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Vaccine Design through Machine Learning and Nanotechnology to Terminate COVID-19 Pandemic

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ABSTRACT

The COVID-19 vaccine development involves high-tech platforms such as viral vectors, antigen carriers, and delivery technology. Nanotechnology tools can play a pivotal role in advancing COVID-19 treatment and vaccine design. Information related to the structural morphology of the SARS-CoV-2 virus, its pathophysiology, and related immunological response is the most important factor at the nanotechnology point of view. In the absence of a specific antiviral against SARS- CoV-2, present therapeutics target the multifaceted molecular interactions involved in viral infections and major comprises repurposing already existing antiviral molecules used for other RNA viruses. Furthermore, various kinds of vaccine candidate's structure could be screened by using ma- chine learning. Recently, it is equally important to look for a suitable Nano-carrier delivery technology to make these repurposed therapeutics as well as new vaccine development safer and more effective affordable methodologies so that nanotechnology can reach patients.

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Keywords: COVID-19 Pandemic, Vaccine Design, Machine Learning, Nanotechnology, Immune Response, Antiviral Agent.

Introduction

Incidents of viral outbreaks have increased at an alarming rate over the past decades. The most re- cent human coronavirus known as COVID-19 (SARS-CoV-2) has already spread around the world [1-4]. However, the ratio between mortality and number of infections seems to be lower in this case in comparison to other human coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [5-7]. Confirmed COVID-19 cases are in the millions, and with hundreds of thousands of deaths from the disease the social, healthcare and economic consequences are likely to persist for years. While drug treatments may emerge, which reduce the impact of the disease, vaccination represents the most appropriate means to bring the virus under control in developed and developing countries equally. Multiple technologies are being deployed to identify a safe and effective vaccine. In the case of COVID-19 most vaccines in early development are targeting the so-called spike protein [8]. This protein is ex- pressed on the surface of the virus and allows the virus to bind to the ACE2 receptor on the cell sur- face, initiating fusion with and uptake by the cell, followed by the chain of events leading to virus replication [9, 10]. A vaccine typically contains an antigen made from weakened or killed forms of the microbe/virus, its toxins, or one of its surface proteins. The antigen stimulates the body's immune system to recognize the agent as a threat, and destroy the associated virus. The antigen pro-tein (s) can be administered directly, usually together with an adjuvant to enhance the immune re-sponse. In the case of COVID-19, the spike protein or epitopes, including the receptor binding do-main, are used as the antigen. Thus, these outbreaks have tested the limits of healthcare systems and have posed serious questions about management using conventional therapies and diagnostic tools. In this regard, the use of nanotechnology offers new opportunities for the development of novel strategies in terms of prevention, diagnosis and treatment of COVID-19 and other viral infections. Therefore, we discuss the use of nanotechnology for COVID- 19 virus management by the development of Nano-based materials, such as disinfectants, personal protective equipment, diagnostic systems and Nano-carrier systems, for treatments and vaccine development, as well as the challenges and drawbacks that need addressing in this study [11-18]. Importantly, Nano-material based platform technologies may also play a key role in the distribution and administration of vaccines through micro-needle patches, single-dose slow-release implants, film-based vaccines, or by using plant viral nanoparticles for antigen delivery, which do not require cold chains. In a global pandemic, in which healthcare systems are operating at the limit, such self-administration technologies may prove extremely valuable [19-22]. The need of the hour is to develop a safe and effective COVID-19 vaccine which can induce an appropriate immune response to terminate this pandemic. It is the universal priority to spot the international funding mechanisms to support the development, manufacturing, and stockpiling of the coronavirus vaccines. Furthermore, the use of novel technologies for vaccine development requires extensive testing for the safety and efficacy of a vaccine. Beyond antigen delivery, nanoparticles can covalent deliver adjuvants to help prime the desired immune responses [23, 24]. Consequently, the scientific community needs to construct various processes and capacities for the large scale nanotechnology platformed manufacturing and administration of

the coronavirus vaccines near future.

Methods

Annotation of Literature and Database Records

We annotated peer-reviewed journal articles stored in the PubMed database and the Clinical Trials.gov database. From the peer-reviewed articles, we identified and annotated those coronavirus vaccine candidates that were experimentally studied and found to induce protective neutralizing anti- body or provided immunity against virulent pathogen challenge. Additionally, nanotechnology and COVID-19 were used as key words for relevant research articles.

Phylogenetic Analysis

The protein nsp3 was selected for further investigation. The nsp3 proteins of 14 coronaviruses be- sides SARS-CoV-2 were downloaded from the UniProt. New UniProt portal for the latest SARS-CoV-2 coronavirus protein entries and receptors, updated independent of the general UniProt release cycle. Multiple sequence alignment of these nsp3 proteins was performed using MUSCLE and visualized via SEAVIEW. The phylogenetic tree was constructed using PhyML, and the amino acid conservation was estimated by the Jensen-Shannon Divergence (JSD) [25-29]. It was characterized differential transcription between two samples as the difference in the relative abundance of the transcript isoforms present in the samples. The magnitude of differential transcription of a gene between two samples can be measured by the square root of the Jensen Shannon Divergence (JSD) between the gene's transcript abundance vectors in each sample. The JSD score was also used to generate a sequence conservation line using the nsp3 protein sequences from coronaviruses.

Results

Vaccine design concerns the selection of antigens, vaccine platforms, and vaccination routes and regimen. The choice of vaccine platform determines the relative immunogenic strength of vaccine- derived viral antigens, whether an immune adjuvant is required and the nature of protective immunity [30-33]. These attributes also determine the suitability of a vaccine for a particular route of vaccination, and whether a prime–boost vaccination regimen is required to increase vaccine-mediated protective immunity and its durability. Furthermore, the selection of live attenuated viral vaccines or a respiratory mucosal route of vaccination will require more stringent safety testing. Recently, global immune deficiency is a risk factor for anti-COVID-19 vaccine efficacy [34-36], particularly in elderly who have been exposed to a myriad of factors that contribute to weakening of the immune system. These mechanistic reasons for these factors include weakness of antigen recognition, decreased immune cell quantity and functionality, increased level/length and timing of humoral immune alterations of components, reduced initiation of cellular responses, and memory cell disorders. Other associations with immunodeficiency include age-dependent humoral and immune cell alterations; immuno-senescence; malnutrition; protein-energy-micronutrient deficit and telomere shortening. In addition, past or current treatments affect the scalable ineffectiveness of vaccines in both older adults and children, especially in immunocompromised.

COVID-19 Vaccine Design Using Machine Learning

The recently published Vaxign-ML pipeline was applied to compute the protegenicity (protective antigenicity) score and predict the induction of protective immunity by a vaccine candidate [37-39]. Vaxign-ML predicts the protegenicity score using an optimized supervised machine learning model with manually annotated training data consisted of bacterial and viral protective antigens [37]. These protective antigens were tested to be protective in at least one animal challenge model. The performance of the Vaxign-LM models was evaluated, and the best performing model had a weighted F1-score and Matthew's correlation coefficient in nested cross-validation. The phylogeny and sequence conservation of coronavirus nsp3. Phylogeny of 15 strains based on the nsp3 protein sequence alignment and phylogeny analysis. The conservation of nsp3 among different coronavirus strains. The red line represents the conservation among the four strains (SARS-CoV, SARS-CoV-2, MERS, and BtCoV-HKU3). As shown in Figure 1, the phylogenetically close four strains have more conserved nsp3 sequences than all the strains being considered. Reverse vaccinology (RV) is a milestone in rational vaccine design, and machine learning (ML) has been applied to enhance the accuracy of RV prediction [40, 41]. However, ML-based RV still faces challenges in prediction ac-curacy and program accessibility. This study presents Vaxign-ML, a supervised ML classification to predict bacterial protective antigens (BPAgs). To identify the best ML method with optimized conditions, five ML methods were tested with biological and physiochemical features extracted from well-defined training data. Nested 5-fold cross-validation and leave-one-pathogen-out validation were used to ensure unbiased performance assessment and the capability to predict vaccine candidates against a new emerging pathogen. The best performing model (eXtreme Gradient Boosting) was compared to three publicly available programs (Vaxign, VaxiJen, and Antigenic), one SVM- based method, and one epitope-based method using a high-quality benchmark dataset. Vaxign-ML showed superior performance in predicting BPAgs. Vaxign-ML is hosted in a publicly access [42-44].

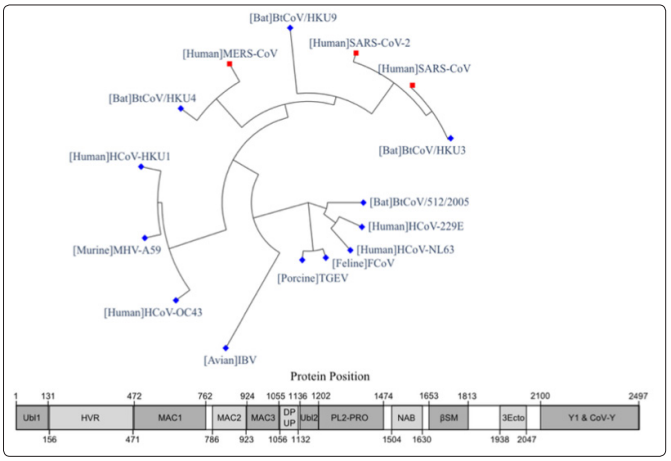


Figure 1: The phylogeny and sequence conservation of coronavirus

Vaccine Platforms for COVID-19 Pandemic

The vast majority of vaccines currently licensed for human use can be divided into virus-based or protein-based vaccines (see Figure 2). The virus-based vaccines can consist of inactivated virus that is no longer infectious, or live-attenuated virus. Since whole-inactivated viruses do not replicate, adjuvants are required to stimulate the immune system. Live-attenuated virus vaccines are classically generated by passaging in cell culture until it loses its pathogenic properties and causes only a mild infection upon injection [45, 46]. Protein-based vaccines can consist of a protein purified from the virus or virus-infected cells, recombinant protein or virus-like particles [47, 48]. Virus-like particles consist of the structural viral proteins necessary to form a virus particle, but lack the viral genome and non-structural proteins [49, 50]. Protein-based vaccines require the addition of an Adjuvant to induce a strong immune response. Two COVID-19 vaccines based on these classical plat- forms are currently in clinical trials, one based on

whole-inactivated virus and one consisting of re- combinant protein (see Figure 2 and Table 1).

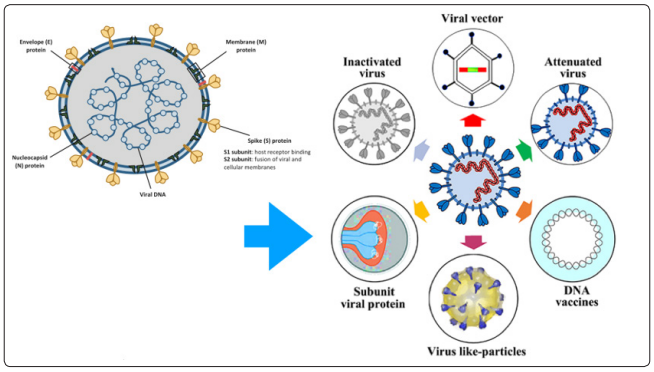
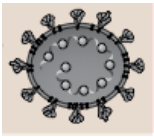
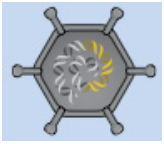
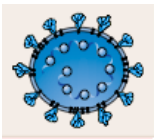
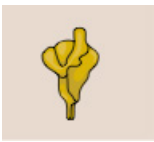
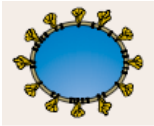
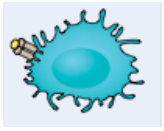


Figure 2: Summary of Strategy types for COVID-19 Vaccine Development

Table 1: An overview of the different vaccine platforms in development against COViD-19

Platform	**Classical**		**Next generation**	
Virus	**Description**	**Morphology**	**Description**	**Morphology**
Type	**Whole-inactivated virus**		**Viral vector**	
Example	Polio vaccine		VSV-Ebola vaccine	
COVID-19	PiCoVacc		AZD1222, Ad5-nCoV	
Clinical Phase	1		1/2/3	
Type	**Live-attenuated virus**		**DNA**	
Example	MMR vaccine		Not currently licensed	
COVID-19	*		INO-4800 i	
Clinical Phase	preclinical stage		1	
Type	**Protein subunit**		**RNA**	
Example	Seasonal influenza vaccine		Not currently licensed	
COVID-19	NVX-CoV2373		mRNA-1273, BNT162	
Clinical Phase	1/2		1/2	
Type	**Virus-like particle**		**Antigenpresenting cells**	
Example	*		Not currently licensed	
COVID-19	1		LV-SMENP-DC, COVID-19/aAPC	
Clinical Phase	preclinical stage		1/2	
*preclinical stage				

The main advantage of next-generation vaccines is that they can be developed based on sequence information alone. If the viral protein(s) important to provide protection from infection or disease, and thus for inclusion in a vaccine (that is, the vaccine antigen), is known the availability of coding sequences for this viral protein(s) suffices to start vaccine development, rather than having to depend on the ability to culture the virus. This makes these platforms highly adaptable and speeds up vaccine development considerably, as is clear from the fact that the majority of COVID-19 vaccine clinical trials currently ongoing involve a next-generation platform. A schematic representation is shown of the classical vaccine platforms that are commonly used for human vaccines, and next-generation platforms, where very few have been licensed for use in humans (see Figure 3). The stage of development for each of these vaccine platforms for COVID-19 vaccine development is shown; online vaccine trackers are available to follow these vaccines through the clinical development and licensing process. Assembled form three identical chains, the S protein is functionally subdivided in S1 and S2 domain; S1 contains the receptor binding domain.

The SARS-CoV-2 structure was reproduced and adapted from the CDC Public Health Image Library. The S protein structure was prepared on the PyMol molecular graphics system [51, 52].

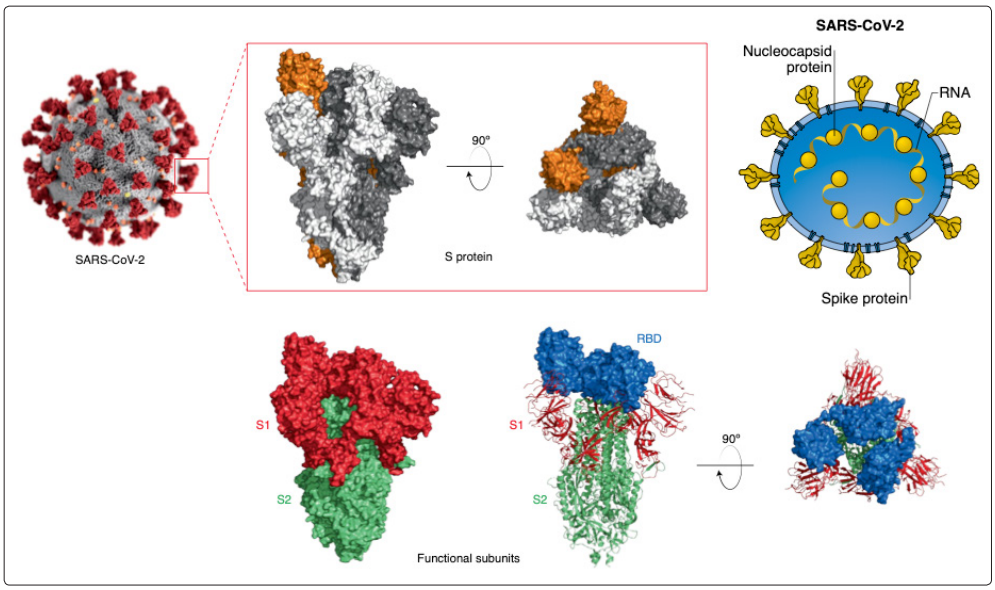


Figure 3: E The Spike Protein (S protein) Protruding from the Coronavirus SARS-CoV-2 is the Primary Target for Various Ongoing Vaccine development

Next-generation Vaccines through Nanotechnology

Nanoparticles Platform for Immunological Considerations

Viruses are nanoscale objects and therefore can be regarded as naturally occurring nanomaterials; per that definition, LAVs, IVs and viral vectors are nanotechnologies [13, 53, 54]. Nanoparticles and viruses operate at the same length scale, this is what makes nanotechnology approaches in vaccine development and immuno-engineering so powerful. Nanoparticles, natural or synthetic, mimic the structural features of viruses whereas chemical biology, biotechnology and Nanochemistry enables the development of next-generation designer vaccine technologies. From a vaccine technology development point of view, this is an exciting time and novel technologies and approaches are poised to make a clinical impact for the first time. Protein nanoparticles and their size; sizes for the synthetic Nanocarriers vary between 10–1000 nm. Components of nanoparticle-based vaccines and key steps involved in nanoparticles-based vaccine processing by APCs (see Figure 4) [55-58]. The antigenic cargo is processed by the APC and epitopes are presented by MHC-I and MHC-II leading to production of CD8+ cytotoxic T cells or CD4+ T helper cells required for antiviral antibody production (or a combination thereof). Rapid development of an efficacious vaccine against the viral pathogen severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is essential, but evaluate research on the potential risk of immune enhancement of disease by vaccines and viral infections, including coronavirus infections, together with emerging data about COVID-19 disease. Vaccine-associated enhanced disease has been rarely encountered with existing vaccines or viral infections. Rigorous clinical trial design and post licensure surveillance should provide a reliable strategy to identify adverse events, including the potential for enhanced severity of COVID-19 disease, after vaccination.

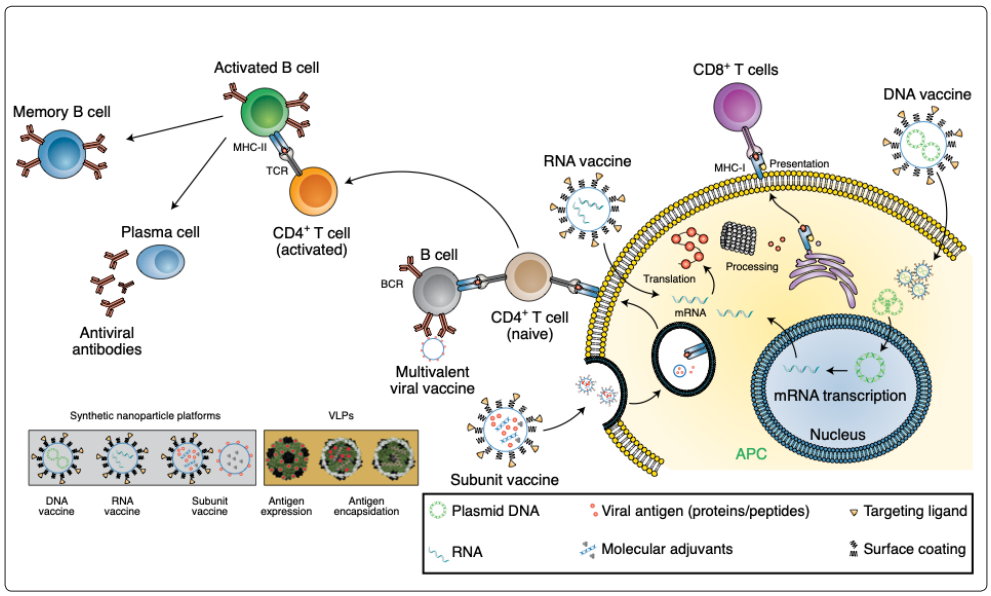


Figure 4: Vaccine processing and immune response Nanoparticle-based vaccine formulations

Recent Nanotechnology Based Vaccine Design

Nano-carriers have potential to design risk-free and effective immunization strategies for severe acute respiratory syndrome coronavirus 2 vaccine candidates such as protein constructs and nucleic acids. We discuss recent as well as ongoing nanotechnology-based therapeutic and prophylactic strategies to fight against this COVID-19 pandemic, outlining the key areas to step in. Nanoparticles and viruses operate at the same size scale; therefore, nanoparticles have an ability to enter cells to enable expression of antigens from delivered nucleic acids (mRNA and DNA vaccines) and/or directly target immune cells for delivery of antigens (subunit vaccines). Many vaccine technologies employ these direct benefits by encapsulating genomic material or protein/peptide antigens in nanoparticles such as lipid nanoparticles (LNPs) or other viruses such as Ads. As summarized in Table 2, BioNTech/Pfizer and Moderna encapsulate their mRNA vaccines within LNPs while the University of Oxford/ Astrazeneca (from here on out referred to as Oxford/ Astrazeneca) and CanSino incorporate antigen-encoding sequences within the DNA carried by Ads. Novavax decorates recombinant S proteins of SARS-CoV-2 onto their proprietary virus like particle (VLP) nanoparticles [13, 59-65]. Figure 5 graphs detailing the vaccines currently in development for SARS-CoV-2 according to the WHO and the Milken Institute as of August 11, 2020 showed 202 vaccine candidates, the vaccines by type, the number of vaccines using adjuvants, and the vaccine candidates in clinical trials including executive research trend. The six major types of candidate vaccine for coronavirus disease 2019 (COVID-19) are illustrated (live attenuated virus, recombinant viral vectored, inactivated virus, protein subunit, virus-like particles and nucleic acid based), showing the number of candidate vaccines that are currently under clinical and preclinical development. The nucleic acid-based platform includes both mRNA vaccines (6 clinical and 16 preclinical) and plasmid DNA vaccines (4 clinical and 11 preclinical) as shown in Figure 6.

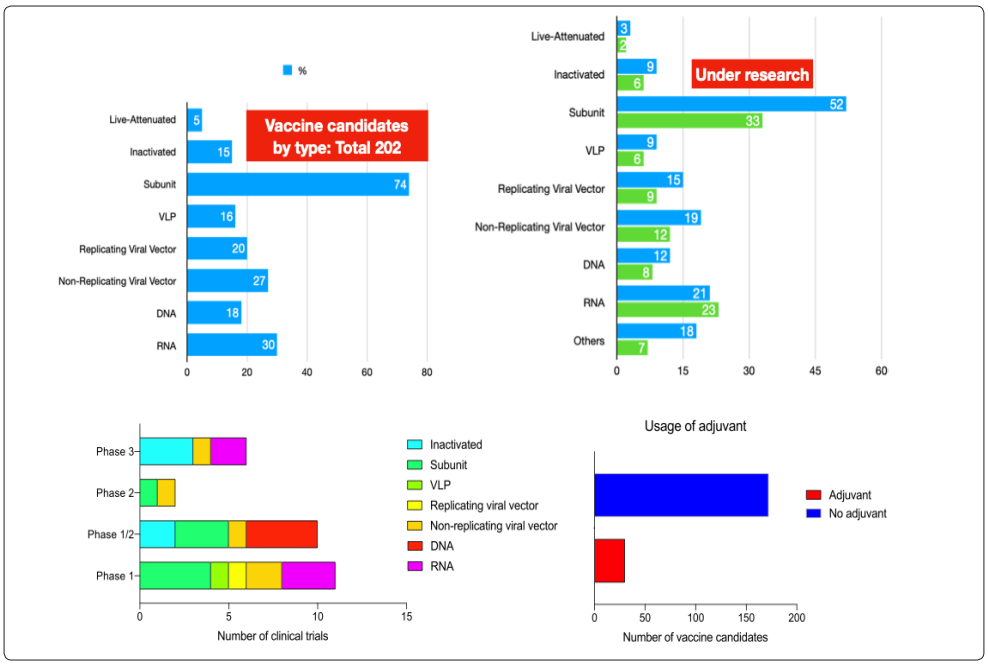


Figure 5: Graphs detailing the vaccines currently in development for SARS-CoV-2 according to the WHO

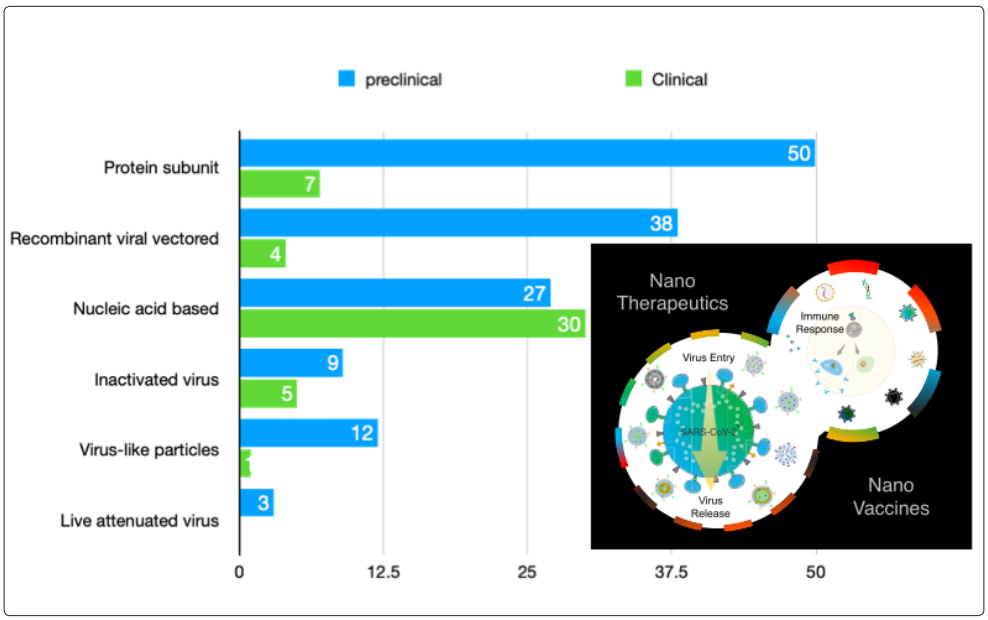


Figure 6: The global CoVID-19 vaccine landscape.

Table 2: Nanoparticle-based COVID-19 Vaccine Candidates in Clinical Evaluation

Type of vaccine	Platform	Clinical trial status	Developer
LNP encapsulated mRNA	RNA	Phase 3 (NCT04470427)	Moderna/ NIAID
LNP encapsulated mRNA	RNA	Phase 1/2 (2020-001038-36) (NCT04368728)	BioNJTech/ Fosum Pharma/Pfizer
LNP-nCoVsaRNA	RNA	Phase 1 (ISRCTN17072692)	Imperial College London
Full length recombinant SARS-CoV-2 glycoprotein nanoparticle	Protein subunit	Phase 1⁄2 (NCT04368988)	Novavax

Nanotechnology Applications for Global COVID-19 Vaccine Landscape

COVID-19 is known to be very contagious and has many routes of transmission. Recent studies have shown that SARS-CoV-2 spread through micro-droplets emitted mainly from person to person or through touching contaminated surfaces. This is where nanotechnology offers a lot of opportunities for the development of more efficient and promising disinfectant systems. Studies based on nanotechnology for the development of new materials, open perspectives for surfaces with self- cleaning properties. Figure 7 showed that the schematic representation of SARS-CoV-2 infection and the nanotechnologies tools to prevent and control COVID-19 is well illustrated. The virus entering into cell by the angiotensin-converting enzyme 2 (ACE2) receptor and use the host cell's machinery to reproduce and contaminate new host cells. Nano-based materials could help in: enhanced the speed and sensitivity of virus detection; help in the development of more efficient and safer treatment and vaccines and improve the safety of healthcare workers through the development of Nanobased Personal Protective equipment (PPE) [66-68]. The use of nanomaterials can give new properties making the materials more resistant, efficacious, comfortable and safer for use. Addition- ally, graphene as a sensing material is selected, and SARS-CoV-2 spike antibody is conjugated onto the graphene sheet via an interfacing molecule as a probe linker (see Figure 7). Recently, nanoparticles have caught attention as a promising approach to the development of a new generation of vaccines, since the nanoparticles can both serve as a carrier for the antigen and behave as an adjuvant in many cases. In addition, Nanobased vaccines can protect antigens against premature degradation and provide sustained release, enhanced antigen stability, and provide targeted de- livery of an immunogen, as well as increase the period of antigen exposure and uptake by antigen presenting cells (APCs). Furthermore, nanoparticles are able to interact with immune machineries, inducing cellular and humoral immunological responses. For an instance, gold nanoparticles coated with thiol-modified antisense oligonucleotides (ASOs), specific for the N gene of SARS-CoV-2, capable of diagnosing positive cases in 10 min. According to the study, changes in surface plasmon resonance observed using a UV–vis spectrophotometer indicate the selective agglomeration of coated nanoparticles in the presence of a SARS- CoV-2 target RNA sequence (see Figure 8). With the addition of RNAseH, the hybrid RNA chain breaks down, leading to the formation of a visually detectable precipitate. Consequently, advances in bio/nanotechnology and advanced Nano/manufacturing coupled with open reporting and data sharing lay the foundation for rapid development of innovative vaccine technologies to make an impact during the COVID-19 pandemic. While any vaccine is still months-to-years away from clinical reality, the parallel and rapid efforts from academic laboratories and industry provide hope for success. A plethora of nanotechnology platforms are being pivoted against SARS-CoV-2; while highly promising, many of these may be several years away from deployment and therefore may not have an impact on the SARS-CoV-2 pandemic. Figure 9 showed the distribution of patents dealing with SARS-CoV viruses within the coronavirus and Nano search defined with possible mechanisms of the antiviral activity of Ag S Nano-crystals detailed on 2 the above nanoparticles applications.

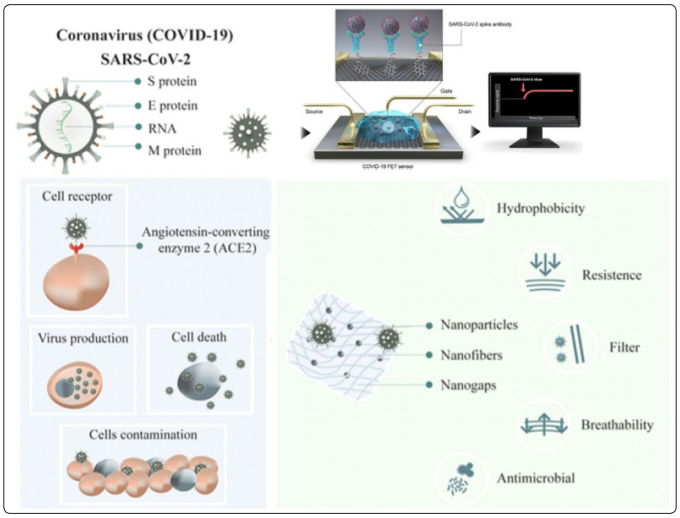


Figure 7: Schematic Representation of SARS-CoV-2 Infection and the Nanotechnologies Tools To Prevent and Control COVID-19.

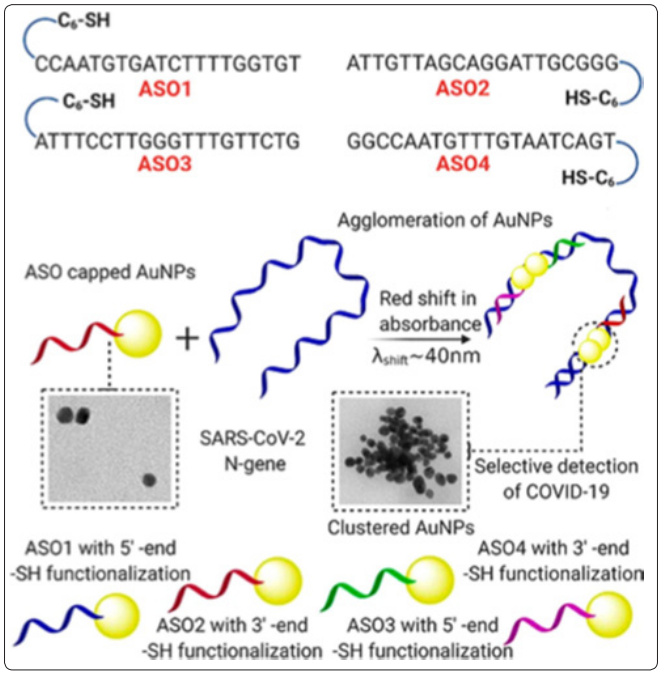


Figure 8: The Representative Schemes for Differentially Functionalized ASOs with their Sequences

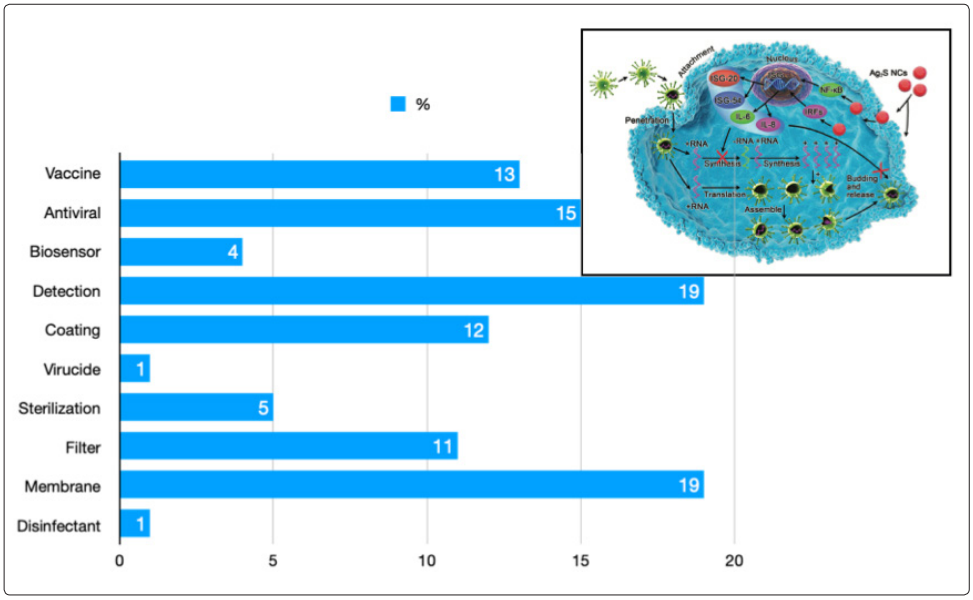


Figure 9: Distribution of Patents Dealing with SARS-CoV Viruses within the Coronavirus and Nano Search Defined with Possible Mechanisms of the Antiviral Activity of Ag S Nano-crystals

Future Nano-Vaccine Models of Relevance in the Fight Against COVID-19

Vaccination is one of the greatest medicine interventions in the benefit of global health. In the case of respiratory diseases, the current flu vaccines successfully con- tribute to the fight against season- al influenza. Vaccines rely on the induction of adaptive immune responses able to neutralize the pathogen upon entering the organisms. Although vaccines can be formulated with the pathogen it- self after attenuation or inactivation processes by chemical or physical treatments, the ideal vaccines are likely constituted by fractions of the pathogen to achieve enhanced safety for the subject (absence of reactogenicity and no risk of pathogen reversion) and the production personnel. In particular for viral infections, vaccine developers should pay special attention to guarantee that the vaccine candidate does not induce immuno-pathology (infiltration of eosinophils into the lungs after the virus challenge), which exacerbates lung inflammation. This phenomenon has been described for coronavirus vaccine candidates In this regard, nanotechnology has much to offer to the fight against COVID-19 through the generation of Nanovaccines [17, 19, 69-73], which comprise nanoparticles acting as delivery vehicles of the antigens that trigger protective immunity. It is well known that particulate antigenic complexes are efficiently captured by the antigen processing cells, which are fundamental to induce adaptive immune responses that cope with the pathogen once it enters the organism. Moreover, several nanomaterials have intrinsic immunostimulatory properties that favor vaccine activity. Therefore nanomaterials can be used for the design of efficient vaccines. In this regard, VLPs are a prominent approach to develop Nanovaccines since they are highly immunogenic macromolecular complexes that are safe (they do not contain the pathogen genome) and typically resemble the antigenic properties of the pathogen. The successful recombinant vaccines in the market are, in fact, based on VLPs (vaccines against the Hepatitis B Virus and Human Papillomavirus). Besides VLPs, other nanoparticles have been exploited in the vaccinology field; including liposomes and particles composed of gold, chitosan, and PLGA; among others. As shown in Figure 10, some strategies used for the interaction between viruses and Nanosystems that could be explored against COVID-19 and terminate it eventually.

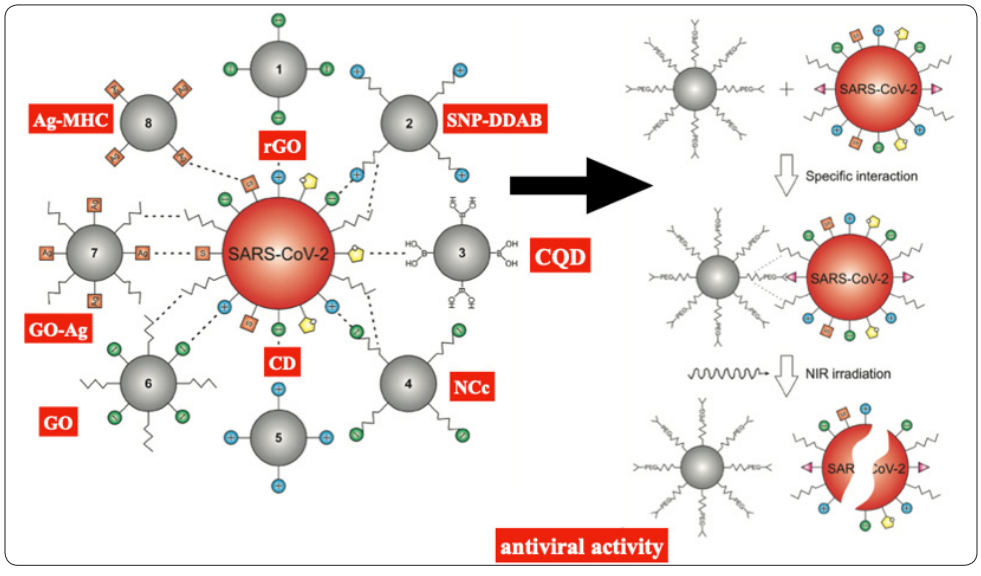


Figure 10: Strategies Used for the Interaction Between Viruses and Nanosystems that Could be ex- Plored Against COVID-19

The above presented analysis revealed that nanotechnology has allowed the development of several biosensors, Nanovaccines and antiviral composites with high effectivity for close related viruses, thus this compilation is a valuable guide for the development of agents against SARS-CoV-2. Therefore, nanotechnology has much to offer in the fight against the COVID-19 pandemic and the following months will be critical to exploit the unique properties of nanosized sensors, vaccines and antiviral nanocomposites in the fight against this unprecedented global health crisis at multiple levels; especially in the prevention of viral spread and infection establishment, but also in a timely and accurate diagnostic.

Discussion

The COVID-19 pandemic has fast-tracked their development as vaccine platforms for emerging viruses. If current predictions become reality, the first vaccines against COVID-19 will be licensed within a year. These licensed vaccines are likely to include some of the next-generation platforms described here. This in itself will be a major public health achievement, yet will simultaneously result in a permanent change to the vaccine platform landscape and an increased vaccine manufacturing capacity for these novel platforms. Plans should be developed to ensure that the large-scale manufacturing infrastructure being built now to respond to the COVID-19 pandemic is maintained for potential future vaccine needs, as has been done for influenza vaccines. Once next-generation platforms are licensed, their use for other pathogens or disease indications are likely to become more easily attainable. Since these platforms only require sequence information to initiate vaccine development, this will increase the flexibility to adapt vaccines to antigenic changes in circulating strains, and to newly emerging viruses in general. The wider array of possibilities for pre-emptive and reactive vaccine design, as well as faster development and manufacturing options, will permanently change our ability to rapidly respond to emerging viruses. As such, the investments made now in vaccine platform development and manufacturing will pay off when we are able to respond even faster when a new virus emerges in the future.

Conclusion

The current global health threat by the novel coronavirus disease COVID-19 requires an urgent deployment of advanced therapeutic options available. The role of nanotechnology is highly relevant to counter this coronavirus. Nano intervention is discussed in terms of designing effective Nanocarriers to counter the conventional limitations of antiviral and biological therapeutics. This strategy directs the safe and effective delivery of available therapeutic options using engineered Nanocarriers, blocking the initial interactions of viral spike glycoprotein with host cell surface receptors, and disruption of virion construction. Controlling and eliminating the spread and reoccurrence of this pandemic demands a safe and effective vaccine strategy.

Transparency Declarations

None to declare.

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