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## Chapter

# Sensor Surface Design with NanoMaterials: A New Platform in the Diagnosis of COVID-19

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## Abstract

Mass testing for COVID-19 is essential to defining patient management strategies, choosing the best clinical management, and dimensioning strategies for controlling viral dissemination and immunization strategies. Thus, it is of utmost importance to search for devices that allow a quick and reliable diagnosis of low cost that can be transposed from the bench to the bedside, such as biosensors. These devices can help choose the correct clinical management to minimize factors that lead to infected patients developing more severe diseases. The use of nanomaterials to modify biosensors' surfaces to increase these devices' sensitivity and their biofunctionality enables high-quality nanotechnological platforms. In addition to the diagnostic benefits, nanotechnological platforms that facilitate the monitoring of anti-SARS-CoV-2 antibodies may be the key to determining loss of protective immune response after an episode of COVID-19, which leads to a possible chance of reinfection, as well as how they can be used to assess and monitor the success of immunization strategies, which are beginning to be administered on a large scale and that the extent and duration of their protection will need to be determined. Therefore, in this chapter, we will cover nanomaterials' use and their functionalities in the surface design of sensors, thus generating nanotechnological platforms in the various facets of the diagnosis of COVID-19.

**Keywords:** COVID-19, SARS-CoV-2, nanotechnological platforms, nanomaterials, biosensors, diagnosis, sensor surface design

## 1. Introduction

SARS-CoV-2 is a virus in the coronavirus family, discovered in December 2019 in Wuhan, China, and the cause of COVID-19 [1]. Coronaviruses (CoV) are RNA viruses and can cause anything from the common cold to more serious diseases with neurological, gastrointestinal, and pulmonary involvement [2]. They are zoonotic viruses;

that is, they can be transmitted between animals and people due to their ability to recombine their viral proteins between coronaviruses of different hosts [3].

COVID-19 was defined as Pandemic on March 11, 2020 (1), and by February 1, 2021, there are already 103,221,369 individuals infected worldwide, and the number of global deaths already exceeds 2,232,563 [4]. Before SARS-CoV-2, two other CoVs causing a pandemic disease were identified: the first was SARS-CoV in 2002, originating in Foshan (China), which caused Severe Acute Respiratory Syndrome (SARS); the second was MERS-CoV, which originated in the Arabian Peninsula in 2012, causing the Middle East Respiratory Syndrome (MERS) [5].

A significant bottleneck in COVID-19 is mass diagnosis. The real-time reverse-transcription polymerase chain reaction (RT-PCR) is the “gold standard” method for demonstrating the presence of SARS-CoV-2. This diagnosis is reliable; however, most countries have suffered from a lack of supplies and equipment and its high cost. IgM and IgG antibodies can be detected in the serum of patients with COVID-19, where their monitoring can indicate recent or late infection and the duration of the post-infection protective immune response.

The development of easy-to-use alternative platforms is encouraged with specific attention paid to sensitivity and simplicity to specifically detect targets at a very low concentration, in about minutes, enabling portable on-site screening upon further optimizations of the detection limit. However, the accuracy of these techniques depends on several factors; variations in these factors might significantly lower the sensitivity of detection.

Nanomaterials can be applied in several types of sensors due to their physical and chemical properties, making them possible to detect by colorimetric, fluorescence, magnetism, surface plasmon resonance, and electrochemical [6–10]. In electrochemical sensing, the conductive nanomaterials are interesting for application due to their well-known ability to improve the catalytic activity, the electron transfer speed, and the conductivity of the sensors. Furthermore, the superficial area and amplify the analytical signal can be increased by deposition of nanomaterials over electronic surfaces, enhancing the sensitivity regarding target analytes' detection. Therefore, the group has been working with several nanomaterials to develop sensors.

Therefore, in this book chapter, we describe case reports and proof-of-concept for a simple, label-free electrochemical sensor for the fast and direct detection of SARS-CoV-2 through the detection of the specific probe. Early and widespread testing has proven to reduce mortality rates and improve contact tracing. However, the value of testing is directly linked to the availability and accuracy of diagnostic tests as concerns grow. Additionally, we have demonstrated in this work the possibility of a biorecognition element between the target concentration and the viral load exploring different electrode materials and redox markers allows for improved sensor properties with higher effectiveness than the commercially available assay or traditional diagnostic methods.

## **2. Diagnosis of COVID-19: the old and the gold**

Coronaviruses infect human cells mainly by binding proteins from viral spikes (spike proteins) to molecules of the angiotensin-converting enzyme 2 (ACE2), [11] widely expressed in human organs and tissues, such as nasal, bronchial epithelial cells, and pneumocytes. After entering the cell, viral replication occurs and the host cell's subsequent death, whether epithelial, endothelial, or immune cells [12].

Due to the increase in viral replication, the epithelial-endothelial barrier's integrity is compromised, accentuating the inflammatory response, causing edema

and inflammatory infiltrates. Furthermore, it compromises coagulation pathways, increasing fibrin degradation products and alterations in leukocytes and red blood cells. Together with the inflammatory infiltrate, the resulting edema contributes to the ground-glass opacities seen in imaging studies and too low oxygenation [13].

Symptoms and clinical evolution depend on the triad: virus strain, host immunity, and pre-existing conditions, known as comorbidities, such as hypertension, obesity, diabetes, cardiovascular disease, chronic lung disease, chronic kidney disease, and malignancies [14]. Symptoms range from the most common in flu-like conditions, such as fever, cough, and shortness of breath, nausea, diarrhea, loss of smell and taste, and more severe symptoms such as pneumonia leukopenia, kidney failure, myocarditis, meningitis, and thromboembolic events [15].

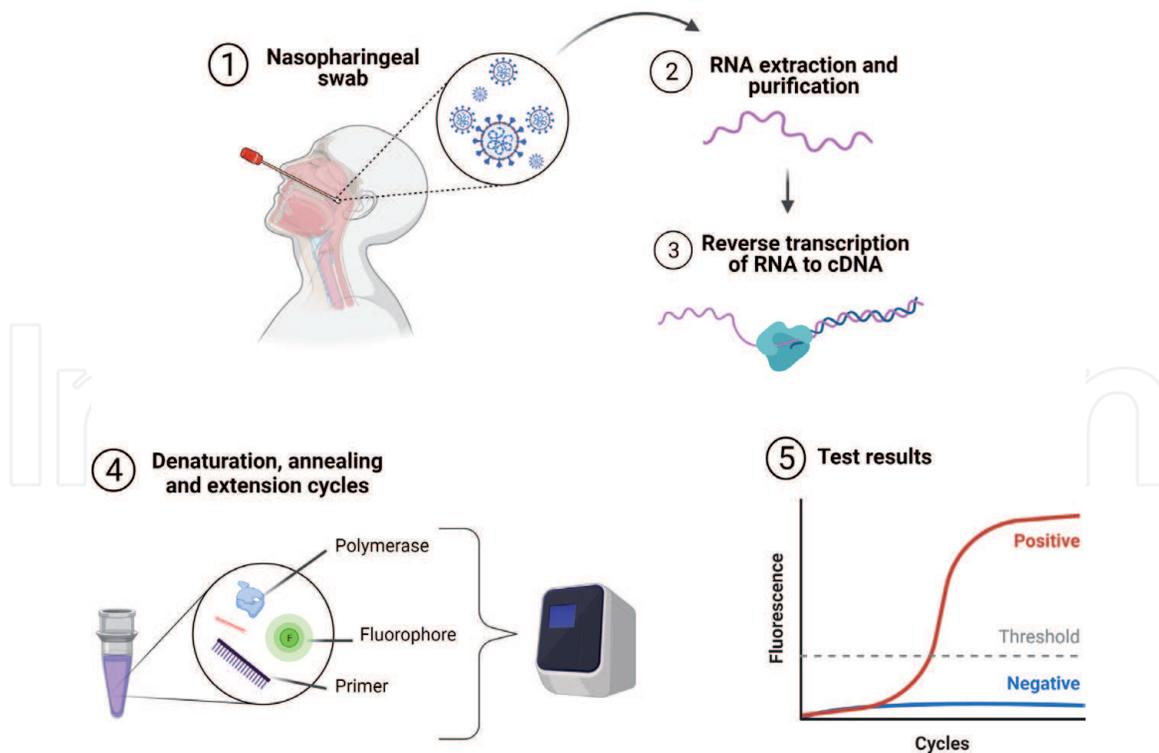
The immune response against COVID-19 has been extensively investigated and is directly related to clinical evolution. The presence of lymphopenia and increased production of chemokines and proinflammatory cytokines have been demonstrated in patients with COVID-19, especially in the most severe cases, which can worsen tissue damage [16]. Serum levels of chemokines (IL-8) and proinflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6, IFN- $\gamma$ , IP-10, and MCP-1) are found in greater quantities patients with COVID-19 severe when compared with individuals with mild disease. This fact indicates that the cytokine storm is associated with the severity of the disease and adverse outcomes, suggesting a possible role of hyperinflammatory responses in the pathogenesis of COVID-19 [16, 17].

Studies on the humoral immune response demonstrate that antibodies, such as IgA, IgM, and IgG against SARS-CoV-2, appear on the first day after the onset of symptoms [18, 19]. IgM levels appear on days 0 to 7, increasing on days 8 to 14 and reaching a plateau, while IgA levels increased from days 0 to 14, whereas IgG levels were detected on days 0 to 7, increased on days 8 to 14, continued to increase until the 15th to the 21st and reached a plateau on the 21st [18]. This kinetics of antibody levels indicates a rapid and almost simultaneous response of these three isotypes during the first weeks of infection by SARS-CoV-2, IgA and IgG remain with higher titers for a longer time when compared to IgM [20, 21].

The amount of antibodies in samples from patients with COVID-19 is dependent on the number of viral RNA present: the lower the viral load, the lower the level of antibodies present, and the severity of clinical evolution [19–21]. Initial data indicate a lower concentration of anti-SARS-CoV-2 antibodies in asymptomatic patients, but more quickly, while in mild symptomatic ones, there is a slower but more continuous production. Serious patients have high levels of antibodies, mainly IgA and IgG. However, there are still gaps about whether specific humoral and cellular immune memory persist and for how long [20]. Despite these limitations in understanding the long-term humoral immune response, the determination of IgA, IgM, and IgG antibodies are widely used in laboratory tests for the detection of COVID-19. Early diagnosis also allows the infected patient to have faster access to medical care and increases their chances of a better prognosis. It will enable the initiation of treatment when the viral load is in low concentrations.

Antibody determination is also important to monitor patients who have been vaccinated since immunization stimulates the immune system's production without having to be infected [22]. Results about vaccines against COVID-19 showed that vaccinated patients increased the production of specific antibodies and their affinity to levels similar to those observed in patients who recovered from COVID-19 [23–25]. Data show that a standardized quantification/determination of antibody levels may be sufficient to monitor vaccinated patients and estimate the quality and duration of this protection [24].

To date, quantitative real-time reverse-transcription polymerase chain reaction (RT-PCR), qRT-qPCR assay is the gold standard for the early detection of virus



**Figure 1.**

Major steps of qRT-PCR as a diagnostic tool at COVID-19 (1) A patient suspected of COVID-19 undergoes collection of cells infected with SARS-CoV-2 through a nasopharyngeal swab. (2–3) Viral RNA is extracted and purified. The enzyme reverse transcriptase converts RNA into cDNA.

(major steps presented in **Figure 1**), but the CRISPR–Cas12-based lateral flow, Immunochromatographic, ELISA, loop-mediated isothermal amplification (LAMP) and other techniques has been developed and applied to screening or to confirm positive COVID-19 patients allowing prompt clinical and quarantine decisions this infection (**Table 1**).

To minimize the cost and logistical problems of sample collection and diagnostics, rapid diagnostic systems based on classical methodological approaches, such as immunochromatography, were quickly implemented in the detection of SARS-CoV-2 antigens or antibodies produced against it. However, the accuracy of these techniques depends on several factors. The bioavailability of the researched molecule, as viral genetic material, viral antigens, and various subclasses of antibodies, the stability of these biomolecules to the procedures of sample collection and transport to the diagnostic platforms, the possibility of storage for later evaluation are significant bottlenecks that have impaired mass testing, especially in developing countries and variations in these factors might significantly lower the sensitivity of detection. The degree of reliability is uncertain in many of them, and implementing a faster and accurate diagnosis system is essential to monitor the disease and define policies to control viral spread.

Biosensors are one of the most popular types of point-of-care devices in various diagnostics areas, which offer several advantages such as the low cost, the capability of miniaturization, and high sensitivity and selectivity. The transposition of the molecular and immunological diagnosis to miniaturization platforms like point-of-care systems implies a drastic reduction in the amount of sample needed, increases specificity, reliable measurements in real-time, and portability. The development of easy-to-use alternative platforms is encouraged with specific attention paid to sensitivity and simplicity to detect targets at a very low concentration in about minutes, enabling portable on-site screening upon further optimizing the detection limit.

Detection type	Sensitivity %	Specificity %	LOD	Biom. of the probe	Biom. target	Methodology	Detection time (m)	Nanomaterials	Database	References
Frosted glass opacity	86–98	25	—	—	—	Computed tomography	5–30	—	P/S/WS	[26, 27]
RT-PCR	90–100	100	0.15–100 copies/ $\mu$ L	Primers	Viral RNA	Real-time Transcript to Reverse	240–360	—	P/S/WS	[28, 29]
RT-dPCR	90	100	2 copies/reaction	Primers	Viral RNA	Real - time Transcripta to Reverse Digital PCR	—	—	P/S/WS	[30]
RT-LAMP	90–100	Low	100 copies/ $\mu$ L	Primers	Viral RNA	Isothermal amplification of the Transcript reversed	30–40	—	P/S/WS	[29, 31, 32]
CRISPR-cas12	95–100	100	10–100 copies/ $\mu$ L	gRNA	Viral RNA	gRNA binds to the target segment making precise cutting	45–75	—	P/S/WS	[33]
RT-RPA	98	100	7659 copies/ $\mu$ L	Primers	Viral RNA	Real-time Transcript to Reverse Recombinase Polymerase Amplification	< 20	—	P/S	[34]
ELISA	86–100 *	89–100	—	Anti-antibody IgM	IgM	Indirect	60–300	—	P/S/WS	[31]
ELISA	86–100 *	89–100	—	Anti-antibody IgG	IgG	Indirect	60–300	—	P/S	[35]
ELISA	*	100	—	Antibody	Ag	Sandwich	60–300	—	P/S/WS	[31]
Lateral flow immunoassay	60–80	85–100	—	Ag	IgM	Immunoassay/Quick Test	2–20	—	P/S/WS	[31]

Detection type	Sensitivity %	Specificity %	LOD	Biom. of the probe	Biom. target	Methodology	Detection time (m)	Nanomaterials	Database	References
Lateral flow immunoassay	60–80	85–100	—	Ag	IgG	Immunoassay/Quick Test	2–20	—	P/S/WS	[31]
Lateral flow immunoassay	91.2 Swab 60.1 Sample solution	100	—	Antibody	Ag	Immunoassay/Quick Test	15–30	—	P/S/WS	[31, 36]
Chimioluminescence	82–97	75–87	—	Ag	IgM	Immunoassay/ Chemiluminescence	30–60	Magnetic microsphere	P/S/WS	[37, 38]
Chimioluminescence	82–97	75–87	—	Ag	IgG	Immunoassay/ Chemiluminescence	30–60	Magnetic microspheres	P/S/WS	[38, 39]

*LOD: limit of detection, RPA: Recombinase Polymerase Amplification, Database: Pubmed (P), Scopus (S), and Web of Science (WS).  
\*Variable sensitivity according to kit and sample collection day.*

**Table 1.**  
*Comparison of methodologies applied to the diagnosis of (SARS)-CoV-2.*

An overview of some methodologies applied to the diagnosis of (SARS)-CoV-2 is presented in **Table 1**. The ELISA-based test was used to validate the antibody-antigen interaction, or RT-PCR was used to validate the primer, particularly the complexity of the assays during inventory shortages, while cyclic voltammetry, electrochemical impedance spectroscopy, differential pulse voltammetry was used to characterize the electrode functionalization.

Multi sensors, lateral flow tests, mobile biosensors, and wearable biosensors are critical parts for precision medicine in COVID-19. Russell, S.M. et al., defined these biosensors' ideal characteristics using some prototypes from recent literature as examples [40]. Multi sensors, lateral flow tests, mobile biosensors, and wearable biosensors are crucial parts for precision medicine in COVID-19. We propose the ideal characteristics of these biosensors using some prototypes from recent literature as examples. Multi sensors, lateral flow tests, mobile biosensors, and wearable biosensors are crucial parts for precision medicine in COVID-19.

In his work, Fukumoto, T. et al. 2020 has developed a fast, easy to use, and inexpensive diagnostic method that is needed to help control the current outbreak of the new coronavirus based on microfluidic microdevices. A new detection kit - the 2019 Novel Coronavirus Detection Kit (nCoV-DK) - cuts detection time in half, eliminating RNA extraction and purification steps. The nCoV-DK test effectively detects SARS-CoV-2 in all types of samples, including saliva, while reducing the time required for detection and risk of human error [41].

Laghrib, F. et al., showed the leading current trends and strategies in diagnosing n-SARS-CoV-2 based on emerging and traditional assessment technologies for continuous innovation. Addressing recent biosensors trends to build a fast, reliable, more sensitive, accessible, friendly system with easily adaptable n-SARS-CoV-2 detection and monitoring technology [42]. Overall, we address and identify evidence from research that supports biosensors' use based on the premise that screening people for n-SARS-CoV-2 is the best way to stem its spread. The detection and notification of infectious pathogens in a fast, sensitive, and specific way is essential for managing the patient and surveillance of outbreaks. With their ability to diagnose in real-time with the high specificity of a low concentration sample, biosensors are much more reliable than the rapid test for coronavirus detection. The use of nano biosensors has been considered the most promising approach for detecting new n-SARSCoV-2 coronavirus disease. Meanwhile, the current work has also tried to improve biosensors' detection sensitivity, simplicity, and performance.

Hui, X. et al. 2020, showed in his work, G quadruplex-based Biosensor: A potential tool for SARS-CoV-2 detection to discover additional advantageous attributes of G-quadruplex as potential to be used in new biosensors, such as ligand binding enhanced and unique folding properties [43]. The newly developed G-quadruplex biosensors include electrochemical and optical biosensors that have shown better performance with potential applications with a wide detection range and a broad spectrum of pathogens SARS-CoV-2, the causative agent of COVID-19 disease. G-quadruplex is a non-canonical nucleic acid structure formed by the folding of guanine-rich DNA or RNA.

### **3. Platform with nanomaterials in the diagnosis of COVID-19: a brave new world**

Biosensors are analytical devices that incorporate a biological recognition element capable of detecting the presence, activity, or concentration of the sample under analysis connected to a transducer. This biological element can be a micro-organism, an antibody, oligonucleotides, lectins, biomolecule enzymes that can

interact with the target substrate. About the transducer, it can be an electrode, fiber optic, or oscillating quartz [42, 44]. Thus, biosensors are one of the most popular types of point-of-care devices in various areas of diagnostics, which offer several advantages such as low cost, the capability of miniaturization, and high sensitivity and selectivity.

Immunosensors are analytical devices of the biosensor class, which detect and transmit information regarding biochemical changes involving integrating a biological element with an electronic interface [45, 46]. This integration can convert a biological signal into an electrical response that is proportional to the concentration of the analyte. Thus, these biosensors can recognize a specific antibody or antigen by forming an antigen–antibody immunocomplex. The recognition event is detected and converted, through a transducer, to a measurable signal (such as electrical current, for example). The primary transducers used in immunosensors are electrochemical, optical, and piezoelectric. Therefore, the incorporation of specific nanomaterial can be intensified by improving the biosensor's sensitivity and versatility.

Genosensors can also be used, a specific type of biosensor based on nucleic acid chemistry phenomena, such as the hybridization process [47]. Nucleic acids have been widely used in the development of biosensors for drug detection, identification of pathogenic microorganisms and other biological substances, and the diagnosis of diseases. The sensory technique through hybridization involves the immobilization of an oligonucleotide probe on the surface of a transducer and subsequent sensor exposure to a sample containing the complementary sequence (target oligonucleotide) with consequent hybridization. Complementary DNA (cDNA) is a DNA synthesized from a messenger RNA molecule in a reaction catalyzed by the enzyme reverse transcriptase. Thus, the incorporation of nanomaterials on the biosensor's surface ensures the enhancement of the electrochemical response.

Our group has been demonstrating through publications and patents expertise in the development of nanomaterials with specific properties, such as increased sensitivity of some devices, biocompatibility, and low genotoxicity, essential properties in developing nanotechnological platforms [48–53]. Toxicity is an important parameter in nanomaterials, but depending on synthesis methodologies it is possible to decrease toxicity. For example, Silva et al. demonstrated some toxicities of nanomaterials, some influenced by the crystalline phase, composition or type of material [54–61]. In relation to quantum dots, synthesis methodologies were developed, making it possible to increase cellular viability and specificity aiming at several applicability as biological probes [52, 53, 62–68].

The development of artificial intelligence software enables more accurate detection and quantification and low-cost analytical platforms [69, 70]. These nanotechnological platform [71] s can be used in large-scale production, with low cost and low consumption of samples and reagents [6, 72].

High-quality, low-cost nanotechnological platforms based on the detection of anti-SARS-CoV-2 antibodies may be the key to defining groups already exposed to the disease, even if asymptomatic, that have a potentially protective immune response, a crucial factor for delimitation priority immunization groups. Besides, we can determine the loss of protective immune response after an episode of COVID-19, which leads to a possible chance of reinfection. Some advantages are the amount of sample of interest, in the order of  $\mu\text{L}$ , simultaneous analysis of several analytes in the same device and miniaturization, being portable, light, and easy to use the equipment. Also, nanotechnological platforms can be used to assess and monitor the success of immunization strategies, which should soon begin to be administered on a large scale, and the extent and duration of their protection will need to be determined.

Several diagnostic methods have been reported, aiming at biomedical applications, especially in the diagnosis of covid-19, to detect the coronavirus in clinical, research, and public health laboratories. Based on biosensors for SARS-CoV-2, diagnostic methods presented have analytical performance and response times ranging from a few minutes to several hours, which make them promise for practical use in health care points, showing as a strong ally for control of endemics and pandemics.

An overview of current efforts to improve point-of-care diagnostic systems based on biosensors using different nanomaterials at COVID-19 is presented in **Table 2**.

Currently, diverse electrochemical biosensors have been lately developed for the detection of the SARS-CoV-2 using modified electrodes with metallic nanoparticle or nano-islands or nanostars, carbon nanofiber (CNF), using inorganic quantum dots, zinc oxide nanowires (ZnO NWs) or nanorods, bimetallic nanoparticles, Graphene Oxide (GO) nanosheet and other modifications show in **Table 2**. These nanomaterials showed excellent applications in biosensors because of their ease of functionalization, large surface area, stability, on the stable immobilization of probe molecules, the blocking reagent to minimize nonspecific binding, high electronic conductivity (accelerate the electron transfer), high carrier/charge mobility, and strong adsorption capability that increase the sensitivity of electrochemical platform due to their excellent unmatched properties followed by enhancement in the electrochemical response toward the selective detection of SARS-CoV-2.

Vadlamani, B S. et al., the synthesis of a TiO<sub>2</sub> functionalized with cobalt but susceptible electrochemical sensor based on nanotubes (Co-TNTs) for rapid detection of SARS-CoV-2 using peak detection (binding domain receptor (RBD)) present on the virus surface [83]. A simple, low-cost, one-step electrochemical anodization route was used to synthesize TNTs, followed by an incipient wetting method for cobalt functionalization of the TNT platform, which was connected to a potentiostat for data collection. This sensor specifically detected the S-RBD protein from SARS-CoV-2, even at very low concentrations (range 14 to 1400 nM (nanomolar)). Besides, our sensor showed a linear response in the detection of viral protein in the concentration range. Thus, our Co-TNT sensor is highly effective in detecting the SARS-CoV-2 S-RBD protein in approximately 30s.

Cuy and Zhou, 2019, showed in their review work that timely detection and diagnosis are urgently needed to guide epidemiological measures, infection control, antiviral treatment, and vaccine research [86]. In this review, biomarkers/indicators for diagnosis of coronavirus 2019 disease or detection of severe acute respiratory syndrome coronavirus 2 in the environment are summarized and discussed. However, antibody detection methods can be combined with real-time quantitative polymerase reverse transcriptase chain reaction to improve diagnostic sensitivity and specificity and boost vaccine research significantly. The deep throat saliva and induced sputum are desired for the RT-qPCR test or other early detection technologies. The ultra-sensitive and specific laboratory diagnostic method and portable devices are essential to control the rapidly evolving COVID-19 pandemic associated with SARS-CoV-2. Currently, computed tomography, RT-qPCR, and LFICS based on the colloid Au NPs (colloidal gold method) have been developed.

Based on the table results, we can verify that the biosensors that showed the best sensitivities are using carbon-based materials due to their conductive properties, metallic oxides (ZnO and TiO<sub>2</sub>) with supercapacitor properties, and nanocomposites (containing the capacitive and metallic systems).

In nanomaterials, the effects of size, morphology, and chemical structures have a strong influence on the optical, electrical, and magnetic properties. Thus, the tuning of these parameters allows maintaining the same material and intensifying the biosensors' responses. Another critical parameter is the synergism between

Detection type	Sensitivity %	Specificity %	LOD	RSD %	Biom. of probe	Biom. target	Methodology	Detection time (m)	Nanomaterials	Database	References
Electrochemical biosensor	—	—	—	—	cRNA	Viral RNA	Genosensors	—	—	P/S	[73]
Electrochemical biosensor	—	—	1 fg/mL	—	Antibodies with 1-pyrenobutyric acid N-hydroxysuccinimide	Ag. Protein S	Field effect transistor FET	< 4	Grafeno leaves	P/S/WS	[74]
Electrochemical biosensor	—	—	—	—	Ag. Protein S	Antibody	Impedance Spectroscopy	—	Polyethylene terephthalate	P/S/WS	[75]
Electrochemical biosensor	Lowest PCR	—	20 ng/mL	—	Antibody Anti- Protein S	Ag. Protein S	Impedance Spectroscopy/ Cyclic voltammetry/ Square wave voltammetry	45	Graphene layer/1-Pyrene butyric acid N-hydroxysuccinimide ester linker (PBASE)	P/S/WS	[76]
Electrochemical biosensor	100	90	1 ng/mL	4.2 for IgG and 3.3 for IgM	Ag. Protein S	IgM/IgG Antibodies	Paper platform	30	—	P/S	[77]
Ultra- sensitive electrochemical biosensor	High	High	3 aM	—	cDNA	Viral RNA	Differential pulse voltammetry/ Smartphone detection	181	Modified SPCE nanocomposite (Au @ SCX8-TB-RGO-AP-LPTarget/HT/CP/Au @ Fe3O4)	P/S/WS	[78]
Electrochemical biosensor Immunosensor	High	High	0.8 pg/mL	—	Ag. Protein N	Ag. Protein N	Square wave voltammetry	20	Carbon nanofiber	P/S	[79]

Detection type	Sensitivity %	Specificity %	LOD	RSD %	Biom. of probe	Biom. target	Methodology	Detection time (m)	Nanomaterials	Database	References
Electrochemical biosensor	High	High	6.5 pfu/mL	—	Antibody Anti-Protein S and N	Ag. Protein S and N in saliva	Immunosensor/ Differential pulse voltammetry	30	Magnetic nanoparticle/Black carbon	P/S/WS	[80]
Electrochemical biosensor	95	High	1.68x10 <sup>22</sup> mg/mL	—	Antibody Anti-Protein S	Ag. Protein S	Differential pulse voltammetry	1	Gold nanoparticle/ Graphene oxide	P/S/WS	[81]
Electrochemical biosensor	High	High	—	—	Ag. Protein S	IgM/IgG Antibodies	Impedance Spectroscopy	30	Zinc oxide nanowires	P	[82]
Electrochemical biosensor	—	—	0.7 nM	—	Titanium dioxide/ Cobalt nanotube	Protein S-RBD	Amperometry	> 1	Titanium dioxide/ Cobalt nanotube	P/S/WS	[83]
Electrochemical biosensor	100	100	6.9 copies/μL	—	cDNA	Ag. Protein N	Genosensors/ Cyclic voltammetry	5	Graphene/Gold nanoparticle	P/WS	[84]
Multiplexed electrochemical platform	High	High	—	Average of 7.07	Protein S/Anti-IgM and IgG antibodies	IgM/IgG Antibodies Ag. Protein N	Immunossensor/ Differential pulse voltammetry/ Impedance Spectroscopy	> 1	Graphene	P/WS	[85]

*LOD: Limit of Detection; RDS: Relative Squared Difference.  
Database: Pubmed (P), Scopus (S) and Web of Science (WS).*

**Table 2.**  
*Comparison of electrochemical biosensors for the detection of (SARS)-CoV-2.*

nanomaterials, several biosensors using more than one type of nanomaterials to further improve sensitivity. Thus, unfortunately, this systematic study of the literature in biosensors does not exist, being difficult to compare the sensitivity properties using different materials and nanocomposites.

#### **4. Conclusion**

Therefore, this chapter showed use of systems in diagnosis COVID-19 and how the nanomaterials may enable an improvement in sensitivity when being incorporated in the surface design of sensors, thus generating nanotechnological platforms. The functional improvement of biosensors using nanomaterials has undoubted benefits, both from the point of view of biological samples, ease of technical execution, better distribution and application logistics and better cost–benefit, being able to direct a whole new generation of rapid diagnoses easily transposable to combat other human diseases. These nanotechnological platforms could be the revolution for the mass diagnosis of COVID-19, without implying an increase in investments since it is a low-cost diagnostic proposal. In this way, they can be immediately translated into clinical practice and used in all parts of the health chain used to combat COVID-19, given its simplicity of use, biosafety, and low cost. The use of nanotechnology to modify diagnostic platforms has a special impact as they generate patents, strengthen technology, and arouse worldwide interest for their technological robustness, which may impact the attraction of resources to countries through the export of these or other forms of sharing that be advantageous.

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#### **Conflict of interest**

The authors declare no conflict of interest.

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## References

- [1] Organization, W.H. Novel Coronavirus (2019-nCoV) Situation Report – 1 2020.
- [2] Benvenuto, D.; Giovanetti, M.; Ciccozzi, A.; Spoto, S.; Angeletti, S.; Ciccozzi, M. The 2019-new coronavirus epidemic: Evidence for virus evolution. *J. Med. Virol.* **2020**, *92*, 455-459, doi:10.1002/jmv.25688.
- [3] Ji, W.; Wang, W.; Zhao, X.; Zai, J.; Li, X. Cross-species transmission of the newly identified coronavirus 2019-nCoV. *J. Med. Virol.* **2020**, *92*, 433-440, doi:10.1002/jmv.25682.
- [4] Hopkings, J. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) 2020.
- [5] Cui, J.; Li, F.; Shi, Z.L. Origin and evolution of pathogenic coronaviruses. *Nat. Rev. Microbiol.* **2019**, *17*, 181-192.
- [6] de França, C.C.L.; Meneses, D.; Silva, A.C.A.; Dantas, N.O.; de Abreu, F.C.; Petroni, J.M.; Lucca, B.G. Development of novel paper-based electrochemical device modified with CdSe/CdS magic-sized quantum dots and application for the sensing of dopamine. *Electrochim. Acta* **2021**, *367*, doi:10.1016/j.electacta.2020.137486.
- [7] da Silva, M.P.G.; Candido, A.C.L.; de Araújo-Júnior, J.X.; Silva, A.C.A.; Dantas, N.O.; de Aquino, T.M.; de Abreu, F.C. Evaluation of the interaction of a guanylhydrazone derivative with cobalt ferrite nanoparticles and PAMAM electrochemical and UV/visible spectroscopic techniques. *J. Solid State Electrochem.* **2020**, *25*, 743-752, doi:10.1007/s10008-020-04848-z.
- [8] de Lima França, C.C.; da Silva Terto, E.G.; Dias-Vermelho, M. V.; Silva, A.C.A.; Dantas, N.O.; de Abreu, F.C. The electrochemical behavior of core-shell CdSe/CdS magic-sized quantum dots linked to cyclodextrin for studies of the encapsulation of bioactive compounds. *J. Solid State Electrochem.* **2016**, *20*, 2533-2540, doi:10.1007/s10008-016-3221-8.
- [9] Martins, B.R.; Barbosa, Y.O.; Andrade, C.M.R.; Pereira, L.Q.; Simão, G.F.; de Oliveira, C.J.; Correia, D.; Oliveira, R.T.S.; da Silva, M. V.; Silva, A.C.A.; et al. Development of an Electrochemical Immunosensor for Specific Detection of Visceral Leishmaniasis Using Gold-Modified Screen-Printed Carbon Electrodes. *Biosensors* **2020**, *10*, 81, doi:10.3390/bios10080081.
- [10] Petroni, J.M.; Lucca, B.G.; da Silva Júnior, L.C.; Barbosa Alves, D.C.; Souza Ferreira, V. Paper-based Electrochemical Devices Coupled to External Graphene-Cu Nanoparticles Modified Solid Electrode through Meniscus Configuration and their Use in Biological Analysis. *Electroanalysis* **2017**, *29*, 2628-2637, doi:10.1002/elan.201700398.
- [11] Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271-280.e8, doi:10.1016/j.cell.2020.02.052.
- [12] Sungnak, W.; Huang, N.; Bécavin, C.; Berg, M.; Queen, R.; Litvinukova, M.; Talavera-López, C.; Maatz, H.; Reichart, D.; Sampaziotis, F.; et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat. Med.* **2020**, *26*, 681-687, doi:10.1038/s41591-020-0868-6.

- [13] Xu, Z.; Shi, L.; Wang, Y.; Zhang, J.; Huang, L.; Zhang, C.; Liu, S.; Zhao, P.; Liu, H.; Zhu, L.; et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir. Med.* **2020**, *8*, 420-422, doi:10.1016/S2213-2600(20)30076-X.
- [14] Yang, J.; Zheng, Y.; Gou, X.; Pu, K.; Chen, Z.; Guo, Q.; Ji, R.; Wang, H.; Wang, Y.; Zhou, Y. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *Int. J. Infect. Dis.* **2020**, *94*, 91-95, doi:10.1016/j.ijid.2020.03.017.
- [15] Esakandari, H.; Nabi-Afjadi, M.; Fakkari-Afjadi, J.; Farahmandian, N.; Miresmaeili, S.M.; Bahreini, E. A comprehensive review of COVID-19 characteristics. *Biol. Proced. Online* **2020**, *22*, 19.
- [16] Qin, C.; Zhou, L.; Hu, Z.; Zhang, S.; Yang, S.; Tao, Y.; Xie, C.; Ma, K.; Shang, K.; Wang, W.; et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin. Infect. Dis.* **2020**, *71*, 762-768, doi:10.1093/cid/ciaa248.
- [17] Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497-506, doi:10.1016/S0140-6736(20)30183-5.
- [18] Guo, L.; Ren, L.; Yang, S.; Xiao, M.; Chang, D.; Yang, F.; Dela Cruz, C.S.; Wang, Y.; Wu, C.; Xiao, Y.; et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). *Clin. Infect. Dis.* **2020**, *71*, 778-785, doi:10.1093/cid/ciaa310.
- [19] Wang, Y.; Zhang, L.; Sang, L.; Ye, F.; Ruan, S.; Zhong, B.; Song, T.; Alshukairi, A.N.; Chen, R.; Zhang, Z.; et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. *J. Clin. Invest.* **2020**, *130*, 5235-5244, doi:10.1172/JCI138759.
- [20] Carsetti, R.; Zaffina, S.; Mortari, E.P.; Terreri, S.; Corrente, F.; Capponi, C.; Palomba, P.; Mirabella, M.; Cascioli, S.; Palange, P.; et al. Different Innate and Adaptive Immune Responses to SARS-CoV-2 Infection of Asymptomatic, Mild, and Severe Cases. *Front. Immunol.* **2020**, *11*, 3365, doi:10.3389/fimmu.2020.610300.
- [21] Figueiredo-Campos, P.; Blankenhaus, B.; Mota, C.; Gomes, A.; Serrano, M.; Ariotti, S.; Costa, C.; Nunes-Cabaço, H.; Mendes, A.M.; Gaspar, P.; et al. Seroprevalence of anti-SARS-CoV-2 antibodies in COVID-19 patients and healthy volunteers up to 6 months post disease onset. *Eur. J. Immunol.* **2020**, *50*, 2025-2040, doi:10.1002/eji.202048970.
- [22] CDC Vaccines: The Basics 2012.
- [23] Anderson, E.J.; Roupheal, N.G.; Widge, A.T.; Jackson, L.A.; Roberts, P.C.; Makhene, M.; Chappell, J.D.; Denison, M.R.; Stevens, L.J.; Pruijssers, A.J.; et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *N. Engl. J. Med.* **2020**, *383*, 2427-2438, doi:10.1056/NEJMoa2028436.
- [24] Folegatti, P.M.; Ewer, K.J.; Aley, P.K.; Angus, B.; Becker, S.; Belli-Rammerstorfer, S.; Bellamy, D.; Bibi, S.; Bittaye, M.; Clutterbuck, E.A.; et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* **2020**, *396*, 467-478, doi:10.1016/S0140-6736(20)31604-4.
- [25] Xia, S.; Zhang, Y.; Wang, Y.; Wang, H.; Yang, Y.; Gao, G.F.; Tan, W.; Wu, G.; Xu, M.; Lou, Z.; et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV:

a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect. Dis.* **2021**, *21*, 39-51, doi:10.1016/S1473-3099(20)30831-8.

[26] Wong, H.Y.F.; Lam, H.Y.S.; Fong, A.H.T.; Leung, S.T.; Chin, T.W.Y.; Lo, C.S.Y.; Lui, M.M.S.; Lee, J.C.Y.; Chiu, K.W.H.; Chung, T.W.H.; et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology* **2020**, *296*, E72–E78, doi:10.1148/radiol.2020201160.

[27] Udugama, B.; Kadhiresan, P.; Kozłowski, H.N.; Malekjahani, A.; Osborne, M.; Li, V.Y.C.; Chen, H.; Mubareka, S.; Gubbay, J.B.; Chan, W.C.W. Diagnosing COVID-19: The Disease and Tools for Detection. *ACS Nano* **2020**, *14*, 3822–3835, doi:10.1021/acsnano.0c02624.

[28] Leblanc, J.J.; Gubbay, J.B.; Li, Y.; Needle, R.; Arneson, S.R.; Marcino, D.; Charest, H.; Desnoyers, G.; Dust, K.; Fattouh, R.; et al. 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. **2020**.

[29] Corman, V.M.; Landt, O.; Kaiser, M.; Molenkamp, R.; Meijer, A.; Chu, D.K.; Bleicker, T.; Brünink, S.; Schneider, J.; Luisa Schmidt, M.; et al. Detection of 2019-nCoV by RT-PCR. *Euro Surveill* **2020**, *25*, 1-8.

[30] Lv, Y.; Wu, R.; Feng, K.; Li, J.; Mao, Q.; Yuan, H.; Shen, H.; Chai, X.; Li, L.S. Highly sensitive and accurate detection of C-reactive protein by CdSe/ZnS quantum dot-based fluorescence-linked immunosorbent assay. *J. Nanobiotechnology* **2017**, *15*, 35, doi:10.1186/s12951-017-0267-4.

[31] Rai, P.; Kumar, B.K.; Deekshit, V.K.; Karunasagar, I.;

Karunasagar, I. Detection technologies and recent developments in the diagnosis of COVID-19 infection. *Appl. Microbiol. Biotechnol.* **2021**, *105*, 441-455, doi:10.1007/s00253-020-11061-5.

[32] Zhang, Y.; Odiwuor, N.; Xiong, J.; Sun, L.; Nyaruaba, R.O.; Wei, H.; Tanner, N.A. Rapid molecular detection of SARS-CoV-2 (COVID-19) virus RNA using colorimetric LAMP. *medRxiv* **2020**, *2*, doi:10.1101/2020.02.26.20028373.

[33] Broughton, J.P.; Deng, X.; Yu, G.; Fasching, C.L.; Servellita, V.; Singh, J.; Miao, X.; Streithorst, J.A.; Granados, A.; Sotomayor-Gonzalez, A.; et al. CRISPR–Cas12-based detection of SARS-CoV-2. *Nat. Biotechnol.* **2020**, *38*, 870-874, doi:10.1038/s41587-020-0513-4.

[34] Lau, Y.L.; Ismail, I. binti; Mustapa, N.I. binti; Lai, M.Y.; Soh, T.S.T.; Hassan, A.H.; Peariasamy, K.M.; Lee, Y.L.; Kahar, M.K.B.A.; Chong, J.; et al. Development of a reverse transcription recombinase polymerase amplification assay for rapid and direct visual detection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *PLoS One* **2021**, *16*, 2-9, doi:10.1371/journal.pone.0245164.

[35] Lassaunière, R.; Frische, A.; Harboe, Z.B.; Nielsen, A.C.Y.; Fomsgaard, A.; Kroghelt, K.A.; Jørgensen, C.S. Evaluation of nine commercial SARS-CoV-2 immunoassays. *medRxiv* **2020**, 1-15, doi:10.1101/2020.04.09.20056325.

[36] Mertens, P.; De Vos, N.; Martiny, D.; Jassoy, C.; Mirazimi, A.; Cuypers, L.; Van den Wijngaert, S.; Monteil, V.; Melin, P.; Stoffels, K.; et al. Development and Potential Usefulness of the COVID-19 Ag Respi-Strip Diagnostic Assay in a Pandemic Context. *Front. Med.* **2020**, *7*, doi:10.3389/fmed.2020.00225.

- [37] Cai, X.F.; Chen, J.; Hu, J. li; Long, Q.X.; Deng, H.J.; Liu, P.; Fan, K.; Liao, P.; Liu, B.Z.; Wu, G.C.; et al. A peptide-based magnetic chemiluminescence enzyme immunoassay for serological diagnosis of coronavirus disease 2019. *J. Infect. Dis.* **2020**, *222*, 189-195, doi:10.1093/infdis/jiaa243.
- [38] Giri, B.; Pandey, S.; Shrestha, R.; Pokharel, K.; Ligler, F.S.; Neupane, B.B. Review of analytical performance of COVID-19 detection methods. *Anal. Bioanal. Chem.* **2021**, *413*, 35-48, doi:10.1007/s00216-020-02889-x.
- [39] Infantino, M.; Grossi, V.; Lari, B.; Bambi, R.; Perri, A.; Manneschi, M.; Terenzi, G.; Liotti, I.; Ciotta, G.; Taddei, C.; et al. Diagnostic accuracy of an automated chemiluminescent immunoassay for anti-SARS-CoV-2 IgM and IgG antibodies: an Italian experience. *J. Med. Virol.* **2020**, *92*, 1671-1675, doi:10.1002/jmv.25932.
- [40] Russell, S.M.; Alba-Patiño, A.; Barón, E.; Borges, M.; Gonzalez-Freire, M.; De La Rica, R. Biosensors for Managing the COVID-19 Cytokine Storm: Challenges Ahead. *ACS Sensors* **2020**, *5*, 1506-1513, doi:10.1021/acssensors.0c00979.
- [41] Fukumoto, T.; Iwasaki, S.; Fujisawa, S.; Hayasaka, K.; Sato, K.; Oguri, S.; Taki, K.; Nakakubo, S.; Kamada, K.; Yamashita, Y.; et al. Efficacy of a novel SARS-CoV-2 detection kit without RNA extraction and purification. *Int. J. Infect. Dis.* **2020**, *98*, 16-17, doi:10.1016/j.ijid.2020.06.074.
- [42] Laghrib, F.; Saqrane, S.; El Bouabi, Y.; Farahi, A.; Bakasse, M.; Lahrach, S.; El Mhammedi, M.A. Current progress on COVID-19 related to biosensing technologies: New opportunity for detection and monitoring of viruses. *Microchem. J.* **2021**, *160*, 105606.
- [43] Xi, H.; Juhas, M.; Zhang, Y. G-quadruplex based biosensor: A potential tool for SARS-CoV-2 detection. *Biosens. Bioelectron.* **2020**, *167*, 112494, doi:10.1016/j.bios.2020.112494.
- [44] Turner, A.P.F. Biosensors: Fundamentals and applications - Historic book now open access. *Biosens. Bioelectron.* **2015**, *65*, A1.
- [45] Ermolaeva, T.; Farafonova, O.; Karaseva, N. Possibilities and Prospects of Immunosensors for a Highly Sensitive Pesticide Detection in Vegetables and Fruits: a Review. *Food Anal. Methods* **2019**, *12*, 2785-2801.
- [46] Ramírez, N.B.; Salgado, A.M.; Valdman, B. The evolution and developments of immunosensors for health and environmental monitoring: Problems and perspectives. *Brazilian J. Chem. Eng.* **2009**, *26*, 227-249, doi:10.1590/s0104-66322009000200001.
- [47] Goumi, Y. El Electrochemical Genosensors: Definition and Fields of Application. *Int. J. Biosens. Bioelectron.* **2017**, *3*, doi:10.15406/ijbsbe.2017.03.00080.
- [48] Silva, A.C.A.; Silva, M.J.B.; Da Luz, F.A.C.; Silva, D.P.; De Deus, S.L.V.; Dantas, N.O. Controlling the cytotoxicity of CdSe magic-sized quantum dots as a function of surface defect density. *Nano Lett.* **2014**, *14*, 5452-5457, doi:10.1021/nl5028028.
- [49] Silva, A.C.A.; Da Silva, S.W.; Morais, P.C.; Dantas, N.O. Shell thickness modulation in ultrasmall CdSe/Cd<sub>x</sub>Se<sub>1-x</sub>/CdS core/shell quantum dots via 1-thioglycerol. *ACS Nano* **2014**, *8*, 1913-1922, doi:10.1021/nn406478f.
- [50] Morais, P. V.; Gomes, V.F.; Silva, A.C.A.; Dantas, N.O.; Schöning, M.J.; Siqueira, J.R. Nanofilm of ZnO nanocrystals/carbon nanotubes as biocompatible layer for enzymatic

biosensors in capacitive field-effect devices. *J. Mater. Sci.* **2017**, *52*, 12314-12325, doi:10.1007/s10853-017-1369-y.

[51] Almeida Silva, A.C.; Gratens, X.; Chitta, V.A.; Franco, S.D.; Souza Da Silva, R.; Condeles, J.F.; Dantas, N.O. Effects of ultrasonic agitation on the structural and magnetic properties of CoFe<sub>2</sub>O<sub>4</sub> nanocrystals. *Eur. J. Inorg. Chem.* **2014**, doi:10.1002/ejic.201402563.

[52] Silva, A.C.A.; Freschi, A.P.P.; Rodrigues, C.M.; Matias, B.F.; Maia, L.P.; Goulart, L.R.; Dantas, N.O. Biological analysis and imaging applications of CdSe/Cd<sub>x</sub>Se<sub>1-x</sub>/CdS core-shell magic-sized quantum dot. *Nanomedicine Nanotechnology, Biol. Med.* **2016**, *12*, 1421-1430, doi:10.1016/j.nano.2016.01.001.

[53] Silva, A.C.A.; Azevedo, F.V.P.V.; Zóia, M.A.P.; Rodrigues, J.P.; Dantas, N.O.; Melo, V.R.Á.; Goulart, L.R. Magic Sized Quantum Dots as a Theranostic Tool for Breast Cancer. In *Recent Studies & Advances in Breast Cancer*; Open Access eBooks: Wilmington, 2017; pp. 1-10 ISBN 978-81-935757-2-7.

[54] Souza, G.L. de; Moura, C.C.G.; Silva, A.C.A.; Marinho, J.Z.; Silva, T.R.; Dantas, N.O.; Bonvicini, J.F.S.; Turrioni, A.P. Effects of zinc oxide and calcium-doped zinc oxide nanocrystals on cytotoxicity and reactive oxygen species production in different cell culture models. *Restor. Dent. Endod.* **2020**, *45*, 54, doi:10.5395/rde.2020.45.e54.

[55] Duarte, C.A.; Goulart, L.R.; Filice, L. de S.C.; Lima, I.L. de; Campos-Fernández, E.; Dantas, N.O.; Silva, A.C.A.; Soares, M.B.P.; Santos, R.R. dos; Cardoso, C.M.A.; et al. Characterization of Crystalline Phase of TiO<sub>2</sub> Nanocrystals, Cytotoxicity and Cell Internalization Analysis on Human Adipose Tissue-Derived Mesenchymal

Stem Cells. *Materials (Basel)*. **2020**, *13*, 4071, doi:10.3390/ma13184071.

[56] Carvalho Naves, M.P.; de Moraes, C.R.; Silva, A.C.A.; Dantas, N.O.; Spanó, M.A.; de Rezende, A.A.A. Assessment of mutagenic, recombinogenic and carcinogenic potential of titanium dioxide nanocrystals in somatic cells of *Drosophila melanogaster*. *Food Chem. Toxicol.* **2018**, *112*, 273-228, doi:10.1016/j.fct.2017.12.040.

[57] Reis, É. de M.; de Rezende, A.A.A.; Santos, D.V.; de Oliveria, P.F.; Nicolella, H.D.; Tavares, D.C.; Silva, A.C.A.; Dantas, N.O.; Spanó, M.A. Assessment of the genotoxic potential of two zinc oxide sources (amorphous and nanoparticles) using the in vitro micronucleus test and the in vivo wing somatic mutation and recombination test. *Food Chem. Toxicol.* **2015**, *84*, 55-63, doi:10.1016/j.fct.2015.07.008.

[58] Reis, É. de M.; Rezende, A.A.A. de; Oliveira, P.F. de; Nicolella, H.D.; Tavares, D.C.; Silva, A.C.A.; Dantas, N.O.; Spanó, M.A. Evaluation of titanium dioxide nanocrystal-induced genotoxicity by the cytokinesis-block micronucleus assay and the *Drosophila* wing spot test. *Food Chem. Toxicol.* **2016**, *96*, 309-319, doi:10.1016/j.fct.2016.08.023.

[59] Silva, A.; Zóia, M.A.P.; Correia, L.I.V.; Azevedo, F.V.P.V.; Paula, A.T. de; Maia, L.P.; Carvalho, L.S. de; Carvalho, L.N.; Costa, M.P.C.; Giaretta, L.C.; et al. Biocompatibility of Doped Semiconductors Nanocrystals and Nanocomposites. In *Cytotoxicity*; InTech, 2018.

[60] Silva, A.C.A.; Dantas, N.O.; Silva, M.J.B.; Spanó, A.M.; Goulart, ; Luiz Ricardo Functional Nanocrystals : Towards Biocompatibility, Nontoxicity and. In *Advances in Biochemistry & Applications in Medicine*; 2017; pp. 1-27.

- [61] Souza, G.L.; Silva, T.R.; Vieira, M.S.; Dantas, N.O.; Silva, A.C.A.; Moura, C.C.G. Development and study of cytotoxicity of calcium oxide nanocrystals - ScienceDirect. *Dent. Mater.* **2018**, *34*, e83.
- [62] Silva, A.C.A.; Correia, L.I.V.; Silva, M.J.B.; Zóia, M.A.P.; Azevedo, F.V.P.V.; Rodrigues, Jéssica Peixoto Goulart, L.R.; Ávila, Veridiana de Melo Dantas, N.O. Biocompatible Magic Sized Quantum Dots: Luminescent Markers and Probes. In: Correia, L.I.V., Ed.; IntechOpen: Rijeka, 2018; p. Ch. 6 ISBN 978-1-78923-295-0.
- [63] Silva, A.C.A.; Deus, S.L.V. De; Silva, M.J.B.; Dantas, N.O. Highly stable luminescence of CdSe magic-sized quantum dots in HeLa cells. *Sensors Actuators, B Chem.* **2014**, *191*, 108-114, doi:10.1016/j.snb.2013.09.063.
- [64] Pilla, V.; De Lima, S.R.; Andrade, A.A.; Silva, A.C.A.; Dantas, N.O. Fluorescence quantum efficiency of CdSe/CdS magic-sized quantum dots functionalized with carboxyl or hydroxyl groups. *Chem. Phys. Lett.* **2013**, *580*, 130-134, doi:10.1016/j.cplett.2013.07.007.
- [65] Almeida Silva, A.; Freitas Neto, E.; da Silva, S.W.; Morais, P.; Dantas, N. Modified Phonon Confinement Model and Its Application to CdSe/CdS Core-Shell Magic-Sized Quantum Dots Synthesized in Aqueous Solution by a New Route. *J. Phys. Chem. C* **117**, 1904-1914, doi:10.1021/jp308500r.
- [66] Almeida Silva, A.; Silva, M.J.; da Luz, F.A.; Silva, D.; de Deus, S.; Dantas, N. Controlling the Cytotoxicity of CdSe Magic-Sized Quantum Dots as a Function of Surface Defect Density. *Nano Lett.* **14**, 5452-5457, doi:10.1021/nl5028028.
- [67] Silva, A.C. a; da Silva, S.W.; Morais, P.C.; Dantas, N.O. Shell Thickness Modulation in Ultrasmall CdSe/CdS<sub>x</sub>Se<sub>1-x</sub>/CdS Core/Shell Quantum Dots via 1-Thioglycerol. *ACS Nano* **2014**, *8*, 1913-1922, doi:10.1021/nn406478f.
- [68] Dias, E.H.V.; Pereira, D.F.C.; de Sousa, B.B.; Matias, M.S.; de Queiroz, M.R.; Santiago, F.M.; Silva, A.C.A.; Dantas, N.O.; Santos-Filho, N.A.; de Oliveira, F. In vitro tracking of phospholipase A 2 from snake venom conjugated with magic-sized quantum dots. *Int. J. Biol. Macromol.* **2019**, *122*, 461-468, doi:10.1016/j.ijbiomac.2018.10.185.
- [69] Sandino, J.; Pegg, G.; Gonzalez, F.; Smith, G. Aerial Mapping of Forests Affected by Pathogens Using UAVs, Hyperspectral Sensors, and Artificial Intelligence. *Sensors* **2018**, *18*, 944, doi:10.3390/s18040944.
- [70] Naudé, W. Artificial Intelligence Against Covid-19: An Early Review. *IZA Discuss. Pap. No. 13110* **2020**, 1-17.
- [71] Silva, A.C.A.; Dantas, N.O.; Silva, M.J.B.; Spanó, M.A.; Goulart, L.R. Functional Nanocrystals : Towards Biocompatibility, Nontoxicity and Biospecificity. In *Advances in Biochemistry & Applications in Medicine*; Rojeet Shrestha, Ed.; Open Access eBooks: Wilmington, 2017; pp. 1-27 ISBN 978-81-935757-1-0.
- [72] de Lima França, C.C.; da Silva Terto, E.G.; Dias-Vermelho, M. V.; Silva, A.C.A.; Dantas, N.O.; de Abreu, F.C. The electrochemical behavior of core-shell CdSe/CdS magic-sized quantum dots linked to cyclodextrin for studies of the encapsulation of bioactive compounds. *J. Solid State Electrochem.* **2016**, *20*, 2533-2540, doi:10.1007/s10008-016-3221-8.
- [73] Mahshid, S.S.; Flynn, S.E.; Mahshid, S. The potential application of electrochemical biosensors in the COVID-19 pandemic: A perspective on

the rapid diagnostics of SARS-CoV-2. *Biosens. Bioelectron.* **2021**, *176*, 112905, doi:10.1016/j.bios.2020.112905.

[74] Seo, G.; Lee, G.; Kim, M.J.; Baek, S.H.; Choi, M.; Ku, K.B.; Lee, C.S.; Jun, S.; Park, D.; Kim, H.G.; et al. Rapid Detection of COVID-19 Causative Virus (SARS-CoV-2) in Human Nasopharyngeal Swab Specimens Using Field-Effect Transistor-Based Biosensor. *ACS Nano* **2020**, *14*, 5135-5142, doi:10.1021/acsnano.0c02823.

[75] Rashed, M.Z.; Kopechek, J.A.; Priddy, M.C.; Hamorsky, K.T.; Palmer, K.E.; Mittal, N.; Valdez, J.; Flynn, J.; Williams, S.J. Rapid detection of SARS-CoV-2 antibodies using electrochemical impedance-based detector. *Biosens. Bioelectron.* **2021**, *171*, 112709, doi:10.1016/j.bios.2020.112709.

[76] Mojsoska, B.; Larsen, S.; Olsen, D.A.; Madsen, J.S.; Brandslund, I.; Alatraktchi, F.A. Rapid SARS-CoV-2 detection using electrochemical immunosensor. *Sensors (Switzerland)* **2021**, *21*, 1-11, doi:10.3390/s21020390.

[77] Yakoh, A.; Pimpitak, U.; Rengpipat, S.; Hirankarn, N.; Chailapakul, O.; Chaiyo, S. Paper-based electrochemical biosensor for diagnosing COVID-19: Detection of SARS-CoV-2 antibodies and antigen. *Biosens. Bioelectron.* **2021**, *176*, 112912, doi:10.1016/j.bios.2020.112912.

[78] Zhao, H.; Liu, F.; Xie, W.; Zhou, T.C.; OuYang, J.; Jin, L.; Li, H.; Zhao, C.Y.; Zhang, L.; Wei, J.; et al. Ultrasensitive supersandwich-type electrochemical sensor for SARS-CoV-2 from the infected COVID-19 patients using a smartphone. *Sensors Actuators, B Chem.* **2021**, *327*, doi:10.1016/j.snb.2020.128899.

[79] Eissa, S.; Zourob, M. Development of a Low-Cost Cotton-Tipped Electrochemical Immunosensor for the Detection of SARS-CoV-2.

*Anal. Chem.* **2021**, doi:10.1021/acs.analchem.0c04719.

[80] Fabiani, L.; Saroglia, M.; Galatà, G.; De Santis, R.; Fillo, S.; Luca, V.; Faggioni, G.; D'Amore, N.; Regalbuto, E.; Salvatori, P.; et al. Magnetic beads combined with carbon black-based screen-printed electrodes for COVID-19: A reliable and miniaturized electrochemical immunosensor for SARS-CoV-2 detection in saliva. *Biosens. Bioelectron.* **2021**, *171*, 112686, doi:10.1016/j.bios.2020.112686.

[81] Hashemi, S.A.; Golab Behbahan, N.G.; Bahrani, S.; Mousavi, S.M.; Gholami, A.; Ramakrishna, S.; Firoozsani, M.; Moghadami, M.; Lankarani, K.B.; Omidifar, N. Ultra-sensitive viral glycoprotein detection NanoSystem toward accurate tracing SARS-CoV-2 in biological/non-biological media. *Biosens. Bioelectron.* **2021**, *171*, 112731, doi:10.1016/j.bios.2020.112731.

[82] Li, X.; Qin, Z.; Fu, H.; Li, T.; Peng, R.; Li, Z.; Rini, J.M.; Liu, X. Enhancing the performance of paper-based electrochemical impedance spectroscopy nanobiosensors: An experimental approach. *Biosens. Bioelectron.* **2021**, *177*, 112672, doi:10.1016/j.bios.2020.112672.

[83] Vadlamani, B.S.; Uppal, T.; Verma, S.C.; Misra, M. Functionalized TiO<sub>2</sub> Nanotube-Based Electrochemical Biosensor for Rapid Detection of SARS-CoV-2. *Sensors* **2020**, *20*, 5871, doi:10.3390/s20205871.

[84] Alafeef, M.; Dighe, K.; Moitra, P.; Pan, D. Rapid, Ultrasensitive, and Quantitative Detection of SARS-CoV-2 Using Antisense Oligonucleotides Directed Electrochemical Biosensor Chip. *ACS Nano* **2020**, *14*, 17028-17045, doi:10.1021/acsnano.0c06392.

[85] Torrente-Rodríguez, R.M.; Lukas, H.; Tu, J.; Min, J.; Yang, Y.; Xu, C.;

Rossiter, H.B.; Gao, W. SARS-CoV-2 RapidPlex: A Graphene-Based Multiplexed Telemedicine Platform for Rapid and Low-Cost COVID-19 Diagnosis and Monitoring. *Matter* **2020**, *3*, 1981-1998, doi:10.1016/j.matt.2020.09.027.

[86] Cui, F.; Zhou, H.S. Diagnostic methods and potential portable biosensors for coronavirus disease 2019. *Biosens. Bioelectron.* **2020**, *165*, 112349, doi:10.1016/j.bios.2020.112349.

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