Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Chapter 30

Virus detection using nanosensors

Yeşeren Saylan and Adil Denizli
Department of Chemistry, Hacettepe University, Ankara, Turkey

Chapter Outline

30.1 Introduction 501
30.2 Fundamental of nanosensors 503
30.3 Significance of virus detection 503
30.4 Applications of nanosensors in virus detection 504
30.4.1 Human immunodeficiency virus 504
30.4.2 Hepatitis B virus 504
30.4.3 Human papillomavirus 504
30.5 Conclusion and outlook 507

30.1 Introduction

The definition of a smart city is that a city that functions in an intelligent and sustainable direction by combining all its services into a cohesive unit and employing clever devices to control and monitor [1]. The global population is perpetually increasing and also importantly driving consumption of resources, which is the cause of climate change and resource deficiency. Especially, urban areas are responsible for the larger part of these resource consumption, prompting an increasing need to produce smart solutions that are environment friendly and more energy efficient [2]. Fig. 30.1 illustrated the solutions to these problems, which consist of advances to components of the smart city.

Recently, the concept of smart city has become more popular in international policies and literature [3]. Smart cities play an important role in economic and social prospects and have a tremendous effect on the environment [4]. The city metabolisms comprise of the remark of goods and the yield of waste with consonant adversary externalities that amplify economic and social troubles. In addition the standard of urban sustainability has increased and should respond to people’s necessities through solutions for these aspects [5,6]. The smart city concept is far from being restricted to the utilization of technologies in cities. In point of fact, the use of the name is growing in several sectors without the agreement of definitions. It led to chaos among urban policy makers and hopes that the policies will make their cities smart. Cities search for solutions that allow mixed land uses, transportation linkages, and economical high-quality urban services all over the world. As shown in Fig. 30.2, this more efficient and high-quality transport that responds to economic requirements and associated labor is considered an essential element for the growth of cities [7–10].

Millions of people suffer from several diseases due to numerous medical problems [11]. Today, there is a noteworthy rise in the infectious diseases that affect humans, animals, and plants [12]. Particularly, in undeveloped countries, various diseases, including human immunodeficiency virus (HIV), malaria, and tuberculosis, affect a lot of people [13]. Viruses are parasites and require the host cell to generate and replication. Complex protection mechanisms have been developed by mammalian cells to detect and hinder viral replication. In response, they are capable of breaking down and controlling the host immune reactions. This has allowed the growth of viruses that are proficient at destroying host immune reactions [14].

The detection of pathogenic agents is important for point-of-care applications [15]. Several methods, including polymerase chain reaction [16], enzyme-linked immunosorbent assay [17], reverse-transcription polymerase chain reaction [18], and nanosensor technologies, can detect viruses [19–23], regardless of their drawbacks in terms of utilization and stability [24]. Because of the needs for prompt diagnosis in more stable, economical, and selective nanosensor
technology, various recognition molecules have been analyzed to develop in sensing devices [25]. Nanosensors comprise recognition elements and transducers [26]. The principal bases on the capturing of target and conversion of responses to signals. Nanosensors can be classified into five classes: electrochemical [27], optic [28], piezoelectric [29], thermal [30], and magnetic [31]. Over the previous decades, nanosensors have evolved to be significant for identifying analytes from explosive [32] to protein [33], nucleic acid [34], carcinogens [35], bacteria [36], virus [37] and toxin [38] in food processing [39], environmental monitoring [40], clinical diagnostics [41], and fight against bioterrorism [42].
In this chapter the fundamental concept and types of nanosensors are initially explained and then the use of nanosensor technology is widely reviewed according to the research studies for the assessment of smart utilizations in the diagnosis of infectious; conclusion and outlook are indicated as well.

30.2 Fundamental of nanosensors

A nanosensor has three main modules: a transducer, a receptor, and a detector with a digital output (Fig. 30.3). The target molecule connects with the receptor [43], and the biological detecting component identifies a biological molecule through a reaction. After that, the transducer converts changes to a signal quantified by the detector [44]. Nanosensors offer multiple abilities, including practicable operation, exceptional performance, high specificity and sensitivity, rapid response, condensed size, portability, and real-time analysis [45]. In these days, investigators improve the specificity and sensitivity of the methods by focusing on the nanosensor production quality, extending the affinity between the surface chemistries and employing nanocomposites, such as nanofilm [46], gold nanoparticle [47], or quantum dot [48], for signal amplification studies.

Electrochemical nanosensors have been applied in several applications. These nanosensors include screen-printed electrodes and semiconductors and monitor any changes in dimension, dielectric properties, charge distribution, and shape, while the complex is produced on the electrode. They can be separated into three groups, amperometric, impedimetric, and potentiometric transducers, and utilized to detect various targets [49–51]. Optic nanosensors measure the change of the reflective index of the transducer when the target and recognition element produce a complex. These nanosensors can be classified into two types. In the direct optic nanosensors, signal generation is based on the production of a complex on the transducer surface, whereas the indirect optic nanosensors are mostly designed with various labels to detect the binding and extend the signal. Although indirect sensing nanosensors can create higher signals, they suffer from high reagent cost of labeling step and nonspecific binding [52,53]. They have a multipurpose detection scale and sense various kinds of biomolecules from different specimens [54,55]. Piezoelectric nanosensors measure mass change and viscoelasticity by recording frequency and modifying a quartz crystal resonator [56,57]. The sensing needs isolation equipment that minimizes any hindrance effects because of the high sensitivity to environmental circumstances. These nanosensors have been used in a wide variety of applications to identify targets [58,59]. Thermal nanosensors exploit the fundamental property of biological reactions, such as absorption or evolution of heat. This is reflected as a change in the temperature within the reaction medium. In thermal nanosensors, heat is measured using sensitive thermistors that are frequently selected as temperature transducers. A number of instruments have been laid out in the past decades, and they integrated the fundamentals of enzyme catalysis, calorimetry, flow injection analysis, and immobilization on suitable matrices [60–62]. Magnetic nanosensors carry out magnetic beads coated with a ligand, and they can be detected within a magnetic field. They propose distinct advantages, such as when a sample selected for analysis does not contain any contaminating materials with magnetic properties, background signals are minimized. In addition, not only new avenues of research and clinical methods have been successfully formed, including hyperthermia treatment, magnetic actuation, targeted drug delivery, and the use of magnetic particles, but also bioassays based on fluorescent detection or well-established sequencing methods in genetics have been challenged [63,64].

30.3 Significance of virus detection

Infectious diseases still have a ubiquitous threat to health, especially in rural areas of cities. Underlying cases for such serious maladies can be summarized as the lack of available analysis methods and subsequent treatment strategies due to the limited access of centralized and equipped health-care facilities [65]. Many researchers, such as physicists, chemists, biologists, and medical doctors, have used nanosensors as applications in several fields, including doping analysis [66], diagnosis [67], food safety [68], and laboratory medicine [69]. Among them, clinical applications have been researched as an impressive field of application. Due to the necessity to enhance detecting properties and rapid analysis, new recognition molecules and organizations of them have been examined. With a different combinations, the detection
performance of the nanosensors can be improved. These properties make them suitable for clinical applications that can do rapid and multimolecule detection [70,71].

30.4 Applications of nanosensors in virus detection

30.4.1 Human immunodeficiency virus

Human immunodeficiency virus (HIV) is a lentivirus that is a subset of retroviruses. Lentiviruses are slow viruses, which means that there is an interval between the beginning of the infection and rise of the symptoms. HIV infects the CD4+ T cells and initiates to replicate after entering the bloodstream [72]. The resulting disease is AIDS that is one of the important public health issues. According to the WHO report, more than 35 million people have been infected up to now [73]. There are two classes of HIV, namely, HIV-1 and HIV-2, and HIV-1 is the most prevalent type of disease-causing agents.

Babamiri et al. promoted an electrochemiluminescence nanosensor to detect HIV-1 gene. After hybridization experiments, they observed the signal to be significantly increased. They accomplished a sensitive detection in a range from 3.0 fM to 0.3 nM. They showed that their nanosensor has a good specificity when compared with the noncomplementary sequences [74]. Lu et al. prepared a nanosensor with the aim of determining HIV-1-related glycoprotein 41 (Gp41). They modified the surface of piezoelectric nanosensor by a synthetic peptide, which has 579–613 residues of Gp41. They demonstrated that a nanosensor surface has an immense affinity to the target peptide and can selectively bind Gp41. They calculated the detection limit as 2 ng/mL [75]. Shafiee et al. exhibited an optic nanosensor for HIV-1 detection. They mentioned that the target was adsorbed and influenced a shift with 10 pM resolution and investigated ranging from 10^4 to 10^8 copies/mL [76].

30.4.2 Hepatitis B virus

Hepatitis B virus has been known since the 1940s and causes transient and chronic hepatitis [77]. Hepatitis B virus (HBV) is one of the main infections evaluated to cause almost a million deaths every year due to cirrhosis and malignant liver growth. In addition, 15%–40% of infected patients will have liver failure, liver cirrhosis, or hepatocellular carcinoma, and 15%–25% will unfortunately die [78].

Hassen et al. published a study about the hybridization of DNA to detect the HBV by electrochemical impedance spectroscopy. First of all, they altered DNA probes with magnetic nanoparticles and immobilized nanoparticles into the gold electrode. Following the characterizations, they showed a good DNA immobilization and hybridization with different concentrations of complementary DNA. Moreover, they exhibited that this nanosensor has detected 50 pmol of HBV DNA, and saturation reached 12.65 nM [79]. Uzun et al. also detected an HBV surface antibody using optic nanosensor in human serum. They carried out kinetic studies employing HBV surface antibody-positive human serum samples. They calculated detection limit value and also showed that this nanosensor obeyed the Langmuir adsorption isotherm model [80]. İstek et al. provided an electrochemical nanosensor for sequence-selective DNA hybridization related to HBV detection. They performed the selectivity of the nanosensor in the presence of target and the other DNA sequences. They also calculated the detection limit value of 0.86 µg/mL [81].

30.4.3 Human papillomavirus

Human papillomavirus (HPV) has been studied for cervical cancer development, which is the second-most prevalent form of malignancy among women. Early diagnosis lets patients to be taken care of at an early stage. Hence, there is an extreme clinical utility of diagnostics even with binary positive and negative indications. The Pap smear is generally used for screening, but this method still suffers from low sensitivity and specificity [82,83].

İnan et al. developed a microfluidic nanosensor for detecting HPV-16 E7 antibodies. They observed detection down to 2.87 ng/mL. They validated the nanosensor in serum samples and supplied high responses as compared with control samples. They showed that this nanosensor can be implemented as a pretesting tool to diagnose for broad monitoring of HPV-associated cancers [84]. Teengam et al. reported a colorimetric nanosensor to screen synthetic HPV. They developed a DNA-dependent multiplex paper-based nanosensor (Fig. 30.4). The targets were determined by quantifying the color change of silver nanoparticles that gave a detection limit value of 1.03 nM. The nanosensor displayed high selectivity for the complementary oligonucleotides over single-base mismatch, two-base mismatch, and noncomplementary DNA targets [85]. Peng et al. demonstrated a nanosensor that depended on two-dimensional nanosheets for
HPV detection. These nanosheets were acquired by exfoliating their layered etched powder and exhibited high fluorescence quenching ability to dye-labeled single-stranded DNA and different affinities for single-stranded and double-stranded DNA. They observed that the single-stranded DNA probe showed minimal fluorescent emission under the fluorescence quenching effect of nanosheets. This nanosensor for HPV-18 detections showed high specificity and a low detection limit of 100 pM.

30.4.4 Ebola

Ebola virus infections generate severe illness in humans, and after an incubation time, patients at first present with general influenzas before a fast progression to a progressive disease characterized via shock-like syndrome, multiple organ failure, and hemorrhage. The largest outbreak of Ebola virus infection is discussed in Ref. Natesan et al. produced a digital nanosensor to detect Ebola virus. Their nanosensor had a flow cell assay that captured specific antibodies with microarrayed recombinant antigens and a smartphone fluorescent reader for high-performance clarification of results. They showed that the smartphone reader utilized a hardware attachment that snapped at the back of a smartphone and provided a user interface to handle the operation, communicate with cloud service, and acquire test results. They also developed a secure cloud service for the tele-monitoring of results. They tested these nanosensor results with sera from nonhuman primates that received a live attenuated Ebola vaccine. Ilkhani et al. invented an electrochemical nanosensor to identify Ebola virus. They first marked it with a streptavidin–alkaline phosphatase conjugate and optimized all the steps and then received a low detection limit value. They finally accomplished selectivity and reproducibility. Yanik et al. constructed an optofluidic nanosensor that detects whole viruses. Their nanosensor was based on a light transmission impact and used group-specific antibodies. They applied in a range spanning three orders of magnitude. They modified antibodies against the Ebola glycoprotein on the nanosensors, and transmission spectra were collected after the cleaning process.

30.4.5 Zika

Zika virus is a mosquito-borne virus. Some sporadic human sickness cases were listed in Asia and Africa before 2007. The first report was in the Federated States of Micronesia in 2007. Emerging infectious illnesses, such as the Zika
virus epidemic spanning the Western Hemisphere, have demanded renewed studies regarding the requirement to produce simplified diagnostic tests [94].

Afsahi et al. developed graphene-based nanosensor to detect the Zika virus. They quantified as low as Zika viral antigens concentration (450 pM). They exhibited a potential diagnostic tool by detecting Zika antigen in human serum. They validated the selectivity with Japanese encephalitis NS1 [95]. Kaushik et al. represented an electrochemical nanosensor to detect Zika virus. They applied electrochemical impedance spectroscopy to measure the response and showed that the nanosensor detected Zika virus in a range of 10 pM–1 nM, and the detection limit value is lower than 10 pM [96]. Song et al. published a study based on reverse-transcription loop-mediated isothermal amplification to determine Zika virus. They exhibited the usefulness of this nanosensor by detecting Zika virus in real samples with a sensitivity of 5 pfu [97].

### 30.4.6 Influenza

Influenza is an infectious disease regarded as a wellhead of several clinical issues and enormous economic interruptions [98]. As common methods are insufficient for in-field detection and usually suffer from being time-consuming and difficult, it is essential for researchers to develop effective options to conventional methods [99].

Tam et al. published an article about the immobilization of DNA employing carbon nanotubes to detect influenza. They modified a DNA probe onto the nanosensor surface and characterized the fundamental interaction. They detected the DNA probe hybridization and the target DNA and found the limit of detection as 0.5 nM [100]. Vollmer et al. studied an optic method to detect influenza virus. They performed the binding experiments of single virions from changes of discrete in the resonance frequency of a whispering-gallery mode. They also supported the sensing mechanism with the virus-sized nanoparticles [101]. Bai et al. developed a portable optic nanosensor by employing an aptamer to detect avian influenza virus (AIV) H5N1. The immobilized aptamers by capturing AIV H5N1 cause an improvement in the refraction index. Following the optimization of experimental parameters, their results displayed that the refraction index value was linearly associated with AIV concentration [102].

Emir Diltemiz et al. prepared piezoelectric and optic nanosensors for the detection of hemagglutinin that is the main protein of the influenza virus. They employed 4-aminophenylboronic acid to bind sialic acid. As depicted in Fig. 30.5, they modified the nanosensor surfaces with thiol groups and then immobilized 4-aminophenylboronic acid and sialic acid. Also, they calculated detection limits as $4.7 \times 10^{-2}$ and $1.28 \times 10^{-1}$ \(\mu\)M for piezoelectric and optic nanosensors [103].

![FIGURE 30.5](image)
30.4.7 Other viruses

The real-time virus detection has a high interest in various fields, such as biosecurity, biomedicine, and environmental science [104]. Nanosensor does not need trained personnel and expensive equipment, especially if obtained results can be read by naked eyes [105,106].

Jin et al. published a study about a virus diagnostic tool that combined with an optic nanosensor and microfluidic system to detect human adenovirus. They detected 10 copies of human adenovirus in 30 minutes. They also validated the clinical utility and declared that this tool proposed a sensitive and rapid detection with simplicity, low cost, and short assay time [107]. Guerreiro et al. exhibited a genetically encoded switch-on fluorescent nanosensor comprising acylized green fluorescent protein (cVisensor) with an adenoviral protease cleavable site (Fig. 30.6). They first optimized nanosensor and then established virus detection by stable expression in mammalian cells and utilized for live-cell monitoring of adenovirus infection. They obtained a flow cytometry-based assay using cVisensor cells 48 hours postinfection and showed the limit of detection value as $10^5$ infectious particles/mL [108].

Kim et al. proposed a colorimetric nanosensor that depended on various forms of dsDNA-shielded gold nanoparticles to detect Middle East respiratory syndrome coronavirus. They demonstrated that their nanosensor was capable of verifying the existence of viral molecules and color changes of gold nanoparticles in the UV–vis wavelength range. They planned a pair of thiol-modified probes at either the 5' end or 3' end to coordinate complementary base pairs with upstream of the E protein gene and open reading frames. In addition, they reported that colorimetric nanosensor could discriminate down to 1 pmol/µL of 30 bp Middle East respiratory syndrome coronavirus [109]. Trzaskowska et al. investigated the possibility of using optic nanosensor in the detection of tuberculosis in sputum. First, they designed a portable surface plasmon resonance apparatus and referred its performance with a standard desktop surface plasmon resonance platform via measuring the response to tuberculosis secretory protein. Then, they examined samples of suspended Mycobacterium tuberculosis cultures and sputum samples of tuberculosis patients. They claimed that this nanosensor was able to detect $M.\ tuberculosis$ secretory protein and also able to determine tuberculosis bacteria cultures in the concentration of $1 \times 10^4$ cfu/mL with no significant interfering response from two other bacteria species [110]. Weerathunge et al. offered a colorimetric nanosensor to detect infective murine norovirus. They integrated the gold nanoparticles that have enzyme–mimic catalytic activity with a murine norovirus aptamer and noticed that this nanosensor created a blue color in the being of norovirus. They also found the detection limit as three viruses per assay, which is equal to 30 viruses/mL of the sample [111].

30.5 Conclusion and outlook

Clinical diagnostic systems have a huge research area that still has to deal with many unmet disputes necessary to develop and commercialize the nanosensors. They should be stable, simple, robust, reliable, and affordable and also have high detection capability, especially in clinical applications. Nanosensor feasibility also seems to begin leaving the proof of concept, and several analytes have already been detected to demonstrate the versatility of the nanosensors. In some particular cases the validation with real samples in clinical scenarios strengthens nanosensors suitability. There are still some doubts to overcome as some portable nanosensors have recently been studied at the research level. Though the progression is quite slow, a significant advancement in smartphone technology has helped mobile health diagnostics to deploy at developing countries. The exponential increase in mobile application development and the affordability of these platforms have revolutionized health delivery and opened a new window in global health access.

FIGURE 30.6 Scheme of the working principle of cVisensor [108].
In this review the current developments of nanosensors were summarized in clinical application for virus detection. In comparison with conventional techniques, these nanosensors demonstrate more favorable applications to improve human health.

References

[1] R. Giffinger, C. Fertner, H. Kramar, R. Kalasek, Smart Cities: Ranking of European Medium-Sized Cities, Centre of Regional Science, Vienna, 2007.
[2] G.P. Hancke, B.C. Silva, G.P. Hancke Jr, The role of advanced sensing in smart cities, Sensors 13 (1) (2013) 393–425.
[3] V. Albino, U. Berardi, R.M. Dangelico, Smart cities: definitions, dimensions, performance, and initiatives, J. Urban Technol. 22 (1) (2015) 3–21.
[4] K. Mori, A. Christodoulou, Review of sustainability indices and indicators: towards a new city sustainability index (CSI), Environ. Impact Assess. Rev. 32 (1) (2012) 94–106.
[5] C. Turcu, Re-thinking sustainability indicators: local perspectives of urban sustainability, J. Environ. Plann. Manage. 56 (5) (2013) 695–719.
[6] U. Berardi, Clarifying the new interpretations of the concept of sustainable building, Sustain. Cities Soc. 8 (2013) 72–78.
[7] I.A.T. Hashem, V. Chang, N.B. Anuar, K. Adewole, I. Yaqoob, A. Gani, et al., The role of big data in smart city, Int. J. Inf. Manage. 36 (2016) 748–758.
[8] O. Alvear, C.T. Calafate, J.C. Cano, P. Manzoni, Crowdsensing in smart cities: overview, platforms, and environment sensing issues, Sensors 18 (2018) 460.
[9] M.N.K. Boulos, N.M. Al-Shorbaji, On the internet of things, smart cities and the WHO healthy cities, Int. J. Health Geogr. 13 (2014) 10.
[10] C. Perera, A. Zaslavsky, P. Christen, D. Georgakopoulos, Sensing as a service model for smart cities supported by internet of things, Trans. Emerg. Telecommun. Technol. 25 (2014) 81–93.
[11] M.M. Alvarez, J. Aizenberg, M. Analoui, A.M. Andrews, G. Bisker, E.S. Boydien, et al., Emerging trends in micro-and nanoscale technologies in medicine: from basic discoveries to translation, ACS Nano 11 (2017) 5195–5214.
[12] A.A. Malik, C. Nantasenamat, T. Piacham, Molecularly imprinted polymer for human viral pathogen detection, Mater. Sci. Eng., C 77 (2017) 1341–1348.
[13] P.J. Hotez, Blue marble health and “the big three diseases”: HIV/AIDS, tuberculosis, and malaria, Microbes Infect. 17 (8) (2015) 539–541.
[14] Y.K. Chan, M.U. Gack, Viral evasion of intracellular DNA and RNA sensing, Nat. Rev. Microbiol. 14 (6) (2016) 360–373.
[15] A. Afzal, A. Mujahid, R. Shirihagl, S. Bajwa, U. Latif, S. Feroz, Gravimetric viral diagnostics: QCM based biosensors for early detection of viruses, Chemosensors 5 (1) (2017) 7–31.
[16] S. Payungporn, S. Chutinimitkul, A. Chaisingh, S. Damrongwantanapokin, C. Buranathai, A. Amonsin, et al., Single step multiplex real-time RT-PCR for H5N1 influenza A virus detection, J. Virol. Methods 131 (2) (2006) 143–147.
[17] R. Viswanathan, S. George, M.V. Murhekar, A.M. Abraham, M.P. Singh, S.M. Iadhav, et al., Comparison of two commercial ELISA kits for detection of rubella specific IgM in suspected congenital rubella syndrome cases and rubella IgG antibodies in a serosurvey of pregnant women: comparison of two commercial ELISA kits for detection of rubella specific IgM and IgG antibodies, Diagn. Microbiol. Infect. Dis. 94 (3) (2019) 243–247.
[18] A.C. Gourinat, O. O’Connor, E. Calvez, C. Goarant, M. Dupont-Rouzeyrol, Detection of Zika virus in urine, Emerg. Infect. Dis. 21 (1) (2015) 84–86.
[19] V.D. Krishna, K. Wu, A.M. Perez, J.P. Wang, Giant magnetoresistance-based biosensor for detection of influenza A virus, Front. Microbiol. 7 (2016) 400–408.
[20] K. Navakul, C. Warakulwit, P.T. Yenchitsomanus, A. Panya, P.A. Lieberzeit, C. Sangma, A novel method for dengue virus detection and antibody screening using a graphene-polymer based electrochemical biosensor, Nanomed. Nanotechnol. Biol. Med. 13 (2) (2017) 549–557.
[21] M. Khater, A. de la Escosura-Muniz, A. Merkoçi, Biosensors for plant pathogen detection, Biosens. Bioelectron. 93 (2017) 72–86.
[22] M.K. Tsang, W. Ye, G. Wang, J. Li, M. Yang, J. Hao, Ultrasensitive detection of Ebola virus oligonucleotide based on upconversion nanoprobe/nanoporous membrane system, ACS Nano 10 (1) (2016) 598–605.
[23] C.L. Wong, M. Chua, H. Mittman, L.X. Choo, H.Q. Lim, M. Olivo, A phase-intensity surface plasmon resonance biosensor for avian influenza A (H5N1) detection, Sensors 17 (10) (2017) 2363–2372.
[24] Z. Altintas, M. Gittens, J. Pocock, I.E. Tothill, Biosensors for waterborne viruses: detection and removal, Biochimie 115 (2015) 144–154.
[25] C.I. Justino, A.C. Freitas, R. Pereira, A.C. Duarte, T.A.R. Santos, Recent developments in recognition elements for chemical sensors and biosensors, Trends Anal. Chem. 68 (2015) 237–248.
[26] Y. Saylan, F. Yılmaz, E. Özgür, A. Derazshamshir, N. Bereli, H. Yavuz, et al., Nanotechnology Characterization Tools for Biosensing and Medical Diagnosis, Surface Plasmon Resonance Sensors for Medical Diagnosis, Springer Nature, Berlin, Heidelberg, 2018, pp. 425–458.
[27] S. Eissa, M. Siaj, M. Zourob, Aptamer-based competitive electrochemical biosensor for brevetoxin-2, Biosens. Bioelectron. 69 (2015) 148–154.
[28] Y. Saylan, F. Yılmaz, A. Derazshamshir, E. Yılmaz, A. Denizli, Synthesis of hydrophobic nanoparticles for real-time lysozyme detection using surface plasmon resonance sensor, J. Mol. Recognit. 30 (2017) e2631.
[29] D. Battal, S. Akgönilü, M.S. Yalcin, H. Yavuz, A. Denizli, Molecularly imprinted polymer based quartz crystal microbalance sensor system for sensitive and label-free detection of synthetic cannabinoids in urine, Biosens. Bioelectron. 111 (2018) 10–17.
[30] H. Yang, D. Qi, Z. Liu, B.K. Chandran, T. Wang, J. Yu, et al., Soft thermal sensor with mechanical adaptability, Adv. Mater. 28 (2016) 9175–9181.

[31] Z. Wang, X. Wang, M. Li, Y. Gao, Z. Hu, T. Nan, et al., Highly sensitive flexible magnetic sensor based on anisotropic magnetoresistance effect, Adv. Mater. 28 (42) (2016) 9370–9377.

[32] Q. Zhang, D. Zhang, Y. Lu, Y. Yao, S. Li, Q. Liu, Graphene oxide-based optical biosensor functionalized with peptides for explosive detection, Biosens. Bioelectron. 68 (2015) 494–499.

[33] B. Osman, L. Uzun, N. Beşirli, A. Denizli, Microcontact imprinted surface plasmon resonance sensor for myoglobin detection, Mater. Sci. Eng. C 33 (2013) 3609–3614.

[34] K. Bartold, A. Pietrzyk-Le, K. Golebiewska, W. Lisowski, S. Cauteruccio, E. Licandro, et al., Oligonucleotide determination via peptide nucleic acid macromolecular imprinting in an electropolymerized CG-rich artificial oligomer analogue, ACS Appl. Mater. Interfaces 10 (2018) 27562–27569.

[35] S. Cheng, S. Hidemima, S. Kuroiwa, T. Nakanishi, T. Osaka, Label-free detection of tumor markers using field effect transistor (FET)-based biosensors for lung cancer diagnosis, Sens. Actuators B: Chem. 212 (2015) 329–334.

[36] O. Erdem, Y. Saylan, N. Cihan, A. Denizli, Molecularly imprinted polymers based plasmonic sensors for real-time Enterococcus faecalis detection, Biosens. Bioelectron. 126 (2019) 608–614.

[37] U. Anik, Y. Tepeli, M.F. Diouani, Fabrication of electrochemical model influenza a virus biosensor based on the measurements of neuroaminidase enzyme activity, Anal. Chem. 88 (2016) 6151–6153.

[38] F.C. Dudak, I.H. Boyaci, Peptide-based surface plasmon resonance biosensor for detection of staphylococcal enterotoxin B, Food Anal. Methods 7 (2014) 506–511.

[39] M. Lv, Y. Liu, J. Geng, X. Kou, Z. Xin, D. Yang, Engineering nanomaterials-based biosensors for food safety detection, Biosens. Bioelectron. 106 (2018) 122–128.

[40] Ö. Erdem, Y. Saylan, M. Andaç, A. Denizli, Molecularly imprinted polymers for removal of metal ions: an alternative treatment method, Biomimetics 3 (2018) 38–53.

[41] Y. Saylan, A. Denizli, Molecular fingerprints of hemoglobin on a nanoﬁlm chip, Sensors 18 (2018) 3016–3029.

[42] C. Mao, A. Liu, B. Cao, Virus-based chemical and biological sensing, Angew. Chem. Int. Ed. 48 (2009) 6790–6810.

[43] J.A. Goode, J.V.H. Rushworth, P.A. Millner, Biosensor regeneration: a review of common techniques and outcomes, Langmuir 31 (2015).

[44] N. Verma, A. Bhardwaj, Biosensor technology for pesticides—a review, Appl. Biochem. Biotechnol. 175 (2015) 3093–3119.

[45] Y. Saylan, F. Yılmaz, E. Özgür, A. Derazshamshir, H. Yavuz, A. Denizli, Molecularly imprinting of macromolecules for sensors applications, Sensors 17 (2017) 898–928.

[46] K.H. Cho, D.H. Shin, J. Oh, J.H. An, J.S. Lee, J. Jang, Multidimensional conductive nanoﬁlm-based ﬂexible aptasensor for ultrasensitive and selective HBsAg detection, ACS Appl. Mater. Interfaces 10 (2018) 28412–28419.

[47] L. La Spada, L. Vegni, Electromagnetic nanoparticles for sensing and medical diagnostic applications, Materials 11 (2018) 603–624.

[48] Y. Pang, J. Tian, T. Tu, Z. Yang, J. Ling, Y. Li, et al., Wearable humidity sensor based on porous graphene network for respiration monitoring, Biosens. Bioelectron. 116 (2018) 123–129.

[49] L. Russo, J. Leva Bueno, J.F. Bergua, M. Costantini, M. Giannetto, V. Puntes, et al., Low-cost strategy for the development of a rapid electrochemical assay for bacteria detection based on Au@Ag nanoshells, ACS Omega 3 (2018) 18849–18856.

[50] D.R. Thévenot, K. Toth, R.A. Durst, G.S. Wilson, Electrochemical biosensors: recommended definitions and classification, Anal. Lett. 34 (2001) 635–659.

[51] J. Zhu, H. Gan, J. Wu, H. Ju, Molecular machine powered surface programmatic chain reaction for highly sensitive electrochemical detection of protein, Anal. Chem. 90 (2018) 5503–5508.

[52] C.R. Suri, Immunosensors for pesticide monitoring, Advances in Biosensors, Perspectives in Biosensors, 5, Elsevier Science, Amsterdam, 2003, pp. 161–176.

[53] Y. Saylan, Ö. Erdem, N. Cihan, A. Denizli, Detecting fingerprints of waterborne bacteria on a sensor, Chemosensors 7 (2019) 33.

[54] B. Sciacca, A. François, P. Hoffmann, T.M. Monro, Multiplexing of radiative-surface plasmon resonance for the detection of gastric cancer biomarkers in a single optical fiber, Sens. Actuators B: Chem. 183 (2013) 454–458.

[55] V. Safran, I. Göktürk, A. Derazshamshir, F. Yılmaz, N. Sağlam, A. Denizli, Rapid sensing of Cu²⁺ in water and biological samples by sensitive molecularly imprinted based plasmonic biosensor, Microchem. J. 148 (2019) 141–150.

[56] Y. Saylan, S. Akgonüllü, H. Yavuz, S. Unal, A. Denizli, Molecularly imprinted polymer based sensors for medical applications, Sensors 19 (2019) 1279–1298.

[57] X. Yu, F. Chen, R. Wang, Y. Li, Whole-bacterium SELEX of DNA aptamers for rapid detection of E. coli O157:H7 using a QCM sensor, J. Biotechnol. 266 (2018) 39–49.

[58] M. Bakshhpour, A.K. Piskin, H. Yavuz, A. Denizli, Quartz crystal microbalance biosensor for label-free MDA MB 231 cancer cell detection via notch-4 receptor, Talanta 204 (2019) 840–845.

[59] S. Atay, K. Pişkin, F. Yılmaz, C. Çakar, H. Yavuz, A. Denizli, Quartz crystal microbalance based biosensors for detecting highly metastatic breast cancer cells via their transferrin receptors, Anal. Methods 8 (2016) 153–161.

[60] K. Ramanathan, B. Danielsson, Principles and applications of thermal biosensors, Biosens. Bioelectron. 16 (2001) 417–423.
[61] B. van Grinsven, K. Eersels, O. Akkermans, S. Ellermann, A. Kordek, M. Peeters, et al., Label-free detection of *Escherichia coli* based on thermal transport through surface imprinted polymers, ACS Sens. 1 (2016) 1140–1147.

[62] E. Elgazzar, A. Tataroğlu, A.A. Al-Ghamdi, Y. Al-Turki, W.A. Farooq, F. El-Tantawy, et al., Thermal sensors based on delafossite film/p-silicon diode for low-temperature measurements, Appl. Phys. A 122 (2016) 617.

[63] B. Byrne, E. Stack, N. Gilmartin, R. O’Kennedy, Antibody-based sensors: principles, problems and potential for detection of pathogens and associated toxins, Sensors 9 (6) (2009) 4407–4445.

[64] J. Llando, J.J. Palfreyman, A. Ionescu, C.H.W. Barnes, Magnetic biosensor technologies for medical applications: a review, Med. Biol. Eng. Comput. 48 (2010) 977–998.

[65] U. Demirci, F. Inci, Detection, Capture and Quantification of Biological Moieties From Unprocessed Bodily Fluids Using Nanoplasmonic Platform, US Patent App. 10/228,372, 2019.

[66] A. Saini, N. Kaur, N. Singh, A highly fluorescent sensor based on hybrid nanoparticles for selective determination of furosemide in aqueous medium, Sens. Actuators B: Chem. 228 (2016) 216–230.

[67] J.E. Chang, D.S. Lee, S.W. Ban, J. Oh, M.Y. Jung, S.H. Kim, et al., Analysis of volatile organic compounds in exhaled breath for lung cancer diagnosis using a sensor system, Sens. Actuators B: Chem. 255 (2018) 800–807.

[68] Y. Saylan, S. Akgönül, D. Çimen, A. Derazshamshir, N. Bereli, F. Yılmaz, et al., Surface plasmon resonance nanosensors based on molecularly imprinted nanofilms for detection of pesticides, Sens. Actuators B: Chem. 241 (2017) 446–454.

[69] D.H. Choi, A. Thaxton, I. Cheol Jeong, K. Kim, P.R. Nosnay, G.R. Cutting, et al., Sweat test for cystic fibrosis: wearable sweat sensor vs. standard laboratory test, J. Cyst. Fibros. 17 (2018) e35–e38.

[70] C.I.L. Justino, T.A.P. Rocha-Santos, S. Cardoso, A.C. Duarte, Strategies for enhancing the analytical performance of nanomaterial-based sensors, Trends Anal. Chem. 47 (2013) 27–36.

[71] Y. Saylan, Ö. Erdem, S. Ünal, A. Denizli, An alternative medical diagnosis method: biosensors for virus detection, Biosensors 9 (2019) 65.

[72] F. Inci, O. Tokel, S. Wang, U.A. Gurkan, S. Tasoglu, D.R. Kuritzkes, et al., Nanoplasmonic quantitative detection of intact viruses from unprocessed whole blood, ACS Nano 7 (2013) 4733–4745.

[73] HIV/AIDS. Available from: <https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids> (accessed 01.02.19).

[74] B. Babamiri, A. Salimi, R. Hallaj, A molecularly imprinted electrochemiluminescence sensor for ultrasensitive HIV-1 gene detection using EuS nanocrystals as luminesphore, Biosens. Bioelectron. 31 (2013) 332–339.

[75] C.H. Lu, Y. Zhang, S.F. Tang, Z.B. Fang, H.H. Yang, X. Chen, et al., Sensing HIV related protein using epitope imprinted hydrophilic polymer coated quartz crystal microbalance, Biosens. Bioelectron. 31 (1) (2012) 439–444.

[76] H. Shafiee, E.A. Lidstone, M. Jahangir, F. Inci, E. Hanhauser, T.J. Henrich, et al., Nanostructured optical photonc crystal biosensor for HIV viral load measurement, Sci. Rep. 4 (2014) 4116–4123.

[77] C. Seeger, W.S. Mason, Molecular biology of hepatitis B virus infection, Virology 479 (2015) 672–686.

[78] D. Lavanchy, M. Kane, Global epidemiology of hepatitis B virus infection, Hepatitis B Virus in Human Diseases, Humana Press, Cham, 2016, pp. 187–203.

[79] W.M. Hassen, C. Chaix, A. Abdelghani, F. Tessieux, D. Leonard, N. Jaffrezic-Renault, An impedimetric DNA sensor based on functionalized magnetic nanoparticles for HIV and HBV detection, Sens. Actuators B: Chem. 134 (2) (2008) 755–760.

[80] L. Uzun, R. Say, S. Ünal, A. Denizli, Production of surface plasmon resonance based assay kit for hepatitis diagnosis, Biosens. Bioelectron. 24 (9) (2009) 2878–2884.

[81] M.M. İstek, M.M. Erdem, A.E. Gürsan, Impedimetric nanobiosensor for the detection of sequence-selective DNA hybridization, Hacettepe J. Biol. Chem. 46 (4) (2019) 495–503.

[82] S. Tasoglu, H.C. Tekin, F. Inci, S. Knowlton, S. Wang, F. Wang-Johanning, et al., Advances in nanotechnology and microfluidics for human papillomavirus diagnostics, Proc. IEEE 103 (2) (2015) 161–178.

[83] S. Bedford, Cervical cancer: physiology, risk factors, vaccination and treatment, Br. J. Nurs. 18 (2009) 80.

[84] J.T. Baca, V. Severns, D. Lovato, D.W. Branch, R.S. Larson, Rapid detection of Ebola virus with a reagent-free, point-of-care biosensor, ACS Nano 7 (2013) 4733–4745.

[85] H. Ilkhani, S. Farhad, A novel electrochemical DNA biosensor for Ebola virus detection, Anal. Chem. 89 (2017) 5428–5435.

[86] X. Peng, Y. Zhang, D. Lu, Y. Guo, Ultrathin TiC2 nanosheets based “off-on” fluorescent nanoprobe for rapid and sensitive detection of HPV infection, Sens. Actuators B: Chem. 286 (2019) 222–229.

[87] X. Qiu, G. Wong, J. Audet, A. Bello, L. Fernando, J.B. Alimonti, et al., Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp, Nature 514 (7520) (2014) 47–62.

[88] T.R. Kreil, Treatment of Ebola virus infection with antibodies from convalescent donors, Emerg. Infect. Dis. 21 (3) (2015) 521–523.

[89] J.T. Baug, V. Severns, D. Lovato, D.W. Branch, R.S. Larson, Rapid detection of Ebola virus with a reagent-free, point-of-care biosensor, Sensors 15 (4) (2015) 8605–8614.

[90] M. Natesan, S.W. Wu, C.I. Chen, S.M.R. Jensen, N. Karlovac, B.K. Dyas, et al., A smartphone-based rapid telemonitoring system for Ebola and Marburg disease surveillance, ACS Sens. 4 (2019) 61–68.

[91] H. Ilkhani, S. Farhad, A novel electrochemical DNA biosensor for Ebola virus detection, Anal. Biochem. 557 (2018) 151–155.
A.A. Yanik, M. Huang, O. Kamohara, A. Artar, T.W. Geisbert, J.H. Connor, et al., An optofluidic nanoplasmonic biosensor for direct detection of live viruses from biological media, Nano. Lett. 10 (12) (2010) 4962–4969.

M. Hennessey, M. Fischer, J.E. Staples, Zika virus spreads to new areas—region of the Americas, May 2015—January 2016, Am. J. Transplant. 16 (3) (2016) 1031–1034.

R.J. Meagher, O.A. Negrete, K.K. Van Rompay, Engineering paper-based sensors for Zika virus, Trends Mol. Med. 22 (7) (2016) 529–530.

S. Afshari, M.B. Lerner, J.M. Goldstein, J. Lee, X. Tang, D.A. Bagarozzi Jr, et al., Novel graphene-based biosensor for early detection of Zika virus infection, Biosens. Bioelectron. 100 (2018) 85–88.

A. Kaushik, A. Yndart, S. Kumar, R.D. Jayant, A. Vashist, A.N. Brown, et al., A sensitive electrochemical immunosensor for label-free detection of Zika-virus protein, Sci. Rep. 8 (2018) 9700–9705.

J. Song, M.G. Mauk, B.A. Hackett, S. Cherry, H.H. Bau, C. Liu, Instrument-free point-of-care molecular detection of Zika virus, Anal. Chem. 88 (14) (2016) 7289–7294.

F. Krammer, P. Palese, Advances in the development of influenza virus vaccines, Nat. Rev. Drug Discovery. 14 (3) (2015) 167–182.

A. Moulick, L. Richtera, V. Milosavljevic, N. Cernei, Y. Haddad, O. Zitka, et al., Advanced nanotechnologies in avian influenza: current status and future trends—a review, Anal. Chim. Acta 983 (2017) 42–53.

P.D. Tam, N. Van Hieu, N.D. Chien, A.T. Le, M.A. Tuan, DNA sensor development based on multi-wall carbon nanotubes for label-free influenza virus (type A) detection, J. Immunol. Methods 350 (2009) 118–124.

F. Vollmer, S. Arnold, D. Keng, Single virus detection from the reactive shift of a whispering-gallery mode, Proc. Natl Acad. Sci. U.S.A. 105 (52) (2008) 20701–20704.

H. Bai, R. Wang, B. Hargis, H. Lu, Y. Li, A SPR aptasensor for detection of avian influenza virus H5N1, Sensors 12 (2012) 12506–12518.

S. Emir Diltemiz, A. Ersöz, D. Hür, R. Keçili, R. Say, 4-Aminophenyl boronic acid modified gold platforms for influenza diagnosis, Mater. Sci. Eng., C 33 (2013) 823–830.

W. Zhang, S. Guo, W.S.P. Carvalho, Y. Jiang, M.J. Serpe, Portable point-of-care diagnostic devices, Anal. Methods 8 (2016) 7847–7868.

J. Heukelbach, C.H. Alencar, A.A. Kelvin, W.K. de Oliveira, L.P. de Goes Cavalcanti, Zika virus outbreak in Brazil, J. Infect. Dev. Countries 10 (2016) 116–120.

F. Inci, C. Filippini, M. Baday, M.O. Ozen, S. Calamak, N.G. Durmus, et al., Multitarget, quantitative nanoplasmonic electrical field-enhanced resonating device (NE2RD) for diagnostics, Proc. Natl Acad. Sci. U.S.A. 112 (32) (2015) E4354–E4363.

C.E. Jin, T.Y. Lee, B. Koo, H. Sung, S.H. Kim, Y. Shin, Rapid virus diagnostic system using bio-optical sensor and microfluidic sample processing, Sens. Actuators B: Chem. 255 (2018) 2399–2406.

M.R. Guerreiro, D.F. Freitas, P.M. Alves, A.S. Coroadinha, Detection and quantification of label-free infectious adenovirus using a switch-on cell-based fluorescent biosensor, ACS Sens. 4 (6) (2019) 1654–1661.

H. Kim, M. Park, J. Hwang, J.H. Kim, D.R. Chung, K.S. Lee, et al., Development of label-free colorimetric assay for MERS-CoV using gold nanoparticles, ACS Sens. 4 (2019) 1306–1312.

M. Trzaskowska, A. Napitórkowska, E. Augustynowicz-Kopeć, T. Ciach, Detection of tuberculosis in patients with the use of portable SPR device, Sens. Actuators B: Chem. 260 (2018) 786–792.

P. Weerathunge, R. Ramanathan, V. Torok, K. Hodgson, Y. Xu, R. Goodacre, et al., Ultrasensitive colorimetric detection of murine norovirus using NanoZyme aptasensor, Anal. Chem. 91 (5) (2019) 3270–3276.