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Review Article

Biosensors Applied to Diagnosis of Infectious Diseases – An Update

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Abstract

In the past five decades, biosensors have consolidated their impact in several fields, including clinical applications, due to advantages such as high selectivity and sensitivity, potential for miniaturization, portability, low cost and rapid response. Recent advances in biomarkers discovery and biotechnology are now clarifying the nuances of many biological processes in health and disease, highlighting new targets for diagnosis and therapeutics. This is especially important in the case of infectious diseases, since the number of predicted deaths remains high, with threats of epidemics and pandemics, emerging and re-emerging diseases and pathogen resistance to antibiotics. Therefore, the availability of robust diagnosis methods is crucial. This review presents the current strategies for diagnosis of infectious diseases, notions about biomarkers and ligand selection, besides focusing on the promising technology of biosensors.

Keywords: Biosensors; Sensors; Biomarkers; Diagnosis; Infectious diseases

Abbreviations

ELISA: Enzyme-Linked Immunosorbent Assay; PCR: Polymerase Chain Reaction; MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry; NGS: Next Generation Sequencing; FISH: Fluorescence In Situ Hybridization; SELEX: Exponential Enrichment; SPR: Surface Plasmon Resonance; WHO: World Health Organization; EIS: Electrochemical Impedance Spectroscopy

Introduction

Infectious diseases are caused by pathogenic microorganisms, including bacteria, viruses, fungi and parasites. Some examples among those enumerated by the World Health Organization (WHO) include tuberculosis, meningococcal meningitis, malaria, AIDS, pneumonia, poliomyelitis, hepatitis, Ebola virus disease, dengue and Chikungunya, American trypanosomiasis (Chagas disease), leprosy, toxoplasmosis and leishmaniasis.

The urbanization process and the consequent lack of city planning, poor management of sanitary conditions and water supplies, great inhabitants' density and interference in previously untouched ecosystems conjunctly contribute to the spread of infectious diseases [1]. In spite of the existent vaccination programs, the rise in incidence of certain diseases shows the impact of intentional under vaccination and the urge for public health education programs [2], as well as the need of new immunization strategies and alternatives to overcome pathogen resistance to antibiotics [3].

Although the mortality related to infectious diseases is being reduced worldwide, the number of deaths predicted for 2050 is 13 million and the threats of epidemics and pandemics remain considerable [3]. Moreover, emerging and re-emerging diseases caused by new, uncategorized or persistent pathogens have been reported [4].

This review presents the current strategies for diagnosis of some infectious diseases, notions about biomarkers and ligand selection, besides focusing on the promising technology of biosensors.

Diagnosis strategies for infectious diseases

A diagnostic test is any method for identification of a patient's disease or condition. In the case of infectious diseases, it allows the detection of presence or absence of infection. The importance of simple, accurate, affordable and rapid diagnosis tests is justified by its impact in the clinical management, since early diagnosis affects therapy effectiveness and avoids long-term complications and pathogen transmission [5].

While the standard diagnosis techniques for infectious diseases include well-established methodologies, such as Enzyme-Linked Immunosorbent Assay (ELISA), nucleic acid-based assays, microscopy and microorganism culture [6], the development of new strategies for the evaluation of specific biomarkers in clinical diagnosis is imperative [7]. The diagnosis tests for infectious diseases should present a set of desirable characteristics, such as sensitivity, specificity and reproducibility [5].

Historically, the identification of infectious agents was initially performed by culture and microscopy. Then, antigen detection and Polymerase Chain Reaction (PCR) became widely used. Currently, pathogen identification and host response (e.g., antibodies detection) are both used to diagnosis pathological states [8].

PCR and DNA microarrays are two widely used nucleic acids technologies. PCR employs oligonucleotide primers that are complementary to pathogen genetic material to amplify it, if present in the sample. The reaction product is detected during or after the process. Microarray technology, by the other hand, allows multiple

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target detection through hybridization with the probes immobilized on a surface [9].

Recently, Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS) is being adopted in the comparison of protein fingerprint obtained in a sample with the available databases, for the identification of bacteria, fungi [10] and viral pathogens [11]. There is also the potential of Next Generation Sequencing (NGS) methodologies to revolutionize infectious diseases diagnosis, since it does not rely on pre-established sequence targets, allowing the identification of emerging or mutating pathogens [12,13]. Other strategies are also being developed for clinical diagnosis, including microfluidic [14] and nanotechnological [15] devices.

Biosensors, other promising diagnosis technology that has received attention in the last decades and has several associated advantages will be discussed later in detail.

Biomarkers and their ligands for infectious diseases diagnosis

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [16]. Biomarkers are also defined as specific variables, represented by biomolecules, such as genes, proteins and metabolites, associated to certain populations as distinguishable features [17]. Moreover, this term may be associated with the use of genomics, transcriptomics, proteomics and metabolomics technologies, the monitoring of drug discovery, as well as clinical concepts, such as prediction, progression, regression, outcome, diagnosis and therapeutics [18]. Some examples of biomarkers for infectious diseases include C-Reactive Protein (CRP) and soluble Triggering Receptor Expressed on Myeloid cells 1 (sTREM-1). While CRP is applied for sepsis, severe infection, rheumatologic conditions and coronary artery disease risk stratification; sTREM-1 is a sepsis prognostic marker [8].

The ideal biomarkers should present a whole set of desirable characteristics, including accessibility for measurement, sensitivity and specificity. Its clinical importance should be externally validated; its use should result in cost-effective assays [19] and present reproducibility and stability toward sample variations [20].

Biomarkers identification may be achieved by several approaches, including simple statistical tests, development and analysis of classification models or subset-selection optimization [17]. In the last decades, several biomarkers for infectious diseases have been identified, due to improvements in biomolecules screening techniques and bioinformatics analysis. However, their translation into clinical use is still limited [19].

Depending on the class of biomarker, there are several methods for the selection of specific ligands, including phage display and Systematic Evolution of Ligands by Exponential Enrichment (SELEX) [21].

Nucleic acid ligands

Polymerase Chain Reaction (PCR) and Fluorescence *In Situ* Hybridization (FISH) are two widely used nucleic acid detection technologies. While PCR consists in the *in vitro* specific DNA amplification, FISH is the fluorochrome-labeling of oligonucleotides for hybridization with the complementary target. Both methods rely on the use of known DNA sequences that relates to specific pathogens [22,23]. For the development of such diagnostic systems based on nucleic acid biomarkers and ligands, the general strategy is to compare sequences in order to find species-specific oligonucleotide targets that are present in high copy numbers in the cells [23].

When designing DNA oligonucleotide probes for several applications, including PCR and DNA hybridization assays, some criteria should be followed: assure their complementarity and specificity for the target, avoid competing secondary structures (dimers and hairpins) and choose adequate melting temperature [24,25].

Most efforts in nucleic acid probes design has been related to PCR [24], FISH [26] and microarray technologies [27]. Cho et al. [28] reported the selection of 23-mer primers for *Vibrio cholera* detection by quantitative polymerase chain reaction. The primers pair had the outer membrane lipoprotein *lolB* gene as target and allowed the specific identification of several isolates. Ogura et al. [29] reported a method of microarray probe design based on comparison of edit distance between sequences to avoid cross hybridization with similar probes on the array. Naidoo et al. [30] evaluated *Mycobacterium Tuberculosis*pili (MTP) gene and protein sequences as potential biomarkers for tuberculosis and found they are specific and highly conserved among strains of the *Mycobacterium Tuberculosis* Complex (MTBC), through BLAST and multi-sequence alignment.

These examples show that DNA-based diagnosis and selection of appropriate biomarkers ligands have focused in comparing sequences. However, this paradigm is changing with the application of Next-Generation Sequencing (NGS), which does not rely on previous knowledge about the pathogens genetic sequence [12].

Protein and peptide ligands

Several techniques are employed for protein biomarker discovery and ligands selection, including mass spectrometry, gel electrophoresis and protein microarrays, the later allowing the study of entire proteomes [31]. Also, peptides microarrays may be employed in the selection of peptide ligands, after computational pre-selection [32].

Another notable methodology is called phage display and relies on the expression and presentation of a great diversity of peptides or proteins on bacteriophages surfaces, allowing their selection against a target biomolecule [33]. Therefore, this tool can be used to find new reagents for immunological assays, including phage-displayed peptides that mimetize pathogen antigens, with applications like leprosy diagnosis [34] and development of vaccines for visceral leishmaniasis [35]. Wu et al. [36] selected three single-chain variable Fragments (scFv) for detection of Highly Pathogenic Avian Influenza A (HPAI) viruses strains, which could be important to accelerate diagnosis and control outbreaks. Another application is the presentation of antibodies in the bacteriophage surface for potential therapeutic purposes [37], with targets such as the CCR5 HIV co-receptor [38].

Other ligands

Aptamers are high-affinity ligands selected in vitro. Their targets may be specific proteins isoforms or conformations, being analogous

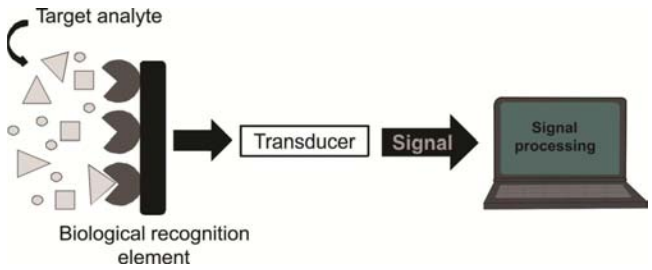

Figure 1: Schematic representation of the general operation principle of biosensors. The biological element is immobilized on a surface. In the presence of a specific target analyte that binds to the immobilized biomolecule, the transducer converts the recognition event into a measurable signal, which can be then processed (Adapted from Ronkainen et al [145]).

to antibodies [39]. Aptamersare selected from libraries through Systematic Evolution of Ligands by Exponential enrichment (SELEX) against several classes of targets, including carbohydrates, proteins and inorganic molecules [40].

Aimaiti et al. [41] selected species-specific aptamers for discrimination of *Mycobacterium tuberculosis* strains through whole cell SELEX process. Shiratori et al. [42] developed DNA aptamers for proteins of several influenza A virus subtypes and applied them in a successful sandwich detection method. Besides diagnostic applications, aptamers have also been used as therapeutics agents, such as the recently reported S15 aptamer, that binds to the envelope protein of all dengue serotypes, neutralizing the infections [43].

These examples show how the integration of physiology, biochemistry, genetics, bioinformatics and other research fields, may improve biomarker discovery and selection of specific ligands, allowing a better understanding of infectious diseases and the development of effective diagnostic systems, such as biosensors [44].

Biosensors for diagnosis of infectious diseases

Biosensors are analytical devices that convert a biochemical recognition event into a measurable signal [45], consisting mainly of a probe (biological recognition element) and a physicochemical detector (transducer) (Figure 1). The objective is to determine the presence, activity or concentration of an analyte in a solution [46], with a broad range of applications, such as industrial [47], environmental [48] and medical [49,50].

Biosensors present several advantages over other analytical tools, such as high selectivity and sensitivity, potential for miniaturization and portability [51], low cost, detection in real time, use of small sample volumes and rapid response [51-53].

Depending on specific criteria, biosensors may be classified into distinct groups. Regarding the transducer type, there are the calorimetric sensors, related to the conversion of enthalpy [54], the piezoelectric, sensitive to mass changes [55], the optical, based on light-associated phenomena [56] and the electrochemical, based on the generation or consumption of electro active species [57].

Another classification system is based on the biological component (probe), which can be DNA molecules [58], enzymes [56], and antibodies [59], among others (Figure 2). Enzymatic biosensors take advantage of the catalytic activity, selectivity and specificity of enzymes. The pioneer works of Clark et al. [60], such as the coupling

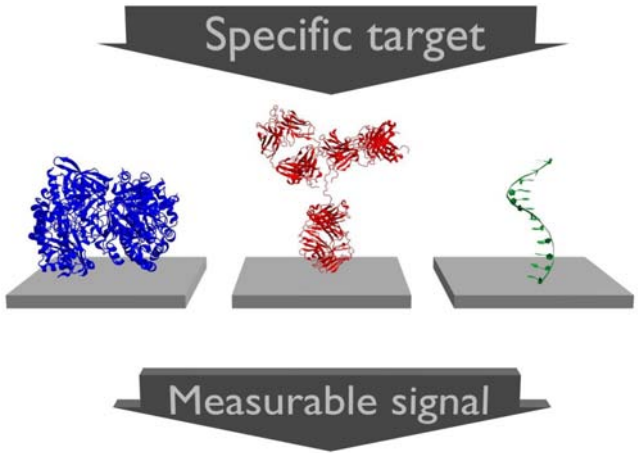

Figure 2: Schematic representation of distinct groups of biosensors, regarding the biological component. The surface-immobilized biomolecules glucose oxidase (PDB1GPE [146]), anti-HIV-1 antibody (PDB 1HZH [147]) and a DNA dodecamer (PDB 1BNA [148]) represent the enzymatic biosensors, immunosensors and genosensors, respectively. Other types of biologic elements for biosensors (not represented) include aptamers, cells and tissues, and microorganisms. The arrows indicate that, as a general principle, the binding of a specific target is converted into a measurable signal.

of the enzyme glucose oxidase to an electrode that recognized the oxygen uptake, yielded one of the most successful classes of biosensors. By the other hand, genosensors contain DNA fragments immobilized on their surface and can detect mutated genes associated with human diseases [61], as well as the genetic identification of pathogens [62-64]. Immunosensors contain antibodies as biological element, whose specific binding sites interact with the antigen to form an antibody-antigen complex [65]. Other types of biologic elements for biosensors include aptamers [66], cells and tissues [67], and microorganisms [68].

Although different types of biosensors have been successfully developed and applied to the medical field, for the diagnosis of pathologies such as cancer [69-72], cardiovascular [73-75], autoimmune [76-78] and neurodegenerative diseases [79-82], this review will focus on infectious diseases.

Biosensors for detection of pathogenic virus

Viruses are infectious agents that may be responsible for several diseases in humans, including Human Papilloma Virus (HPV) [83] (Table 1), dengue virus [43,84-86] and hepatitis virus [62,87-89].

There are 100 genotypes of HPV virus and some of them are associated with cancer, especially in the cervix and anus [83]. The methods used for the diagnosis have limitations, such as low specificity [90]. To overcome this disadvantage, Huang and coworkers described a highly sensitive electrochemical biosensor based on DNA probes for Human Papillomavirus (HPV), using a glassy carbon electrode functionalized with graphene, gold nanorods and polymeric film. They used electrochemical impedance spectroscopy and 1,10-phenanthroline ruthenium dichloride ($Ru(phen)_3^{2+}$)as redox indicator, amplifying the electrochemical signal. The biosensor described proved to be efficient in the viral DNA detection, specifically detecting the target in human serum samples with a detection limit of 4.03×10^{-14} M [83].

Table 1: Characteristics from several biosensors for detection of pathogenic virus.

Organism	Biomarker / probe	Classification	Platform	Linearity range	Detectionlimit	Ref.
HPV	n.s. / DNA oligonucleotide	Electrochemical genosensor	GCE/G/AuNRs/PT	1 x 10^{-8} - 1 x 10^{-13} M	4.03 x 10^{-14} M	[83]
HPV 16	n.s. / 5051 mAb	Electrochemical biomicrosystem	PMMA/gold nanolayer/4-ATP SAM	n.s.	n.s.	[91]
HPV	n.s. / DNA oligonucleotide	Electrochemical genosensor	GE	12.5 – 350.0 nM	3.8 nM	[49]
Hepatitis B virus	n.s. / DNA oligonucleotide	Electrochemical genosensor	GrE/poly(4-aminophenol)	1.89 x 10^{-9} - 1.89 x 10^{-6} M	2.61 nM	[62]
Hepatitis B virus	HBsAg / mAb	Chemiluminescence immunosensor	Polystyreneplate	1.7 - 1920 pg mL^{-1}	0.358 pg mL^{-1}	[88]
Dengue virus	n.s. / DNA oligonucleotides	Electrochemical genosensor	GE /AuNpsPANI	n.s.	n.s.	[94]
Dengue virus	NS1 protein / anti-NS1 antibody	Electrochemical immunosensor	GE/MUA SAM	0.01–2.00 µg mL^{-1} (PBS) 0.01–1.00 µg mL^{-1} (Neat blood)	3 ng mL^{-1} (PBS) 30 ng mL^{-1} (Neat blood)	[84]
Dengue virus	NS1 protein / anti-NS1 antibody	Electrochemical immunosensor	SPE/Thiophene	0.04 – 0.6 µg mL^{-1}	0.015 µg mL^{-1}	[95]

n.s.: not specified; 4-ATP: 4-Aminothiophenol; AuNpPANI: Gold Nanoparticles-Polyaniline Hybrid Composite; G: Grapheme; AuNRs: Gold Nanorods; GCE: Glassy Carbon Electrode; GE: Gold Electrode; GrE: Graphite Electrode; HBsAg: Hepatitis B Surface Antigen; HPV: Human Papillomavirus; mAb: monoclonal Antibody; MUA: 11-Mercaptoundecanoic Acid; PMMA: Polymethylmethacrylate; PT: Polythionine; SAM: Self-Assembled Monolayer; SPE: Screen-Printed Electrode.

Urrego and collaborators described a biosensor for the detection of HPV that was able to perform 98 simultaneous tests. It was based on a monolayer of 4-aminophenol on a surface of poly(methyl methacrylate) with a gold nanolayer and the immobilization of a monoclonal antibody (mAb 5051) specific for HPV 16, one of the most common genotypes among women. Electrochemical impedance spectroscopy was used in the analysis. The biomicrosystem developed was portable, used a small volume of sample and simple equipment [91].

Nasirizadeh et al developed a genosensor using gold electrodes, thiolated oligonucleotides specific for HPV and monitored the interaction of hematoxylin with dsDNA formed after the hybridization process. They used the techniques of cyclic voltammetry and differential pulse voltammetry, observing a remarkable difference between the voltammetric signals in different samples after hybridization. The linear relationship with the concentration of DNA target varied from 12.5 to 350.0 nM and the detection limit was 3.8 nM [49].

Another infectious disease caused by a DNA virus that infects hepatocytes of the liver is hepatitis B. It is a global health problem with approximately 2 billion people infected, corresponding to about a third of the world having positive serology for hepatitis B [92]. Hepatitis B virus infection can harm the liver, with high risk of death from liver cirrhosis and cancer [89]. During the chronic phase of the disease, monitoring is crucial, since it prevents the development of progressive diseases, such as cirrhosis and liver failure, as well as hepatocellular carcinoma.

As an alternative to the traditional methods, Castro and coworkers developed an electrochemical biosensor for the detection of a specific DNA sequence of the hepatitis B virus, using graphite electrodes modified with poly (4-aminophenol), differential pulse voltammetry as detection technique and ethidium bromide as hybridization label (Figure 3). They showed that this device was effective for diagnosis in the serum of infected patients and had a detection limit of 2.61 nM [62].

Shourian et al. [88] developed a colorimetric immunosensor to detect the surface antigen of hepatitis B virus. The strategy used was a sandwich immunoassay system that had gold nanoparticles functionalized with biotin and luminol. A chemiluminescent signal was produced by the gold nanoparticles in the presence of a catalyst and hydrogen peroxide as the oxidant. The immunosensor had a linear range of 1.7 to1920 pg mL^{-1} and the detection limit of 0.358 pg mL^{-1}.

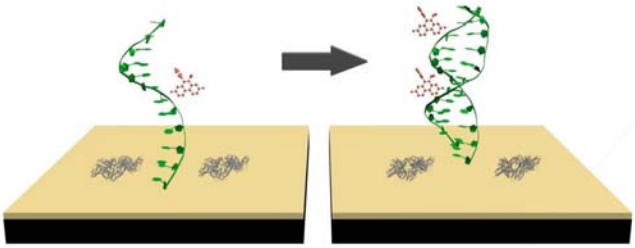

Figure 3: Example of genossensor for detection of a specific DNA sequence before (left) and after (right) the binding of the target (Adapted from Castro et al [62]). A specific DNA oligonucleotide was immobilized on a graphite/poly (4-aminophenol) surface and it was blocked with BSA. Then, the complementary DNA target was applied. Ethidium bromide was used to discriminate the single-stranded and double-stranded DNA.

Dengue is a major public health problem in the world, with 2.5 billion people at risk of contracting the disease. It is transmitted by infected female mosquitoes *Aedesaegypti* and *Aedesalbopictus*, being considered endemic in 98 tropical and subtropical countries.

Current methods for diagnosis of dengue are based on the detection of viral RNA by Reverse Transcription Polymerase Chain Reaction (RT-PCR) or immunoassay methods including ELISA, where the analyte targets are antibodies raised in response to the viruses in the infected patient. However, early diagnosis of disease with these methods can be expensive, time-consuming, and not sensitive and produce false positives [85,93].

Trying to overcome these problems, Nascimento and coworkers described the development of a biosensor based on gold electrodes functionalized with a composite of gold nanoparticles, polyaniline and with SH-terminal groups (AuNpPANI-SH). On this surface, they immobilized 3 specific oligonucleotides for serotypes 1 (T1), 2 (T2)

Table 2: Characteristics from several biosensors for detection of pathogenic bacteria.

Organism	Biomarker / probe	Classification	Platform	Linearity range	Detectionlimit	Re.
Mycobacterium tuberculosis	IS6110 gene / DNA oligonucleotide	Electrochemical genosensor	GCE/rGO-AuNPs	1 x 10^{-15} - 1 x 10^{-9}M	n.s.	[102]
Mycobacterium tuberculosis	Genomic DNA / DNA oligonucleotide	Electrochemical genosensor	GE/ MBA SAM/Fe_3O_4Nps	6 - 40 ng μL^{-1}	6 ng μL^{-1}	[103]
Mycobacterium tuberculosis	n.s. / DNA oligonucleotide	Electrochemical genosensor	GCE/AuNPs	1 x 10^{-14} - 1 x 10^{-9} M	8,7 x 10^{-15} M	[93]
Mycobacterium tuberculosis	IS6110 gene / DNA oligonucleotide	Electrochemical genosensor	SPCE	up to 100 aM	0.5 aM	[104]
Mycobacterium tuberculosis	rpoB gene / DNA oligonucleotide	Optical genosensor	GE	n.s.	n.s.	[105]
Mycobacterium tuberculosis	IS6110, 16S ribosomal RNA, 85B, Rv3130c and Rv3133c / DNA oligonucleotide	Optical genosensor	GE	n.s.	115 ng/mL	[106]
Mycobacterium tuberculosis, Mycobacterium avium	ITS gene / DNA oligonucleotides	Optical genosensor	GE/AuNPs	10^4 CFU mL^{-1} - 10^8 CFU mL^{-1}	4.2 x 10^4 CFU mL^{-1} and 3.7 x 10^4 CFU mL^{-1}, respectively	[107]
Mycobacterium tuberculosis	Serum antibodies / Antigens (W06,W10,W14,W19,W28,W38,W64,W70,W85)	Optical immunosensor	Array chip/8-MOA SAM	n.s.	n.s.	[108]
Mycobacterium tuberculosis	Ag85, ESAT6 and LAM / specific antibodies	Optical immunosensor	Waveguides functionalized with a lipid bilayer	n.s.	0.5 / 100 / 1 pM, respectively	[109]
Mycobacterium tuberculosis	PolyclonalIgYantibodies	Optical immunosensor	Functionalized microtip	n.s.	200 CFU mL^{-1}	[110]
Mycobacterium tuberculosis	n.s. / mAb	Electrochemical immunosensor	Functionalized microtip	n.s.	100 CFU mL^{-1}	[111]
Mycobacterium leprae	n.s. / PCR product	Electrochemical genosensor	GrE /poly(4-aminophenol)	0.35-35.0 ng μL^{-1}	n.s.	[113]
Mycobacterium leprae	IgM and IgG antibodies / ND-O and LID-1 antigens	Lateral flow immunosensor	Nitrocellulose membranes	n.s.	n.s.	[114]
Neisseria meningitidis	Membrane protein 85 (Omp85) / specific antibody	Piezoelectric immunosensor	GE/PVDF	0.3-20 µg mL^{-1}	312 ng/mL	[117]
Neisseria meningitidis	Omp85 gene/ DNA oligonucleotide	Electrochemical genosensor	SPGE	6-100 ng/6 µL	6 ng/6 µl	[118]
Neisseria meningitidis	CtrA gene / DNA oligonucleotide	Electrochemical genosensor	Gold coatedglass electrode	7–42 ng μL^{-1}	n.s.	[119]
Neisseria meningitidis	CtrA gene / DNA oligonucleotide	Electrochemical genosensor	Gold coatedglass electrode	10–60 ng μL^{-1}	n.s.	[120]
Neisseria meningitidis	CtrA gene/ DNA oligonucleotide	Electrochemical genosensor	ZNF/Pt/Si	5–240 ng μL^{-1}	about 5 ng μL^{-1}	[121]
Neisseria meningitidis	rmpM gene / DNA oligonucleotide	Electrochemical genossensor	SPGE	1-12 ng/6 µL	3 ng/6 µL	[122]

n.s.: not specified; 8-MOA: 8-Mercaptooctanoic Acid; AuNPs: Gold Nanoparticles; Fe_3O_4Nps: magnetite Nanoparticles; GCE: Glassy Carbon Electrode; GE: Gold Electrode; GrE: Graphite Electrode; mAb: monoclonal Antibody; MBA: Mercaptobenzoic Acid; Pt/Si: Platinum/Silicon; PVDF: Polyvinylidenedifluoride; rGO: reduced Graphene Oxide; SAM: Self-Assembled Monolayer; SPCE: Screen-Printed Carbon Electrode; SPGE: Screen-Printed Gold Electrode; ZNF: ZnOnanoflowers.

and 3 (T3) and identified the genomic material, using ferricyanide/ferrocyanide potassium as indicator and cyclic voltammetry and electrochemical impedance spectroscopy as detection techniques. The system AuNpPANI-ST exhibited a highly selective response to the genome of dengue fever in human patients and can be used for the construction of a biosensor for serotypes of dengue in low concentration [94].

Cecchetto and coworkers decided to use the Non-Structural protein of dengue (NS1) as target for a biosensor. The authors developed an immunosensor using gold electrodes modified with a self-assembled monolayer of mercaptoundecanoic acid and immobilization of anti-NS1 antibody by covalent bonds. The detection technique was electrochemical impedance spectroscopy and the calibration curve linearity ranged between 0.01–2.00µg mL^{-1} in PBS and 0.01–1.00 µg mL^{-1} in serum, with a detection limit of 3ng mL^{-1} in PBS and 30ng mL^{-1} in serum [84].

Silva et al. [95] developed a screen-printed electrode using a modified graphite ink with thiophene and a layer of gold nanoparticles, immobilized anti-NS1 antibodies and detected the amperometric responses of the NS1 protein of the dengue virus by cyclic voltammetry in the presence of ferrocyanide/ferricyanide. Linearity was obtained from 0.04 to 0.6 µg mL^{-1} and the detection limit was 0.015 µg mL^{-1}.

Biosensors for detection of pathogenic bacteria

Pathogenic bacteria are important targets for detection in several fields, such as medicine and food safety. Different approaches have been developed for the detection of pathogenic bacteria, since these microorganisms contribute to globally important diseases, such as tuberculosis, leprosy and meningitis [96-100] (Table 2).

Tuberculosis is caused by the pathogenic bacteria *Mycobacterium tuberculosis* and is currently the leading infectious cause of death, undoubtedly representing a global public health priority [101]. According to the World Health Organization, in 2013 approximately 5.7 million cases of tuberculosis were reported worldwide.

In recent years, many biosensors platforms have been developed for tuberculosis based on different biological recognition elements and various transducers. Liu et al. [102] developed an electrochemical genosensor for *M. tuberculosis* based on the immobilization of a specific sequence of the IS6110 gene using a reduced graphene oxide-gold nanoparticle-modified electrode as a sensing platform and gold nanoparticles–polyaniline as a tracer label for amplification.

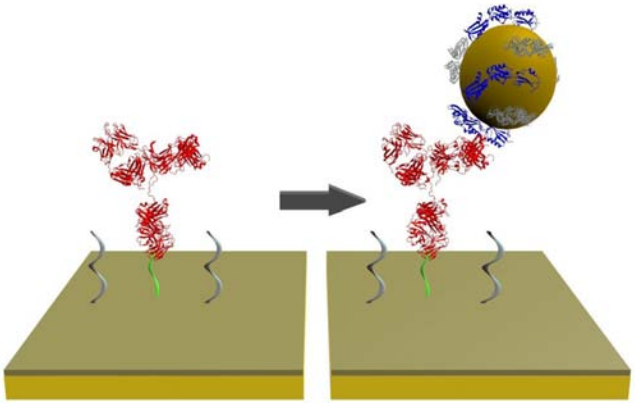

Figure 4: Example of immunosensor for detection of meningococcal antigen before (left) and after (right) the binding of the target (Adapted from Reddy et al. [117]). A gold electrode was modified with polyvinylidenedifluoride thin film deposition. Antibodies were directionally orientated by interaction with protein A and the surface was blocked with casein. Next, gold nanoparticles conjugated with the target antigen and BSA was applied to the surface, in order to allow the antigen-antibody interaction.

The linear response of the sensor was 1 x 10^{-15} to 1 x 10^{-9}M. Costa et al. [103] described an electrochemical genosensor based on self-assembled monolayers of mercaptobenzoic acid and magnetite nanoparticles (Fe_3O_4Nps) on bare gold electrode for immobilization of a DNA probe. The detection limit was 6ng μL^{-1}.

Zhang et al. [93] proposed a novel electrochemical biosensing platform using CdSe quantum dots as a label combined with MspI endonuclease and gold nanoparticles to improve the selectivity and amplify the signal. The sensor linear range of response was 1 x 10^{-14} to 1 x 10^{-9} M and it discriminated mismatched DNA for *M. tuberculosis* with high selectivity. For the detection of very small quantities of pathogen genomic DNA, an electrochemical method was developed and this platform was applied to the detection of *M. tuberculosis* in sputum, pleural fluid and urine samples. This methodology is based on the entrapment of amplified single-stranded DNA sequences on magnetic beads, followed by the post-amplification hybridization assay to provide a higher level of specificity [104].

Other detection systems have been reported, such as Surface Plasmon Resonance (SPR), an optical detection technique that has been widely used for the development of genosensors for *M. tuberculosis* [105-107], and immunoassays [108-111].

Another disease caused by bacteria of the genus *Mycobacterium* is leprosy, a chronic disease caused by *Mycobacterium leprae*. According to WHO, in 2013 about 215,000 cases of leprosy were reported in the world, and the early diagnosis is important to interrupt transmission and prevent severe damage to patients [112].

Afonso et al. [113] developed an electrochemical genosensor based on the immobilization of a specific single-stranded DNA oligonucleotide on a graphite electrode modified with poly (4-aminophenol). The system target was *M. leprae* and the linear range of detection was from 0.35 to 35.0 ng μL^{-1}. In addition, a fast and quantitative test for leprosy was developed by immobilizing two specific antigens on nitrocellulose membranes to detect IgMandIgG antibodies [114].

Meningitis can be caused by various pathogens, such as bacteria, fungi, viruses and parasites. Among the bacteria species that can cause meningitis, the most common are *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilusinfluenzae*, *Listeria monocytogenes* and *Streptococcus* [115,116]. Particularly, *Neisseria meningitidis* has the potential to cause large epidemics.

Among the studied targets for detection, there is Omp85, a virulence gene that codes for a conserved outer membrane protein of *N. meningitidis*. Reddy et al. [117] described the development of an immunosensor using the quartz crystal microbalance as transducer and antibodies against the cell surface outer membrane protein 85 of *N. meningitides* as biologicalrecognition element (Figure 4). In addition, an electrochemical genosensor was developed using specific oligonucleotides for this virulent gene immobilized on screen-printed gold electrodes and the sensor sensitivity was 2.6 ($\mu A/cm^2$)/ng [118].

Other electrochemical genosensors have been described using specific oligonucleotides for other virulent factors. A genosensor was developed through the immobilization of thiol-labeled DNA probe on a gold electrode surface and its hybridization with complementary sequence of the ctrA gene. The sensitivity was 115.8 μA/ng with 0.917 regression coefficient [119], 0.0115 μA/ng with 0.999 regression coefficient [120] and 168,64 μA/ng with 0.98 as regression coefficient [121]. Dash et al. [122] used specific oligonucleotides complementary to the rmpM (reduction-modifiable protein M) virulent gene as a biological recognition element. The sensitivity of the genosensor was 9.5087 μA/ng.

Biosensors for detection of pathogenic protozoan

Protozoa are one of the main classes of parasites that cause diseases in humans. A wide variety of approaches have been applied to the development of biosensors for the diagnosis of protozoan-caused diseases such as malaria, leishmaniasis, American trypanosomiasis (Chagas disease) and toxoplasmosis.

Malaria is transmitted to humans by the bite of more than thirty species of female anopheline mosquitoes. The etiologic agent is a protozoan of genus *Plasmodium*. Five species, *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*, are known to affect humans [44]. According to the WHO, in 2013 about 48 million cases of malaria were reported worldwide, with 584,000 deaths (Table 3).

Various biomarkers have been used to malaria diagnosis [44]. Histidine-rich protein-II is produced and secreted by the parasite during its growth and development and it has been widely used for the development of electrochemical [123-125] and optical immunosensors [126]. Biosensors based on the immobilization of aptamers with high affinity for lactate dehydrogenase, another biomarker for malaria, has been reported in the literature using electrochemical [127] and colorimetric [128,129] transducers. Reddy et al. [117] describes the development of *Plasmodium* lactate dehydrogenase-specific ssDNA aptamers by SELEX using magnetic beads. The selected aptamers were characterized and used for the construction of an aptamer-based electrochemical sensor able to discriminate malaria positive samples from non-infected sample (Figure 5). In addition, Ittarat et al. [130] described a genosensor based on quartz crystal microbalance to differentially diagnose malaria infection by either *P. falciparum* or *P. vivax*.

Table 3: Characteristics from several biosensors for detection of pathogenic bacteria.

Organism	Biomarker / probe	Classification	Platform	Linearity range	Detectionlimit	Ref.
Plasmodium falciparum	Anti-PfHRP-2 antibodies/ *Pf*HRP-2	Electrochemical immunosensor	SPE/Al_2O_3 sol–gel/ AuNPs	n.s.	1 : 102400 dilution of rabbit anti-PfHRP-2	[123]
Plasmodium falciparum	*Pf*HRP-2 / specific antibody	Electrochemical immunosensor	AuNPs/MWCNT/ SPE	n.s.	8 ng mL^{-1}	[125]
Plasmodium falciparum	*Pf*HRP-2 / specific antibody	Piezoelectric immunosensor	GE/DDT/TA	15–60 ng/ml	12 ng/ml	[124]
Plasmodium falciparum	Anti-PfHRP-2 antibodies / PfHRP-2	Optical immunosensor	GE /4-MBA	n.s.	5.6 pgand 0.4 ng	[126]
Plasmodium falciparuma nd Plasmodium vivax	pLDH / aptamer	Electrochemical aptasensor	GE	1- 1000 pM	1 pM	[127]
Plasmodium vivax	pLDH / aptamer	Colorimetric aptasensor	AuNPs/PDDA or PAH	0-500 parasites/µl	80 parasites/µl (PDDA) 74 parasites/µl (PAH)	[128]
Plasmodium falciparum and Plasmodium vivax	pLDH / aptamer	Colorimetric aptasensor	AuNPs	1 pM - 1 nM	1.25 pM (*Plasmodium vivax)* and 2.94 pM (*Plasmodium falciparum)*	[129]
Plasmodium falciparum and Plasmodium vivax	n.s. / DNA oligonucleotide	Piezoelectric genosensor	SEQC/MPA	n.s.	n.s.	[130]
Leishmania infantum	*Leishmania infantum* antibodies / rK39 + LicTXNPxantigens	Fluorescent Immunosensor	Magnetic microspheres	n.s.	n.s.	[132]
Leishmania infantum	*L.infantum* antibodies / *L. infantum* antigens	Optical immunosensor	GE/MUA SAM	1:50-1:6400 dilutions	1:6400 dilution	[133]
Leishmania infantum	Parasite antigens / mABs	Piezoelectric immunosensor	GE/CA	n.s.	1.8 x 10-4 amastigotes/g of infected tissue	[134]
Leishmania donovani	18S rRNA gene / DNA oligonucleotide	Electrochemical genosensor	ITO/NiO	2pg/ml - 2µg/ml	0.02 ±0.002 ng/µl	[135]
Trypanosoma cruzi	*T. cruzi* antibodies / CRA and FRA antigens	Electrochemical immunosensor	GE and PE	n.s.	n.s.	[137]
Trypanosoma cruzi	*T. cruzi* antibodies / *T. cruzi*antigen	Electrochemical immunosensor	SPGE/CA	n.s.	n.s.	[138]
Trypanosoma cruzi	IgG antibodies / specific antigens	Electrochemical immunosensor	SPCE/MPA-AuNPs	11 - 205 ng mL^{-1}	3.065 ng mL^{-1}	[139]
Toxoplasma gondii	IgG antibodies / specific antigen	Piezoelectric immunosensor	PQC/ n-butyl amine PPF	~1:5000–1:75 dilution	~1:5500 dilution	[141]
Toxoplasma gondii	IgG antibodies / specific antigen	Electrochemical immunosensor	GE/MPA	1:200-1:8000 dilutions	1:9600 dilution	[142]
Toxoplasma gondii	IgG antibodies / aptamer	Fluorescence aptasensor	Microplate	0.5−500 IU	0.1 IU	[143]
Toxoplasma gondii	n.s. / DNA oligonucleotides	Fluorescence aptasensor	Fe_3O_4/CdTe	n.s.	8.339 nM	[144]

n.s.: not specified; 4-MBA: 4-Mercaptobenzoic Acid; Al_2O_3sol–gel: Alumina sol–gel; AuNPs: gold Nanoparticles; CA: Cysteamine; CRA: Cytoplasmic Repetitive Antigen; DDT: 1-Dodecanethiol; Fe_3O_4/CdTe: magnetic fluorescent nanoparticles; FRA: Flagellar Repetitive Antigen; GE: Gold Electrode; ITO: Indium Tin Oxide; MPA: 3-Mercaptopropionic Acid; MUA: 11-Mercaptoundecanoic; MWCNT: Multiwall Carbon Nanotubes; NiO: Sol-gel synthesized nickel Oxide; PAH: Poly (Allylamine Hydrochloride); PDDA: Poly (Diallyldimethylammonium chloride); PE: Platinum Electrode; *Pf*HRP-2: *Plasmodium falciparum* Histidine Rich Protein-2; pLDH: Plasmodium Lactate Dehydrogenase; PPF: Plasma-Polymerized Film; PQC: Piezoelectric Quartz Crystals; SAM: Self-Assembled Monolayer; SEQC: Silver Electrode of Quartz Cristal; SPCE: Screen-Printed Carbon Electrode; SPE: Screen Printed Electrode; SPGE: Screen-Printed Gold Electrode; TA: Thioctic Acid.

Leishmaniasis is a tropical disease caused by an intracellular parasite of the genus *Leishmania*. The vector of transmission is the sand fly, which may deposit one of the 20 disease-causing protozoan species during blood ingestion. Clinical presentation depends on the complex interplay between the host cell-mediated immune response, and the specific protozoa and vector species. There are four generally accepted classifications of clinical disease: cutaneous, diffuse cutaneous, mucocutaneous and visceral leishmaniasis [131]. According to the WHO, in 2013 about 215 thousand cases of leishmaniasis were reported worldwide.

Among the immunosensors reported, Sousa et al. [132] developed a new fluorescence-based immunosensor that comprised magnetic polymer microspheres coated with recombinant antigens, to improve the detection of anti-*Leishmaniainfantum* specific antibodies in the serum of infected dogs. Souto et al. [133] described the development of an immunosensor for anti-*L. infantum* antibodies based on detection by SPR technique.

Other kinds of transducers have been used, such as in the piezoelectric immunosensor developed for the detection of *L. infantum* antigens in tissues of infected hosts [134]. In this case, antibodies were immobilized on a gold surface, covered with a thin film of cysteamine and glutaraldehyde, blocked with glycine and placed into contact with extracts of hamster spleens infected with *L. infantum*. The assay was able to detect 1.8 x 10^{-4}amastigotes/g of infected tissue. Moreover, Mohan et al. [135] described an electrochemical genosensor based on the immobilization of a DNA sequence that targeted 18S rRNA gene sequences from *Leishmaniadonovani*.

Chagas disease, also known as American trypanosomiasis,

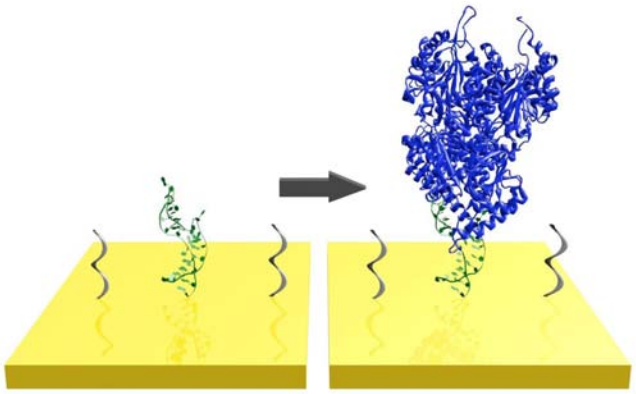

Figure 5: Example of aptasensor for the diagnosis of malaria before (left) and after (right) the binding of the target (Adapted from Lee et al. [127]). The scheme illustrates a specific thiol-modified aptamer immobilized on a gold electrode, together with spacer molecules. Next, the protein target was applied for interaction with the aptamer probe.

is a neglected tropical disease caused by the protozoan parasite *Trypanosomacruzi*. It is found mainly in endemic areas of 21 Latin American countries, where it is mostly vector-borne transmitted to humans by contact with feces of haematophageous bugs of the *Triatominae* subfamily, known as 'kissing bugs', among other names, depending on the geographical area [136].

A polypeptide chain formed by recombinant antigens, cytoplasmic repetitive antigen and flagellar repetitive antigen of *T. cruzi* was adsorbed on gold and platinum electrodes and antigen-antibody interaction was investigated by electrochemical impedance spectroscopy [137]. *T. cruzi* proteins from epimastigote membranes were used for the construction of an amperometric immunosensor for serological diagnosis of Chagas disease. Antibodies present in the serum of patients were captured by the immobilized antigens and the affinity interaction was monitored by chronoamperometry using peroxidase-labeled IgG conjugate [138].

Ferreira et al. [138] described an amperometric bioelectrode for detection of antibodies occurring in sera of patients suffering from American trypanosomiasis. The strategy consisted of the immobilization of parasites proteins on goldelectrodes modified with thiol and the detection limit was 12.4 ng mL^{-1} of IgG. Pereira et al. [139] reported the development of an integrated microfluidic system coupled to a screen-printed carbon electrode applied to the quantitative determination of IgG specific antibodies present in serum samples. The electrode was modified by electrode position of gold nanoparticles and functionalized with *T. cruzi* proteins from epimastigote membranes. The calculated detection limit for electrochemical detection was 3.065 ng mL^{-1}.

Toxoplasmosis is caused by the parasite *Toxoplasma gondii*, an obligate intracellular protozoan, capable of infecting humans. Most infections are asymptomatic or take a mild form, characterized by fever, malaise and lymphadenopathy. However, in cases of immune deficiency or when the parasite is congenitally acquired, it may cause serious illness and even death [140]. The diagnosis and genetic characterization of *T. gondii* infection is crucial for monitoring, prevention and control of toxoplasmosis. Traditional approaches for the diagnosis of toxoplasmosis include molecular and imaging techniques [102].

Most biosensors for toxoplasmosis described in the literature are based on immunoassays for the detection of anti-*T. gondii* antibodies. An agglutination-based piezoelectric immunoassay was developed for directly detecting anti-*T. gondii* immunoglobulin's in infected rabbit serum and blood. The proposed technique is based on the specific agglutination of antigen-coated gold nanoparticles (10 nm diameter), in the presence of the corresponding antibody, which causes a frequency change monitored by a piezoelectric device. The developed system is sensitive to dilution ratios of anti-*T. gondii* antibody as low as 1:5500 [141].

Ding et al. [142] developed an electrochemical biosensor based on an enzyme-catalyzed amplification. *T. gondii* antigen was immobilized on the surface of a gold electrode in order to bind anti-toxoplasma IgG, and this was followed by the addition of anti-toxoplasma IgG horseradish peroxidase conjugate. The transduction methods were quartz crystal microbalance, electrochemical impedance spectroscopy and cyclic voltammetry, with a detection limit of 1:9600 in dilution ratio.

Luo et al. [143] used two aptamers with high affinities to antitoxoplasma IgG as detection probes while developing a quantum dots-labeled dual aptasensor. In the presence of anti-toxoplasma IgG, an aptamer-protein-aptamer sandwich complex is formed and captured on a multi well microplate, whose fluorescence can be read out using quantum dots as label. The aptasensor has linearity within the range of 0.5-500 IU with the lowest detection of 0.1 IU. Also based on fluorimetric detection, He et al. [144] described the use of magnetic fluorescent nanoparticles in the development of a genosensor for the detection of *T. gondii* DNA oligonucleotides, with limit of detection of 8.339 nM.

Conclusion

Since the first ideas five decades ago, biosensors have shown their potential to revolutionize the diagnosis of a variety of health conditions. Today, their impact in clinical management is well established, since rapidity, specificity and sensibility are crucial characteristics for early diagnosis and therapy initiation. The development of new technologies, such as nanotechnology and microfluidics, together with biomarker discovery should improve their effectiveness. In the case of infectious diseases, which have the potential of transmission and outbreaks occurrence, with possible sequels development and lethality, the availability of robust diagnosis methods is crucial.

Biosensors are also important in the democratization of diagnosis. Many methods currently available are inaccessible for a significant part of the world population, since they are expensive, centralized and require specialized technicians for operation. Therefore, the potential of cost reduction, portability and simplicity is largely appreciable, especially in the case of neglected diseases.

What lies ahead is also promising. Advances in fields such as genetics and epigenetics, chemistry and biochemistry, physiology and bioinformatics have the potential of clarifying the nuances of biological processes in the health and disease. New targets of study are emerging and other are being better understood, especially in diagnosis and therapeutics, or even both (i.e., theranostics). Therefore,

the coupling of these findings with promising technologies such as biosensors may change the current landscape of clinical diagnosis.

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