



Research Article

Nano-chemistry and Bio-conjugation with perspectives on the design of Nano-Immune platforms, vaccines and new combinatorial treatments

Luna R Gomez Palacios¹, Sofia Martinez², Cecilia Tettamanti², Daniela Quinteros² and A Guillermo Bracamonte^{1,3*}

¹PhD, Researcher and Assistant Professor, Institute of Research in Physical Chemistry of Córdoba (INFIQC), INFIQC Laser Center, Department of Organic Chemistry, Faculty of Chemical Sciences, National University of Córdoba (National University of Cordoba, Argentina), University City, 5000 Córdoba, Argentina

²Research and Development Unit in Pharmaceutical Technology (UNITEFA), Conicet, Department of Pharmacy, Faculty of Chemical Sciences, National University of Córdoba, University City, 5000 Córdoba, Argentina

³Department of Chemistry and Center for Optics, Photonics and Laser (COPL), Laval University (Laval University), Quebec (QC) G1V 0A6, Canada

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***Corresponding author:** A Guillermo Bracamonte, PhD, Researcher and Assistant Professor, Institute of Research in Physical Chemistry of Córdoba (INFIQC), INFIQC Laser Center, Department of Organic Chemistry, Faculty of Chemical Sciences, National University of Córdoba (National University of Cordoba, Argentina), University City, 5000 Córdoba, Argentina, Tel: +54 351 535-3850/+54 351 535 3867; E-mail: gbracamonte@fcq.unc.edu.ar, guillermobracc@yahoo.ca

ORCID: <https://orcid.org/0000-0003-4760-3872>

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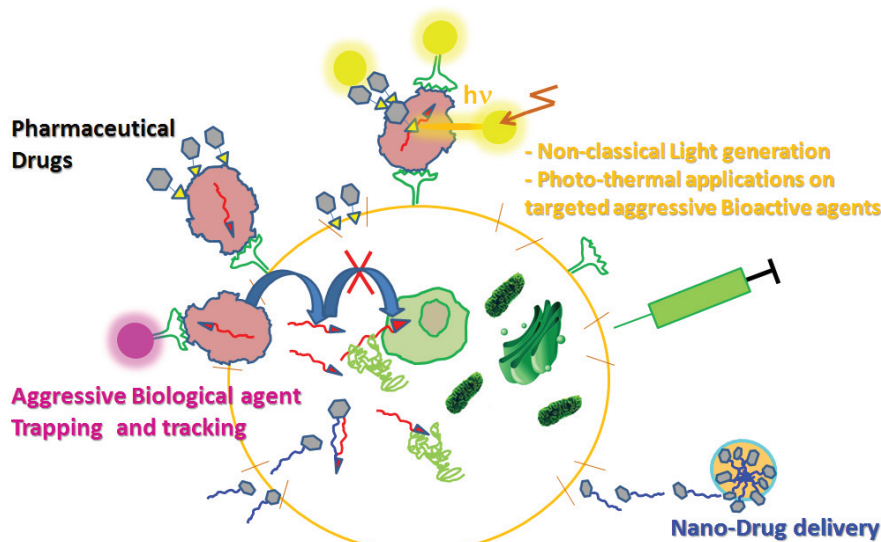
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Abstract

This Mini-Review and Opinion letter, it was addressed different themes and topics implicated in the development of new treatments and vaccines applied to pathologies developed in humans such as by Virus and related pathogens. In this context, it was presented and discussed different strategies used, which were contemplated from the design of small molecules, towards higher sized chemical structures and new Nanoarchitectures. In particular, it was discussed varied studies developed for the Corona Virus treatment; which afforded to the main mechanisms of action of pharmacophores and targeted functional Nanoparticles. In this direction, it was highlighted the importance of Bioconjugation of molecules and variable Nanoarchitectures for their incorporation within cells as well as for the development of Nano-vaccines. Moreover, it was discussed about the development of combinatory treatments based on different strategies recently reported. Similarly, it was presented different studies and developments actually in progress related to the design of functional and Multifunctional Nano-platforms with potential perspectives on Lab-On particles and Nano-vaccines for precision Nanomedicine and new treatments.

Artwork



Targeted recognitions of Biological aggressive vectors with Drugs, chemical structures and Biostructures

Introduction

Nano and Biotechnology could generate new alternatives and varied aspects for the development of new strategies towards vaccines, alternative, and combined treatments [1]. In this aspect, there are many developments to be achieved related from small molecules to higher molecules, synthetic Bio-molecules such as peptides, proteins, natural and synthetic oligonucleotides [2]. This future next generation of molecules should be developed within In-Vitro and In-Vivo controlled conditions for them to pass to other levels of Bio-assays looking for targeted effects.

These considerations in a general manner are intended to show and open the discussion about the multi-factorial challenge that should be developed. However, it is important to highlight that there are many existing methods focused on the treatments of varied pathologies generated for infectious agents such as Biostructures of Viruses. In this manner, it was observed the apparition of the Corona Virus from where it was begun the discussion about requirements and needs in the context of pandemia to manage the SARS CoV-2 [3]. For example, it should be considered the interaction of the receptors of the protein receptors specific for the Corona Virus action. The spiked protein involucrated showed a high interaction and adhesion with targeted cells that permits its incorporation within the Cytoplasm where new interactions are developed as well. In this way, it needs new studies related to the detection of the mechanism involucrated at each mentioned step. In this manner, it could be inferred more about its proliferation in real-time. In-Vitro and In-Vivo [4]. Thus, new pharmacophores with varied strategies would be welcomed to be proposed based on the previously mentioned different steps associated with the development of the illness [5].

In this perspective, the knowledge and know-how required to study and develop new mechanisms and pathways

of Biostructures detection, tracking, blocking, degrading, modifying, and generating immune responses, was vital to design vaccines and treatments. And, there it is from where the molecular interaction knowledge should be inquired and applied for targeted recognitions with consequent responses. For example, the knowledge of the four key amino-acid interactions within the spiked protein related to different regions with varied hydrophobic domains could be modified by the mutation of the Virus with variations on the effect of the host. Similarly, the membrane of the host could be different between variable gene expressions. Therefore, the combinations between them opened additional Biological variables accompanied by different effects. And it should be explained that these variations are related to modifications of the media by aliphatic chains, neutral aromatic moieties, sulfide, thiol, carboxylic, and hydroxyl groups with varied final hydrophilic properties. Then, from these initial interactions, the cargo Biostructure could be inserted as a guest to replicate its genomic material with the use of the host Bio-machinery. In this manner, the illness could be quickly expanded and transferred as well to other living organisms. In this context, new opportunities were opened to still working on the next generation of alternative, and combined treatments, as well as new Vaccines where interactions from the molecular level towards the Nanoscale and beyond are directly related. In this direction the Nanotechnology joined to Biotechnology accompanied with high technological developments could provide faster solutions, with diminished costs and more accessibility to the whole population [6]. In this perspective, it is important to highlight the design and development of versatile Nanoplatforms to tune chemical surface chemistries incorporating varied materials accompanied with the generation of new properties applied for the desired application. For example, it is mentioned a recent publication related to tuning silica Nanophotonics based on fluorescence resonance energy transfer for targeted non-classical light delivery applications

[7] In this report, it was developed Hybrid Silica Nanoparticle with the incorporation of Laser Organic dyes to modulate light emissions (Figure 1).

In the perspective to generate new alternative therapies for varied diseases could be mentioned the potential impact from developments of versatile Nano-platforms towards targeted applications such as i) non-classical light for Bioimaging; ii) tuning light delivery applications for Bio-membrane degradation, and iii) Drug Delivery applications.

Design from molecules towards Nano-vaccines for targeted action pathways

Pathways and mechanisms used as strategies to develop treatments against virus actions: In this context, as was introduced previously the control of chemical structures and Nanostructures formed of varied synthetic materials and Biological materials will be of high interest with perspectives of Nano-vaccines and combined treatments. So, from the current state of the art, it is known many pathways and mechanisms are used as a strategy to develop treatments for Corona Viruses at different levels. For example; it should be highlighted; i) the application of antibody-antigen interactions for detection, separation, Bioconjugation, labeling, and controlled drug delivery, etc.; ii) administration and use of antigens conjugated with molecules and Nanoparticles; iii) other types of structures as molecular receptor blockers; iv) applications of innocuous Viral type particles as vectors, and cargo structures; v) use of peptide and proteins as Bioconjugation agents with potential actions as Nano-vaccines; vi) developments of strategies based on nucleic acids as high Biocompatible structures associated with high interacting moieties with other Biological structures; vii) developments of targeted viral vectors to activate immune-responses as vaccines; and viii) alternative and combined treatments [8].

In all the mentioned strategies there are still existing needs and opened opportunities to take into account in future developments. In addition, it should be noted the high importance of the variable interacting Biological media that should be contemplated for the targeted developments. Thus, in this context, there are many variables to control for a given proposal approach giving alternative solutions In Vitro and In Vivo. And in this direction, the time focused at each step of the developments is vital to generate the knowledge required as well as to evaluate the different mechanisms of actions, pathways, and efficiencies for vaccine developments such as for the COVID-19 [9].

Current trends and recent developments

There are many research works related to the developments of Immuno-treatments, Vaccines, and Combinatory therapies for Corona Viruses and related illnesses with other potential Biological agents too at different phases for their applications. It could be mentioned, for example, the evaluation of neutralizing agents based on a targeted design by the use of protein structures [10], codifying RNA for the antigen of the spiked protein [11]; and application of new chemical agents, Nanomaterials, co-adjuvants [12] and combinatory treatments as well [13]. Even like that, the developments of other approaches are required to avoid negative effects generated from variations of the media in direct relation to intrinsic Biological constitution [14]. In this context there are not so many universal vaccines developed already accepted and incorporated in the market at this moment; because there are potential latent variations that could be generated from the high diversity and variability; as well as it could be generated new conditions for other illness or variants. For these reasons the Research and developments within Life Sciences in many Research fields are still being supported and permit new insights for Corona Virus treatments with improved efficiencies [15,16]. Moreover, for a given illness it should be contemplated

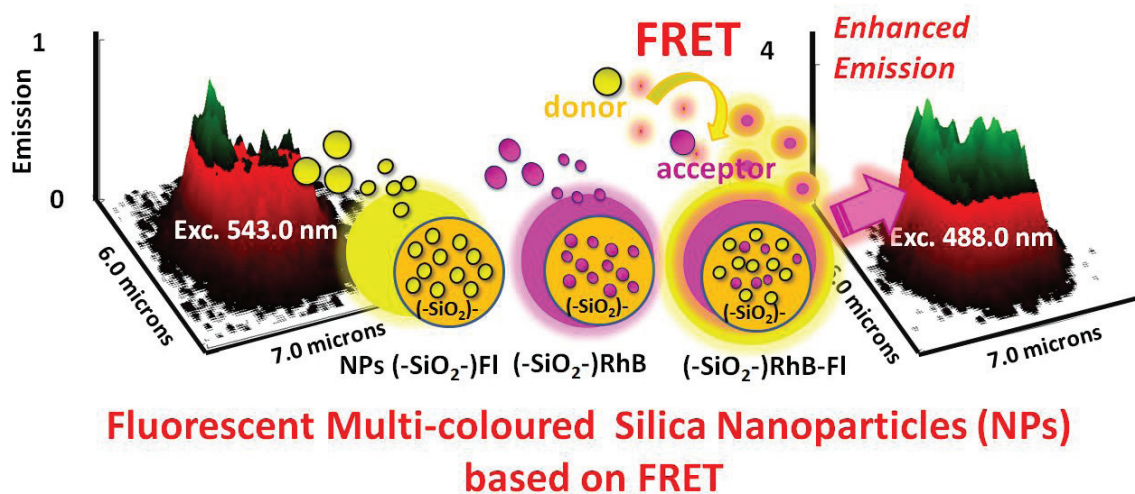


Figure 1: Scheme of Luminescent SiO_2 NPs by covalent linking of Fluorescein (FI) and Rhodamine B (RhB) to obtain mono-colored SiO_2 -FI, SiO_2 -RhB NPs; and multi-colored SiO_2 -RhB-FI NPs. And incorporated 3D fluorescence surfaces from multi-colored SiO_2 -RhB-FI NPs with only optimal excitation of RhB as a fluorescent energy acceptor at 543 nm; and only optimal excitation of FI as energy donor at 488 nm and coupling with RhB as a fluorescent energy acceptor. Reprinted with permissions of A. G. Bracamonte et al. (cite 7), Journal of Nanophotonics, SPIE 2020.

the different levels or degrees of the advance of the targeted illness. For this reason, in this complex and multifactorial Biological event, it should be tracked the different effects and variables that are appearing and modify the effect of currently used treatments to update and improve it. For example, the potential mutations and consequent mechanism involucrated in the development of the illness [17-19]. These mutations could affect the interacting receptors, antibodies, and all membrane components of viruses for example. So, these modifications should be taken into account in the design of the new treatment. In this manner, it is possible to propose a new mechanism of action accompanied with targeted designs of molecules towards Nanoplatforms and combined Nano-formulations. In addition, it should be highlighted potential new approaches from Biotechnology based on synthetic Nano-Biostructures that could show interesting applications in this Research field too (Figure 2).

As it could be observed, in the different virus pathways exist many different recognition sites and interactions that should be accomplished to incorporate their Biostructures. In each of these sites could be focused on developing treatment. Thus, it should be highlighted the immune-modulation factor to be contemplated in this new treatment in evaluation, such as for the case of SARS-CoV-2 [20]. Similarly, it could be taken into account these recognition sites for blocking specific receptors with a consequent stop the development of the infectious illness [21]. In this way, it could be demonstrated the impact of

the design and synthesis of chemical structures, Biomolecules, Bio-Nano-composites, and synthetic Nanoarchitectures. Therefore, the Biodetection, early diagnoses, and application of new treatments could be considered as a continuous activity of Research and development where fundamental and applied Researches are in close relations.

Control of the Bioconjugation factor for improved performances

Introduction to Bioconjugation and applications: From the all mentioned variables to control to develop new alternative chemical and Nano-structures, in this section, it was highlighted the importance of the Bio-compatibility to avoid immunological responses or toxicity. In this particular topic, it should be afforded to the Bioconjugation of the obtained synthetic or hybrid structures. In the majority of the cases is conjugated with biological molecules, Biological Biostructures, and derivatized structures. The basis of this importance comes from the capability to produce a Biocompatible hybrid material joining properties and functionalities only found from the combination of both materials for a given targeted objective [22,23]. However in this hybrid architecture in this particular topic, it is noted the impact of the Biocompatible part that it will be in first direct contact with the Biological media that in many cases play the role of the protective agent through the incorporation pathway for example. Moreover, the excellent properties of Nanoparticles in a variable interval of lengths

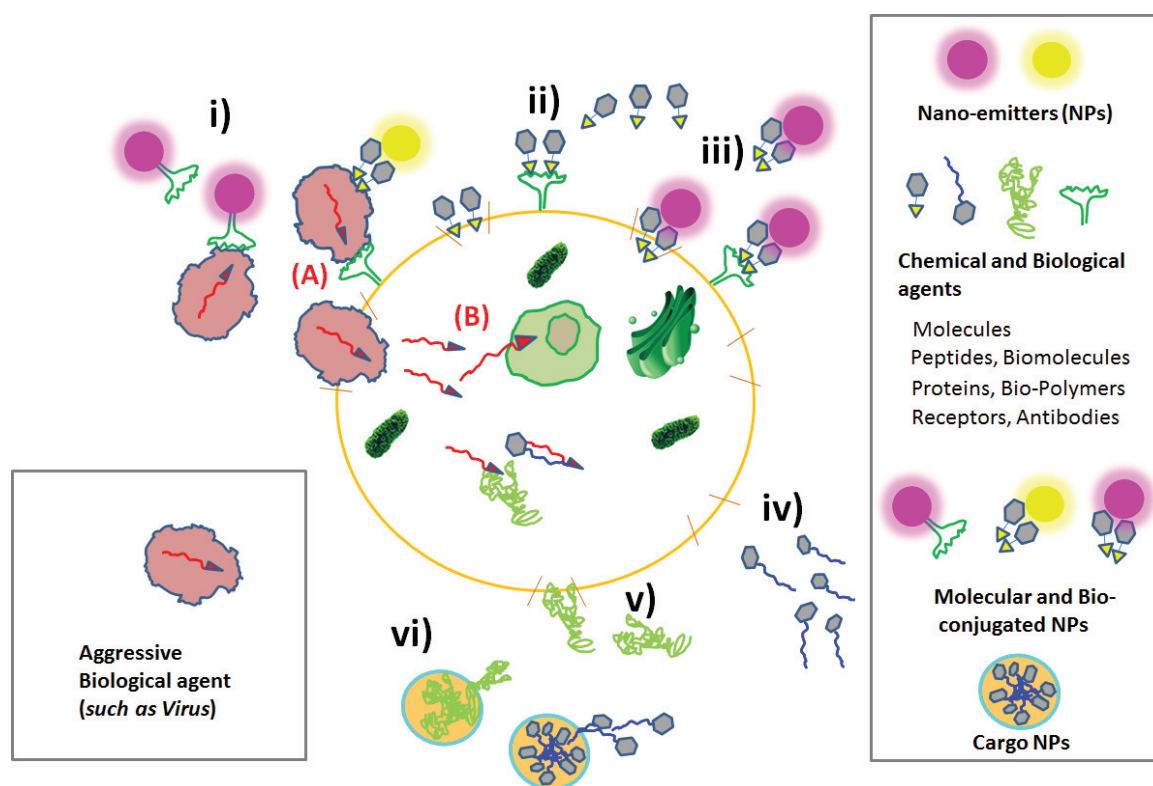


Figure 2: Mechanism of action of potential Biological agents with Cells, and Unicellular microorganisms, and varied treatments based on Molecules, Biomolecules, and Bio-conjugated Nanoplatforms. The Biological agent contains toxic agents (the vector is represented with a red line and blue arrow). The mechanism of actions of pharmacophores, Biological agents, and Nano-pharmaceuticals corresponded by the application of, i) antigens and antibodies linked to Fluorescence Laser dyes, Luminescent Nanoparticles, ii) Targeted Molecules, iii) Modified Nanoplatforms, iv) Natural and synthetic Biomolecules, v) Peptides and Proteins, vi) Cargo and Multifunctional Nanoplatforms (NPs). Reprinted with permissions of Bracamonte, et al. @2021.

could potentially modify their properties accompanied with a consequent effect. In this context Bioconjugated Nanoplatfoms could be directed by natural Biological interactions; while the central Nano-core could be showing higher stability conserving their properties and targeted functionality. And, it should be mentioned that in many cases improved properties and performances could be obtained such as dispersibility, stability, augmented interactions, effect, and improved performances. So, for these reasons, there is a large variety of Bioconjugation techniques and methods developed for the incorporation of different Bio-structures [24].

In this manner, during the last years towards the advance of new technologies, it exists a continuous interest in the development of Nanomaterials for Biological Applications. In this context, Nanomedicine and precision Medicine were focused on the development of vaccines, functional devices, new dispositive of diagnoses, high resolved Imaging systems, and other invasive and non-invasive approaches for early diagnoses and applied treatments [25].

Bioconjugated Nanomaterials for enhanced properties:

Many types of Nanoparticles were developed for potential Clinical applications, and biomedical uses; such as Polymeric Nanoparticles, Carbon Nanotubes, Silica, Silver, and Gold Nanoparticles, Quantum dots, and Magnetic Nanoparticles [26]. In this particular topic, it was mentioned Quantum Dots due to there is an increasing interest to apply these types of tiny Nano-materials for Bio-applications. These structures are frequently used as Nanoplatfoms for drug cargo loading and delivery applications by a proper Bioconjugation depending on the targeted use. Thus, it could be improved their Bio-compatibility, Bio-availability, and Pharmacokinetics [27]. And, in this context, it is known that Quantum Dots are more or less associated with toxic effects depending on their material conformation. However, applying green chemical synthesis and Bioconjugation techniques could be led to Bio-compatible properties such as Graphene Quantum Dots [28].

Moreover, Silica based Nanomaterials showed excellent Optical properties to be tracked within Biological media with relatively low toxic effects. Therefore, it could permit to development of versatile chemical surfaces for Biophotonics and Nanomedicine applications by tuning their

Nanoarchitecture design. For example, it could be noted the use of Silica Nanoparticles for vaccine protection against its degradation at room temperature [29]. So, in this perspective, it could be highlighted the Bioconjugation of Hybrid Silica Nanoparticles with Human Serum Albumin (HSA) affording to improved dispersibility within aqueous media (Figure 3). In this manner, it was converted versatile silanized chemical Nano-surfaces with variable inter-Nanoparticle interactions to well dispersible single Bio-Nano-platfoms.

In this context, it should be noted the importance of the Bioconjugation for the different Nano-materials with varied applications that could afford from Biosensors towards Multifunctional Nano-platfoms and Nanomedicine applications such as Nano-vaccines. Therefore, some vaccines were accepted for massive immunization by conjugation with targeted proteins against typhoid fever (Typbar-TCV® y PedaTyph™). This development was applying the conjugation of the antigen of the polysaccharide VI with the tetanus toxoid protein [30]. Moreover, should be mentioned a recent report of a vaccine developed based on Bioconjugates that entered phase II in Cuba; where Valdes-Balbin, et al. conjugated SARS-CoV-2 RBD (as binding domains of the receptor) with the tetanus toxoid protein. This strategy produced a strong immune response in laboratory animals [31]. So, it was highlighted that even being different the Tetanus and typhus, the use of related Bio-molecules permitted improved interactions and Bio-compatibility. In this way, it is awaiting advances in Nanotechnology by developments of Bio-conjugated Nano-vaccines that could lead to improved efficiencies and effectiveness for the desired effect in comparison to previous ones already developed.

Finally, should be highlighted other strategies for vaccines developments by non-traditional strategies such as remote controlling of Magnetically-Propelled particles with Ultra-sound-assisted methods [32]; and Macro-Biostructure delivery such as Cellular membranes for targeted interactions [33], that could provide interesting approaches.

Concluding remarks and perspectives

In this communication, it was afforded to the discussion of different mechanisms and strategies involucrated in the development and evaluation of new vaccines, alternatives,

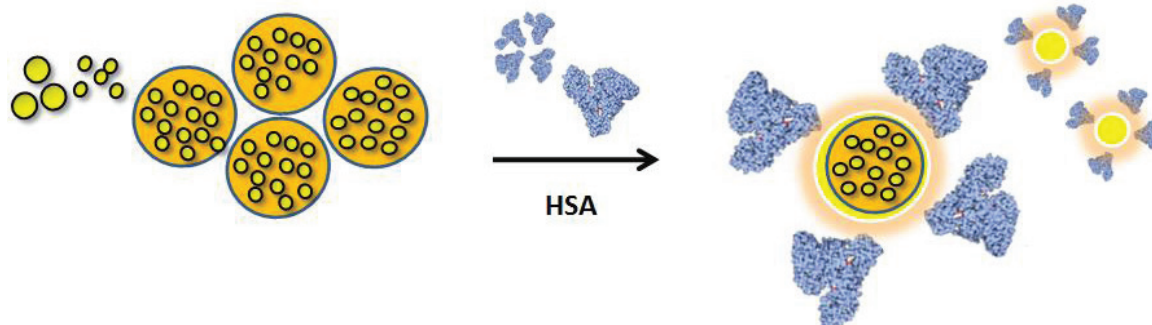


Figure 3: Scheme of Luminescent Silanized Nanoparticles bioconjugation with Human Serum Albumin (HSA). Reprinted with permissions of D. Quinteros-A.G. Bracamonte, et al. @2021.

and combined treatments. In this context, it was presented some examples from Corona Viruses. Thus, it was highlighted the participation of varied chemical structures for specific interactions, as well as antibodies and antigens; and other types of biomolecules such as peptides, proteins, nucleotides, RNA, and DNA, etc. Moreover, it was mentioned the importance of the design of Nanostructures contemplating Bioconjugation techniques, methods, and particular Biological structures depending on needs and applications. In addition, it was highlighted the functional and Multi-functional approach based on the different components joined that provided the final properties.

In the mentioned design it should contemplate targeted recognition sites, blocking agents, proper modification for the incorporation within membranes, cytoplasm, and organelle, smart responsive detection systems, tracking signaling. Moreover, it could be added remote smart Laser activations of varied coupled phenomena such as photonics, thermal effects, non-classical light generation and delivery, accompanied with pharmacophores delivery as well. In this context, it was noted the importance of the control from the molecular level toward the Nano-scale applied for the development of Nano and Micro-devices with potential uses within Biophotonics, Biotechnology, and Nanomedicine [34]. In this perspective, it could be mentioned the high added value, scientific, and technological interest such as the development of Nano- and Micro-syringes for delivery of Nano-vaccines based on DNA against the COVID-19 [35]. In addition, from this concept other miniaturized approaches as Lab. On Particles open new opportunities to develop new Multi-functional Nanoplatforms [36]. (Figure 4). Thus, Luminescent Nanoparticles and Micro-particles with smart responsive coupled Optical active properties for early diagnoses and treatments could be proposed by the right tuning of the targeted Nanoarchitecture [37]. And, in this

just single phrase, it was incorporated many challenges that are still being waiting for further developments considering in addition of the previous variables discussed from the infective guest and the host cells. In this direction, all potential developments from Multidisciplinary Research fields could be incorporated. Thus, as it was mentioned from the beginning the design and synthesis of molecules could provide a high impact on the design of Nanotechnology if it targeted particular properties with a specific function such as Photosensitizers [38,39] with potential perspectives within Photodynamic Viral therapies [40]. Moreover, particular properties from the Nano-scale such as high Energy Electromagnetic fields from Plasmonic structures, shown by a high sensitive phenomenon such as Metal Enhanced Fluorescence (MEF) [41,42] could lead to tuneable Nanostructures with potential uses for Biodegradation of Biomolecules and Biostructures as well [43,44]. Thus, it was reported new detection and coupled treatment against the Corona Virus by Dual-Functional Plasmonic Photothermal Biosensors [45]. By this manner, then looking for controlled and confined miniaturization of technology, all these developments could be added within varied substrates and Chips; such as Micro-, and Nanofluidics Chips and devices [46,47]. For example, it was recently reported Smart labeling of self-illuminating Photosensitizers for Deep Tumor Therapy [48]. Moreover, it could be mentioned Hybrid Nano-Biostructures as Multifunctionalized biocatalytic nanoreactors for combinatory treatment of breast cancer [49]. Other similar examples could be found in literature applied for Virus and Infectious diseases as well [50]. And finally, it should be highlighted the importance of the accurate targeting of the specific action of the Pharmacophore, or Nano-vaccine due to collateral undesirable effects that could provide Neurological disorders [51]. So, all proposals are welcomed contemplating long ways for their developments and applications.

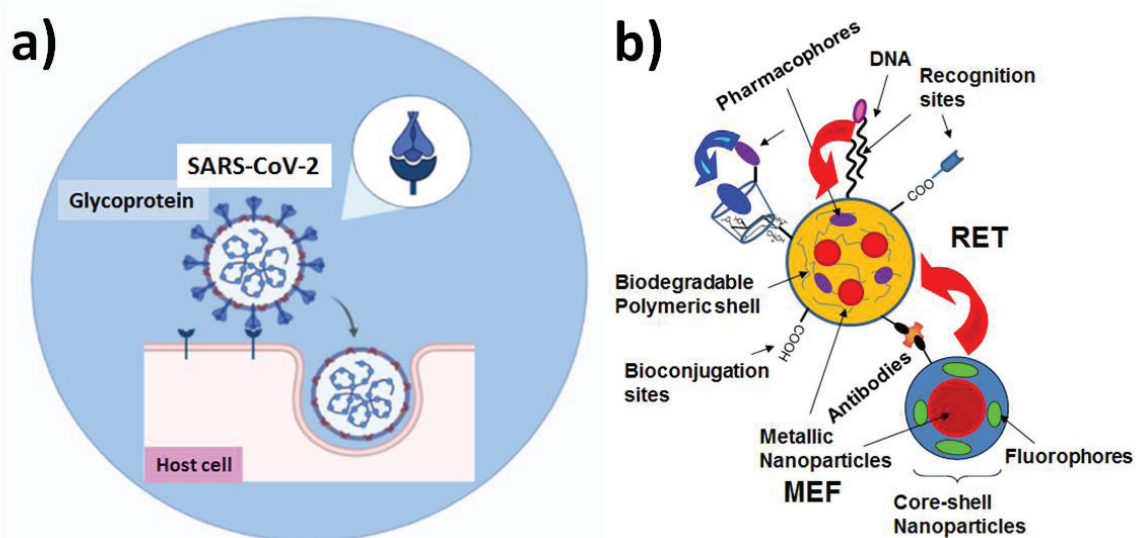


Figure 4: a) Scheme of Corona Virus incorporation within Cells; b) Schematic representation of Multifunctional Nanomaterials for targeted applications based on the design and synthesis of hybrid Nanoarchitectures by incorporation of varied materials. Reprinted with permissions of Bracamonte et al. (cites 30 and 32) *J Nanotechnol Nanomaterials, Sci Arch.* CC, and authored Book *Frontiers in Nano- and Micro-device Design for Applied Nanophotonics, Biophotonics, and Nanomedicine*, Bentham publishers 2021.



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