assay and it would take them about 24 hours to develop into matured biofilms. So, the abovementioned biosensor would allow medical professionals to act on the early stages of bacterial infections[173] (Fig. 9).

Fungal infections detection

The fungal kingdom consists of around 1.5 million different species and 400 species out of these are pathogenic to humans.[174] Yeast fungi are commensal symbionts mostly found in mucous membranes and human skin.[175] Immunocompromised people, preterm neonates, patients with invasive devices, and people on broad-spectrum antibiotics are more susceptible to fungal infections. *Candida* spp. provide adverse infection in humans. There are up to 150 species of *Candida* and among these, seven of the fungal species, namely *C. krusei*, *C. albicans*, *C. guilliermondii*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. lusitaneae*, are responsible for 95% of the infections in humans. According to estimations about 300 million people are affected by candidiasis and candidemia.[176] Conventional methods for the diagnosis of fungal infection are culture-based which remain the gold standard but are very time consuming (require 2–4 days) and lack sensitivity. Other methods such as ELISA and PCR require trained professionals, costly reagents, special equipment and are prone to false positive and false negative results.[177] This is where a biosensor comes in which can accurately detect the presence of infections from specific fungi.

Lately, an impedimetric biosensor has been developed with an ability to recognize concanavalin A and wheat germ agglutinin in the *Candida* species. Lectins are carbohydrate-binding proteins that can bind to the microorganism cell wall. This biosensor could differentiate among *Candida* spp. with a detection limit within the range of 102 to 106 CFU ml^{-1}. The biosensor is based on lectin-modified AuNPs and cysteine monolayers. The nano-based biosensor could sensitively detect and discriminate heterogeneous viable cells of *C. krusei*, *C. albicans*, *C. parapsilosis* and *C. tropicalis*[176] (Fig. 10).

Parasitic infection detection

Parasites are interdependent organisms that rely on other hosts for their survival to get nutrition. Infections due to them are most common in rural and developing regions where people have a weakened immune system or contaminated food sources.[178] Some of the habitual parasites include single-cell protozoans like *Plasmodium* and helminths such as tapeworm and flukes that get transmitted through the mouth and skin or

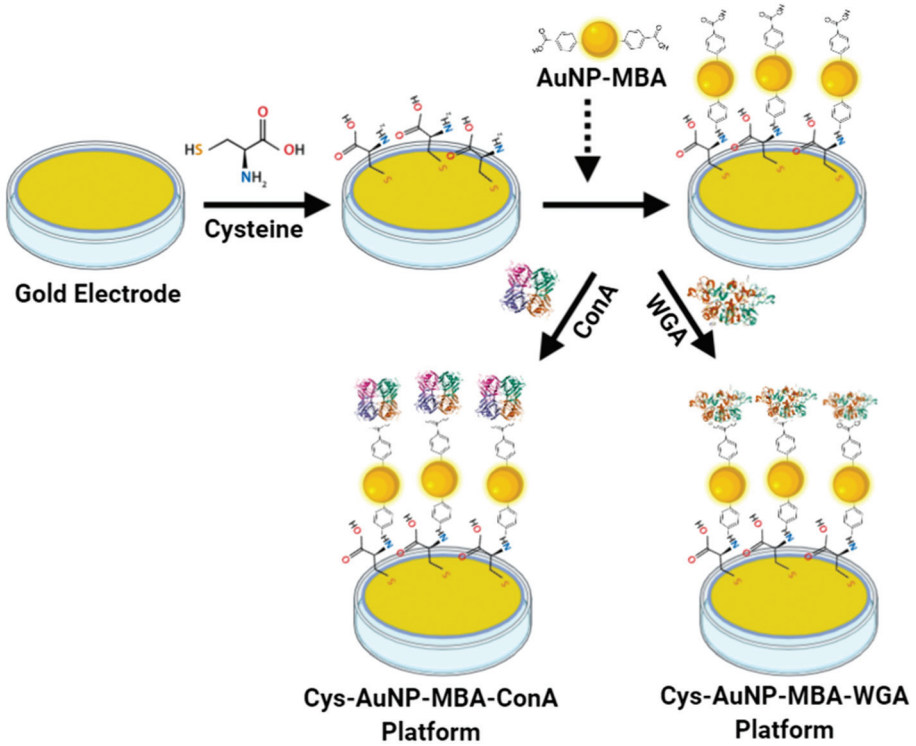

Fig. 10 Biosensors for the diagnosis of fungal infections. The preparation of an impedimetric biosensor for *Candida* spp. using concanavalin A (ConA) and wheat germ agglutinin (WGA) as recognition agents of the fungal cells.

stool causing giardiasis, malaria, toxoplasmosis, and trichomoniasis. They are diagnosed *via* blood, urine, and sputum tests. However, the increasing impact of diseases such as malaria globally has led to the recent advances in faster diagnosis using novel biosensors as biomarkers to identify the liver-based or dormant stage of the malarial parasite. There are reviews on certain effective biosensors recently discovered such as *Plasmodium falciparum* histidine-rich protein 2 (PfHRP-2),[179] parasite lactate dehydrogenase (pLDH), and *P. falciparum* glutamate dehydrogenase (PfGDH) that have the potential of a better analytical character, sensitivity, detection, and storage.

PfHRP-2

Initially, the development of this biosensor started with an ELISA assay that checked if it was a suitable reagent for the development of a sensor.[179] AuNPs with a AgCl reference electrode were used as a sensor to inactivate the anti-PfHRP monoclonal antibody following which a sandwich ELISA with an HRP conjugate was created with signal detection using 3,3′,5,5′-tetramethyl-benzidine dihydrochloride (TMB). The performance of the sensor was further optimized and characterized reaching a limit of 2.14 ng ml^{-1} thereby forming an ideal analytical tool for resource-limited settings.[180]

pLDH

It is an aptamer-based electrochemical sensor that recognizes sensitive proteins based on the pI of PfGDH and acts by recognizing the DNA aptamer and its association with the target PfLDH. It has an expanded range of detection with lower detection. The aptamer is fixed on a gold electrode and assembled onto a monolayer with 6-mercaptohexanol as a blocking agent. Ferrocyanide was used for surface modification, and by adjusting the pH between negative and redox probes it reached a detection range of 0.84 pM.[181] This biosensor has greater efficacy in diluted serum and could regenerate without the loss of bound aptamers.[179]

pfGDH

The glutamate dehydrogenase enzyme plays an essential role in carbon and nitrogen metabolism and in assimilating ammonia. The *Plasmodium* parasite has three GDH isoenzymes which have a unique N-terminal residue absent from mature human enzymes and host RBCs. Thus, the collaboration of GDH together with gold and monoclonal antibodies can diagnose *P. falciparum* with a sensitivity of 86.6%. This aptasensor is a thiolated ssDNA aptamer that binds to PfGDH antigen with high affinity with an optimum frequency of 2 Hz.[182]

Commercialized biosensor for biomedical applications

Biosensors for commercial use are not a new thing; there are more than just plenty of them used for detection in the food industry, environmental and biomedical sectors.[183,184] This

Table 3 Commercialized biosensors for biomedical application

Target analytes	Related conditions	Types of biosensors	Ref.
Glucose	Diabetes	Enzymatic-electrochemical, lateral flow immunochromatographic assays (LFAIs), reverse iontophoresis	294
Human chorionic gonadotropin (hCG)	Pregnancy, fertility and ovulation	Lateral flow immunochromatographic assay, fluorescence labeled antibodies assay	295
Streptococcus spp.	Throat or skin infection	Lateral flow immunochromatographic assay, fluorescence labeled antibodies assay	296 and 297
Mycobacterium tuberculosis	Tuberculosis	Lateral flow immunichromatographic assay, fluorescence labeled antibodies assay	298
Alpha fetoprotein (AFP)	Cancer	Lateral flow immunichromatographic assay, electrochemical	35
Bacillus anthracis	Anthrax	Standard lateral flow assay, fluorescence labeled antibodies assay	299

section is focused on this last one. Leland C. Clark, an American biochemist, is known as the father of biosensors because back in 1956 he developed a device intended to detect oxygen in the blood, water, and other liquids. Later on, the first commercial biosensor was developed by Yellow Springs Instruments (YSI Inc); its function was to detect glucose.[185,186] It has to be pointed out that despite the variety of biosensors in the biomedicine area, the majority are aimed at, precisely, glucose detection. Other commercial biosensors' purposes are the detection of biomolecules such as hormones or pathogenic agents.[187]

Table 3 displays examples of commercialized biosensors.[188] Nanotechnology-based biosensors are rarely mentioned because they are still under development and research, especially because the interaction between biomolecules and NMs is not quite clear nor is there reproducibility and mass-scaled production.[189,190] The companies that manufacture and are important in the biosensor market are Abbot Laboratories (USA); Becton, Dickinson, and Company (USA); Medtronic (USA), Illumina (USA), iKang Healthcare Group (China), Roche (Switzerland), Bayer (Germany), and Research International (UK), among others.

Future prospects of nano-biosensors

Biosensor-based devices tend to present ground-breaking and promising accessories in modern biomedical applications and will be the future of next-generation diagnostics. Specifically, advancement in the capability of biosensors for *in vitro* detection and *in vivo* imaging of DNA methylation,[21] and histone acetyltransferase detection,[22] can be a valuable step towards understanding molecular genetics in-depth. Engineering bioreceptors with modified molecular manipulators like DNA polymerases and Cas9 as representative of the DNA-modifying enzyme group in DNA sensor design can heighten the specificity several fold.[191] Manipulating host cells such as red blood cells to deliver nano biosensors *in vivo* for biomedical applications like bio-imaging can be a novel approach for disease diagnosis.[192] Miniature, mobile, multifunctional, conductive hydrogel-based, flexible, and wearable sensors for real-time personalized health monitoring and controlling cybernetic prosthetics can be considered as a growing branch of the commercialized application of nanobiosensors in the future.[193,194] The exploitation of novel nanostructured materials like quantum dots,[195] photonic crystals,[196] borophene,[197] and biological markers like transcription factors[198] are the tip of the ice-berg with immense possibilities.

Additionally, nanotechnological advancement in biosensor development is revolutionary and could be further heightened with strategic investments of scientific resources in smart technologies like the Internet of things (IoT) built with advanced telecommunication networks, big data analytics, and artificial intelligence (AI) with deep learning accessibility.[199–201] Emerging discussions including nano-biosensor and smart technologies like IoT have given rise to novel concepts such as the Internet of Nano-Things (IoNT) and the Internet of Bio-Nano-Things (IoBNT).[202] IoT in simple terms refers to all the physical devices like a smartphone throughout the globe, connected with the internet, and sharing data instantaneously *via* a unique identifier, enabling secure data transfer without the requirement of human-to-human or human-to-computer interactions.[203] Hybridizing this technology with the implementation of nanotechnology to sense biological macromolecules with the precision and accuracy achievable through IoBNT is now considered as the next big intervention that needs further exploration. These mega heterogeneous data or big data generated can be further processed swiftly into information with high throughput value *via* AI with deep learning accessibility, which otherwise would have a cost-deficit and be time-consuming. Amalgamating AI, which is the simulation of human intelligence in machines that are designed to think like humans and reflect human actions, could be further advanced and made automated.[204] Blending the application of AI for biomedical monitoring-based biosensors for point of care diagnostics is another growing sphere of technological hybridization. This combination could decipher the importance of machine-learning algorithms for the futuristic nano-based biosensors along with the IoT, computational techniques, and microchip-based essential disease biomarkers for real-time health monitoring and improving patient compliance.[23,24]

Conclusion

Biosensors present a promising approach for the effective and accurate detection of biological protein markers associated with various non-communicable and communicable diseases. Their precision and accuracy can be improved with the

amalgamation of nanotechnology, directing the path towards nano-based biosensors/nanobiosensors. The review presents a detailed outline of the application of nano-based biosensors in NCDs like cancer, metabolic, neurological, and neonatal disorders, highlighting some of the possible biomarkers that could be detected. The communicable diseases of viral, bacterial, fungal, and parasitic infections are also discussed in the review, presenting a unique perspective to understand the pathophysiology of the disease and possible markers that could be explored in the near future for promising output. These intermediate molecules can be considered specific to the particular pathway they are involved in; therefore developing a customized biosensor for detecting them may be beneficial. Furthermore, with the advancement of nanotechnology, novel nanostructured materials like quantum dots, photonic crystals, borophene, *etc.* are evolving which can enhance the accuracy and persistence of the nanobiosensors. The commercial perspective of nano-based biosensors, which is one of the key aspects required for proper funding and manpower, is discussed. Future prospective conceptualizations and application or implementation of novel computational techniques, IoT, big data analytics, AI with deep learning accessibility and microchip-based techniques linked with nano-based biosensors could essentially be a remarkable tool for disease detection. Therefore, investigation acknowledging these smart systems linked to nano-based biosensors must be encouraged for the development of next-generation diagnostics.

Conflicts of interest

The authors declare no conflict of interest with the manuscript.

Acknowledgements

The authors are grateful to their respective institutions for their support. RG Kerry would like to thank the Department of Science & Technology, Government of Odisha, India, for Biju Patnaik Research Fellowship (Ref. No. ST-BT-MISC-0008-2018-1933/ST), for perusing Ph.D. in Biotechnology (with registration ID:- 05-Biotechnology-2017-18), at Department of Biotechnology, Utkal University, Bhubaneswar, Odisha, India. JK Patra, G Das and HS Shin are grateful to Dongguk University, the Republic of Korea for support. JK Patra acknowledges the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1G1A1004667), the Republic of Korea for support. All figures are prepared using inkscape version 1.0.0 software.

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