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Journal of Nanotechnology and Nanomaterials Short Communication

Detection of Viruses and Development of New Treatments: Insights into Antibody-Antigen Interactions and Multifunctional Lab-On-Particle for SARS CoV-2

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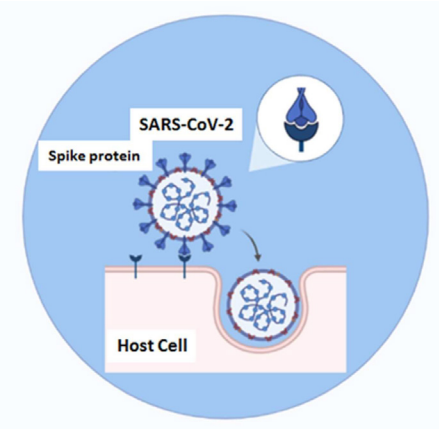
Abstract

The design of new drugs, molecules, nano-, and microstructures for targeted applications is of high impact in Life Sciences. In this context, and mainly for the Corona Virus Pandemic, a fast response is highly required. Thus, the developments of novel approaches are urgently need, seeking improved and highly sensitive solutions in the field of bio detection, in addition to new treatments of SARS CoV-2. In this manner, this short communication discusses the following topics: i) the importance of non-covalent interactions from antibody-antigen recognition events; ii) the genomic factor from virus towards interactions and infections; iii) the importance of the non-covalent interactions on optical detection systems, and iv) the development of new approaches of detection and new treatments based on Smart Responsive Multifunctional Nano-, Microparticles and lab-on particles too. Moreover, it was analyzed the current state of the COVID-19 pandemic, the importance of new treatments in progress and the development of new vaccines and alternative treatments. As well, it is discussed the improvement of highly sensitive and innovative multifunctional Nanophotonic approaches for SARS CoV-2 detection and potential targeted treatments based on non-classical light delivery.

Keywords: Coronavirus, SARS CoV-2, Bio detection, Lab-on-particles, Nanoplatforms, Antibody-antigen interactions, Vaccines

Art Work



Introduction to Antibody-antigen Interactions and Their Potential Use on Lab.-On-Particles

The Corona Virus disease is a severe respiratory problem generated via severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). The latest strain of the disease was deadly enough to halt the global routines of human development. In this context, a number of research studies have been conducted to provide knowledge and to combat with this severe illness.

In this way, from the molecular control towards the Nanoscale it could be afforded to new developments that could give some insides in this field based on variable interactions. The knowledge of chemical structures involucrate could permit to manage molecular interactions for covalent and non-covalent targeting of Biomolecules such as antibodies, antigens, RNA, DNA, etc., depending on needs. Similarly, these interactions could derive from nanoscales, offering an approach to nanoplatforms interacting with biological media. The importance of the control of targeted interactions from the nanoscale is highly required for the detection, trapping and tracking of biomolecules and biostructures. Thus, the development of these types of interactions poses a new challenge for the design of strategies for biodetection and treatments. Innovative solutions could be therefore suggested from multi-functional approaches. In this perspective, looking for detection of Viruses it could be proposed Optical Nano-, and Micro-platforms with varied shapes and sizes. By this manner the targeted interaction on diminished sizes could be a more efficient strategy for the Biostructure trapping, identification, and detection. But the specific interaction should be well known to be conjugated on the smart responsive particle. Thus, it is of high interest as for example, the Research on biosynthesis of antibodies from small animals, later applied to animal models, and then to humans in clinical trials. The isolation of potent SARS-CoV-2 neutralizing antibodies showed a protective effect from disease in a small animal model [1]. In this way, an antibody cocktail of SARS-CoV-2 spike protein showed to prevent quick mutational escape seen with individual antibodies [2]. Thus, this strategy showed a possible solution to the extra difficulty related with the fast genomic mutation. Likewise, neutralization monoclonal antibodies of SARS-related viruses were registered [3]. Even if these biostructures are natural and obtained from a biosynthetic pathway, the purity and quality of the antibodies used for targeted applications should be considered. For example, when a DNA vaccine for Zika-Virus was tested in animals or clinical trials, a differentiated response was found, according to the quality of the antibodies generated [4]. Hence, for all developments, the evaluation of variables linked to biological variations and responses between the biological systems, ranging from small animals to applications in humans, should be taken into account. Antibodies generated from small animals to humans showed variations in their interactions and effects, requiring further studies [5]. The immune responses and their uses could play dominant roles in the accuracy and precision of targeted interactions and functionalities. Therefore, this accuracy and precision could be joined on Multifunctional particles as well as surfaces where it could be collected the Biostructures for further processing. For example, after an Optical detection of Biostructures interacting on modified surfaces it could be coupled to smart responsive actions such as: i) trapping of Biostructures, ii) genomic material extraction for identification; and iii) incorporation of treatments depending on needs.

This important factor related with the targeted interaction should be considered carefully for new synthetic approaches designed and synthesized based on accurate 3D structures. The implication of multiple antigenic sites determined from SARS-CoV 2 spike proteins, depending on the different types of mutation, could generate more or less effective a designed chemical structure as pharmacophore (Figure 1) [6]. Dynamic binding studies by biolayer interferometry showed different association constants according to the amino acid compositions within different domains of interactions. These domains, in the SARS-CoV-2 S glycoprotein, were well resolved and differentiated by Cryogenic Electron Microscopy (Cryo-EM). And slight differences, such as four amino acid compositions led to different interactions. Here, the importance of molecular interaction levels for consequent bio-targeting responses should be noted. In this manner, these variable interactions could be used for designing functional platforms for the detection of Biostructures, with incorporation of high precision medicine approaches [7]. Thus, not only detection should be required; biostructures should be tracked and separated for treatment. Recent studies into molecular traps against COVID-19 [8] were based on non-covalent interactions of primary receptor for the spike (S) fusion protein, allowing cell entry of SARS-CoV-2. This primary receptor is the peptidase angiotensin converting enzyme 2 (ACE2), expressed on epithelial cells in many tissues such as lung, heart, blood vessels, kidneys, and gastrointestinal tract. So, in this context, in the next section it was afforded other examples coupling the detection of Virus and new treatments on Lab.-On-Particles approaches. In this way, it should be highlighted that this is a multidisciplinary Research field that involucrate from detection and isolation of natural or Biosynthetic antibodies-antigens towards synthetic Biology approaches joining even to theorical calculations. In this manner, it could be leaded to improved targeted interaction with consequent efficiencies in the desired application on Multifunctional Nanoplatforms.

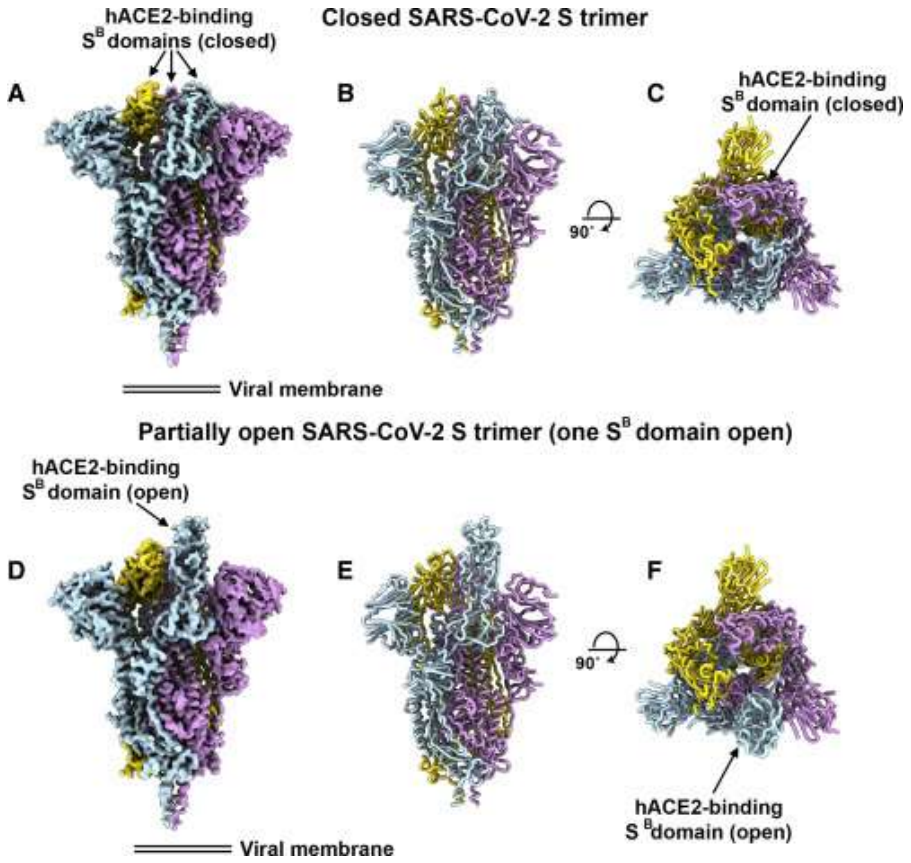


Figure 1: Cryo-EM structures of SARS-CoV-2 S glycoprotein **(A)** Closed SARS-CoV-2 S trimer unsharpened cryo-EM map; **(B and C)** two orthogonal views from the side; **(B)** and top **(C)** of the atomic model of the closed SARS-CoV-2 S trimer; **(D)** partially open SARS-CoV-2 S trimer unsharpened cryo-EM map (one SB domain is open); **(E-F)** two orthogonal views from the side; **(E)** and top **(F)** of the atomic model of the closed SARS-CoV-2 S trimer. The glycans were omitted for clarity. Reprinted with permissions from D. Veesler et al. [6].

The Genomic Factor in the SARS CoV-2

We should note the factor associated with the genomic variability of the SARS CoV-2 generated in the Guangdong Province, China [9]. In such study, to determine the genetic multiplicity of this virus, 53 genomes were generated from infected individuals of Guangdong. To do that, authors combined metagenomics sequencing with tiling amplicon methods. Thus, a large genetic diversity resulted, leading to variations in the different levels of the interactions involved. These variations could be linked to SARS CoV-2 structural variations and genomic information. As known, the coronaviruses are enveloped with single stranded RNA of ~20-30 kb, with four structural proteins and other accessories [10-12] However, the spreading of the disease has been prevented by controlling the access to infected places, while treatments are being developed. This genomic variability was controlled within the contaminated region with travel restrictions. In addition, all types of vectors were and are still being controlled to avoid the spread of the biostructures.

The genomic factor and analysis [11] for the detection of these variabilities should also be considered, with resulting bio-implications in their detection and variable effects depending on the host [12]. Antibody architecture variability could largely affect the biodetection of a small biostructure within the nanoscale of 100-120 nm [13]. In addition to the intrinsic nature of the biostructures, genomic variations and responses from individuals could affect the detection, the effect and transmission of the disease [14]. All these factors could be included in the interactions with similar synthetic and natural nanostructures, leading to the capture and detection of these biostructures outside or inside hosts. For instance, synthetic hybrid nanoarchitectures with tuned properties, such as nanophotonics [15] could lead to potential uses for coronavirus detection, tracking and treatment.

Biodetection of SARS CoV-2 and New Insights from Nano-biotechnology

The biodetection of viruses referred to as cargo biostructures with genetic information could be sequenced and amplified by several sequencing technologies such as Polymerase Chain Reaction (PCR) [16]. New related methodologies [17] are in progress. This technique could address the problem associated to genetic variability [18] due to its precision. However, new and faster approaches should be developed for biodetection, such as those based on the concept of lab-on-particles [19,20].

In these types of nanoplatforms, their surfaces and properties could be tuned in order to detect varied biostructures. We should highlight the importance of the accurate control of the size within the nanoscale of the nanoplatform, in view of the tracked virus or biostructure. In particular, the tracked virus showed variable reduced size, comparable to those of nanoplatforms.

Hence, new biotechnological approaches for biodetection should be considered, in addition to new treatments developing nano-bio-optics [21]. The types of developments result from the control of optical properties on nanoplatforms, in conjunction with other functional materials and properties. Thus, non-classical light generation [22] and new metamaterial properties [23] could be recorded and potentially applied to coronaviruses.

In addition, their incorporation into different optical set-ups should be taken into account, depending on the targeted signals. In this way, these optical active nanoplatforms could be considered as nano-tools or components of portable instrumentations. For example, the polydopamine-doped virus like structured nanoparticles, designed for photoacoustic imaging guided synergistic chemo-/photothermal therapy [24]; and functional carbon quantum dots by means of medical countermeasures to human coronavirus [25].

Future perspectives about developments based on modified silica waveguides [26] use Wave Optical Light Scattering (WOLS) [27] and microfluidics towards nanofluidics to confine single biostructures [28]. This mention, it is just only to contemplate versatile and faster techniques for improved Biodetection approaches and new developments. As well, it could be used the concept of non-classical Light Delivery for Biosensing, Bioimaging and Photothermal treatments [29,30].

The development of nanostructured surfaces to be incorporated into the standard advanced instrumentation with different spectroscopical techniques, in addition to new optical set-ups, could also afford new optical approaches for biodetection, as in the case of Surface Enhanced Raman Spectroscopy (SERS) technique. The SERS showed high sensitivity that allowed its application in single molecule level detections [31], used in DNA detection [32]. A thermoplasmonics SARS CoV-2 detection system was recently developed from SERS (Figure 2) [33]. In that work, a Plasmonic Photothermal (PPT) was

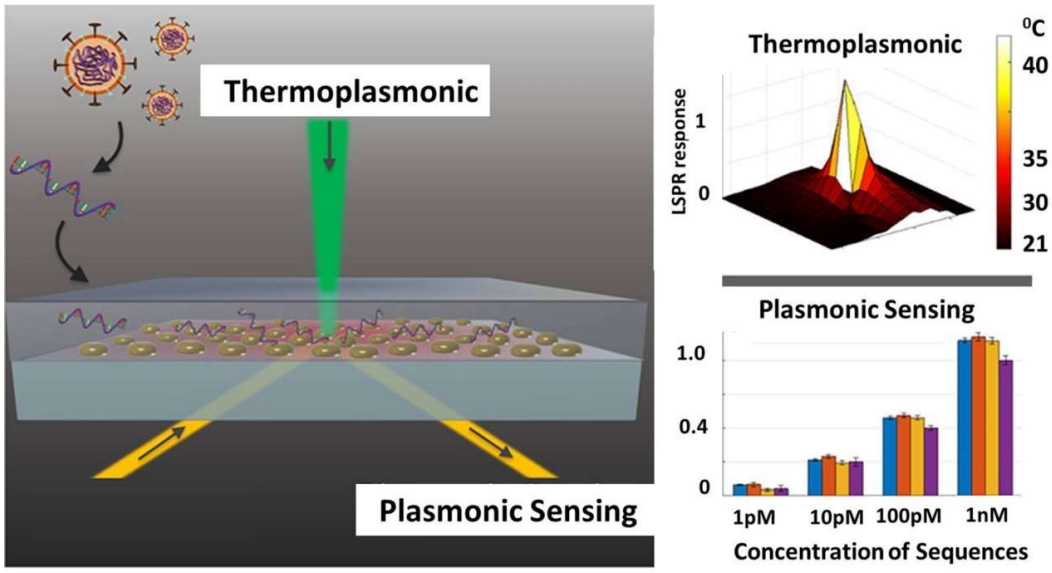


Figure 2: Schema of thermoplasmonics approach based on Surface Enhanced Raman Spectroscopy (SERS). Reprinted with permissions from Wang et al. [35].

combined with Localized Surface Plasmon Resonance (LSPR) sensing. The PPT treatment generated the free genomic material to be tracked by functionalized gold nano-islands with complementary DNA strands. Thus, a highly sensitive detection approach was developed for SARS CoV-2 through *in situ* hybridization and detection via Plasmon Laser excitation. In this way, detection limits were obtained below 0.22 pM.

Concerning related genotyping and limit of detection based on optical active nanoplatforms, single nanoplatform analysis by imaging within in-flow optical set ups should be considered. Hence, low values were found, such as those of femto-M concentration for similar lengths of single DNA strands, as compared to SARS CoV-2 DNA [34]. In this approach, detection was based on a coupled plasmonic methodology by Fluorescence Resonance Energy Transfer (FRET) and Metal Enhanced Fluorescence (MEF) [35], was validated in blood samples as PCR free genotyping applied to the gene of sex-determining region (SRY) [36].

Therefore, the innovation in combination by joining different Nanophotonic approaches could provide new opportunities to achieve knowledge towards real applications. The development of new multifunctional nanophotonic platforms could lead to new detection systems with extra functions such as controlled delivery of non-classical light [37], drugs, biomolecules [38], biostructures like antigens [39] and genes [40,41], and photothermal treatments [42,43].

Similarly, optical active microchips and micro- and nano-fluidic chips could be designed in varied formats based on different approaches for tracking biostructures in different real samples and media. In this context, it should be highlighted the impact of portable technology with affordable use worldwide by the incorporation of optical active materials and set-ups within devices. As example, it could be mentioned the virus detection using nanoparticles and deep neural network by enabled smartphone systems [44]. This technology was presented as a nanoparticle-enabled smartphone (NES) system for rapid and sensitive virus detection. The strategy used comprised capturing the virus on a micro-chip and labelling with platinum nano-probes. In the presence of hydrogen peroxide, distinct visual gas bubble patterns were formed, analyzed by a convolutional neural network on the smartphone, affording an easy, accessible and fast way to detect viruses.

In addition to these technologies developed, in part, from the control of the nanotechnology, there are still challenges to be addressed and needs related to developments in nanotechnology and nanomedicine *in vivo* and real time. In this way, further developments of the varied interactions between the spiked protein of SARS CoV-2 with the cell receptors towards the internalization within the cells are still required in this field. Thus, other applications could be implemented including: i) tracking of the consequent proliferation of the virus *in vivo* and real time; and ii) application of targeted combinatory treatments [45] using strategies based on the multi-step pathways of the illness development. For instance, it could be mentioned the different chemical environment involved in the spiked interactions, such as varied amino acid compositions according to mutations generated variable hydrophobic aliphatic regions, neutral aromatic moieties, thiol and sulfides groups, carboxylic and hydroxyl groups with hydrophilic properties. Then, after internalization, extra interactions should be considered until replicating the RNA (Figure 3).

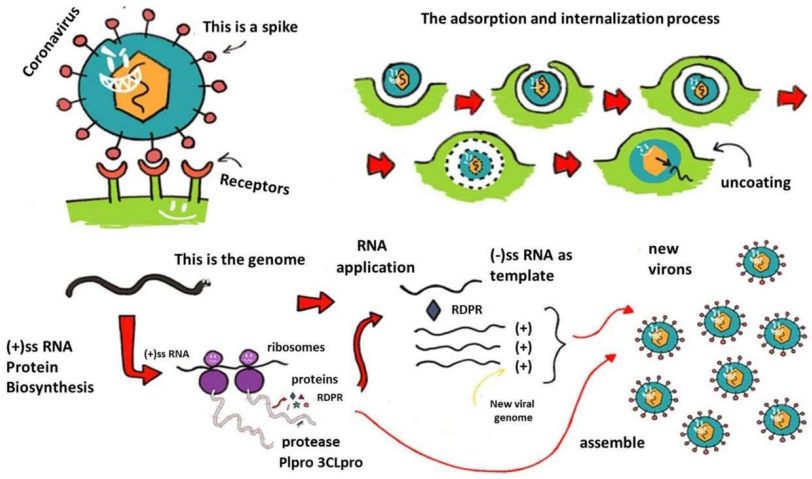


Figure 3: Lifecycle of a coronavirus entering a host cell and replicating inside. The (+)-stranded RNA is released upon viral entry; this starts the process of generating the viral coat and replicating the RNA genome. Reprinted with permissions from Liu et al. [47].

Thus, through the different steps, new opportunities are opened for the development of new biotechnological approaches. In this context, the development of vaccines is important as well [46]. The development of vaccines and new approaches for treating coronaviruses mostly includes strategies at different levels, for example i) antibodies; ii) antigen administration; iii) cell receptor blockers; iv) non-infective virus like particles; v) protein-based vaccines; vi) strategies at genomic level such as nucleic acid vaccines; vii) viral vector vaccines with immune responses; and viii) other pathways with combined treatments [47]. These possibilities may sum the biological variations and trials required for the implementation of vaccines developed with a long-term vision. It should be highlighted that just only the fundamental knowledge for a given illness could be achieved with many years of research and developments, for then assays *in vitro* and *in vivo* to understand the mechanisms of actions and vaccine efficacies against COVID-19 [48]. In this way, it should be highlighted as well, that actually there is a race towards COVID-19 vaccines in advanced status such as trials in phase I with the application of neutralizing antibodies responses by designed proteins [49]; and mRNA vaccines encoding the S-2P antigen of the spiked protein [50]. In addition, the possibility of developments with co-adjuvants [51] and combinatory treatments are being taken into account [52]. However, after a vaccine is developed as well it should be tested in varied populations due to it could be some non-controlled biological factors modifying the desired effect [53]. And in this way, even if at the moment there are few vaccines already developed, exist the discussion of the application and of new strategies for improved effects [54,55]. Thus, the biological evolution of the disease and its applied treatments are still being evaluated [56-58].

Finally, it could be highlighted that from analysis of specialists in these fields such as United Nations (UN) [59] on the basis of previous experiences [60,61], prevention and treatment to control the pandemic are especially required [62]. By this manner, it should be mentioned that within higher levels of protections, it could involucrate even technological developments such as science robotics [63] depending on the situation and particular needs [64]. So, the high technological capability at varied levels such from the Nano-, Micro-, and Macro-scales will add an important factor to achieve the success in the Biodetection and Bioprotection against this situation as well as other ones in the Future. In this perspective, the design, synthesis, and fabrication of portable Instrumentation could provide the next generation of Nano-, and Microdevices [65] available worldwide.

Conclusion

In this brief manuscript the importance and impact of non-covalent interactions for SARS CoV-2 detection and the developments of new potential treatments have been shown and discussed. The genetic variability that could affect largely the interactions of the host cells to the effect of the illness was highlighted. As well, this topic should be contemplated for detection and development of new treatments.

In this context, some new approaches for detection were showed based on modified surfaces and Lab-On particle developments; where non-covalent interactions were considered important. In this manner, antibodies and antigens should also be contemplated for accurate detection of SARS CoV-2. In addition, the genomic variability should be evaluated by PCR, as well as new PCR free approaches should be developed based on Nano-arrays or single Nanoplatforms. Thus, the potential role of developments in the field of biotechnology based on Nanophotonics detection systems for improved new treatments in the near future were discussed. Finally, it should be highlighted the high impact implication of Multidisciplinary Research fields for Nanotechnology, and Lab.-On-Particles, towards portable devices, Chips, and Miniaturized Instrumentation.

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Conflict of Interest

The authors confirm that this article's content has no conflict of interest.

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