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Nanovaccine approach to prevent binding of SARS-CoV-2 surface glycoprotein with ACE2 and TMPRSS2 receptor

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Abstract
The present worldwide health risk through the COVID-19 needs a quick arrangement of modern therapeutic strategies available. The role of nanomedicine is highly suitable against this "entity". Nano interference is argued in terms of developing significant nanocarriers to counter the standard barriers of antiviral and biological therapeutics. This way promotes the safe and possible delivery of available therapeutic strategies by modified nanocarriers, inhibiting the primary interactions of spike glycoprotein to host cell surface receptors, and disturb vision formation. Controlling and terminating the spread and reappearance of this pandemic commands a safe and beneficial vaccine options. Nanocarriers have probable to outline risk-free and possible immunization ways for SARS-CoV-2 vaccine candidates like protein constructs and nucleic acids.

Keywords: SARS-CoV-2, immunopathology, nanomedicine, drug delivery, vaccine

Introduction
The novel coronavirus, officially recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative factor of the COVID-19 disease epidemics. Wuhan (China) was the starting center of this pandemic, and now with more than 8.3 million recorded infections and over 449,099 deaths as of June 17, 2020. The human race is also encountering a crisis condition because of compulsory quarantines and lockdowns [1]. α, β, γ, and δ are the four classes of the coronavirus family, all consisting ass (+) RNA genome. The membrane envelops enclosing the viral genome are expressed with glycoprotein spike transmembrane proteins. The word "coronavirus" is termed for the club-shaped protein spikes on their outer surface when observed by a transmission electron microscope. The causative agent behind the COVID-19 pandemic belongs to the β class [2]. The similar coronavirus class was responsible for the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). Fever, dry cough, fatigue, and breathing problem are the beginning indications of a SARS-CoV-2 infected patient. This is the more infectious virus in its class and mainly effects the lower respiratory system leading viral pneumonia. Vital organs involving cardiac, liver, kidneys, gastrointestinal tract, and the central nervous system may also be affected, causing multiple organ complicacies [3].

SARS-CoV-2 life cycle and pathophysiology
SARS-CoV-2 has ass RNA genome of nearly 34 kb and a nucleocapsid of helical symmetry. The integrity of the SARS-CoV-2 particle is conserved through 4 proteins. The spike glycoprotein that allows the attachment of the virus to host cells attained through membrane fusion. The huge membrane protein that maintains the membrane integrity of the viral particle. The envelope protein is the smallest protein and plays a structural role and helps in assembly and budding. The nucleocapsid protein predominantly binds to the SARS-CoV-2 RNA and supports nucleocapsid formation [4]. The ACE2 is the key receptor for entry of SARS-CoV-2 in the cells of the host. Cellular proteases (TMPRSS2) control the viral entry mechanism through splitting the spike protein and initiating further penetration mechanisms (Fig. 1). Spike proteins promote the entry of the virus into host cells and are the area of marks for different antibodies. The surface glycoprotein of visions is the location for recognition and membrane fusion. The spike protein (a trimer) gets divided into S1 and S2 subunits. The S1 subunits include the receptor binding domain (RBD) and are formed in post-transfusion conformation [5].

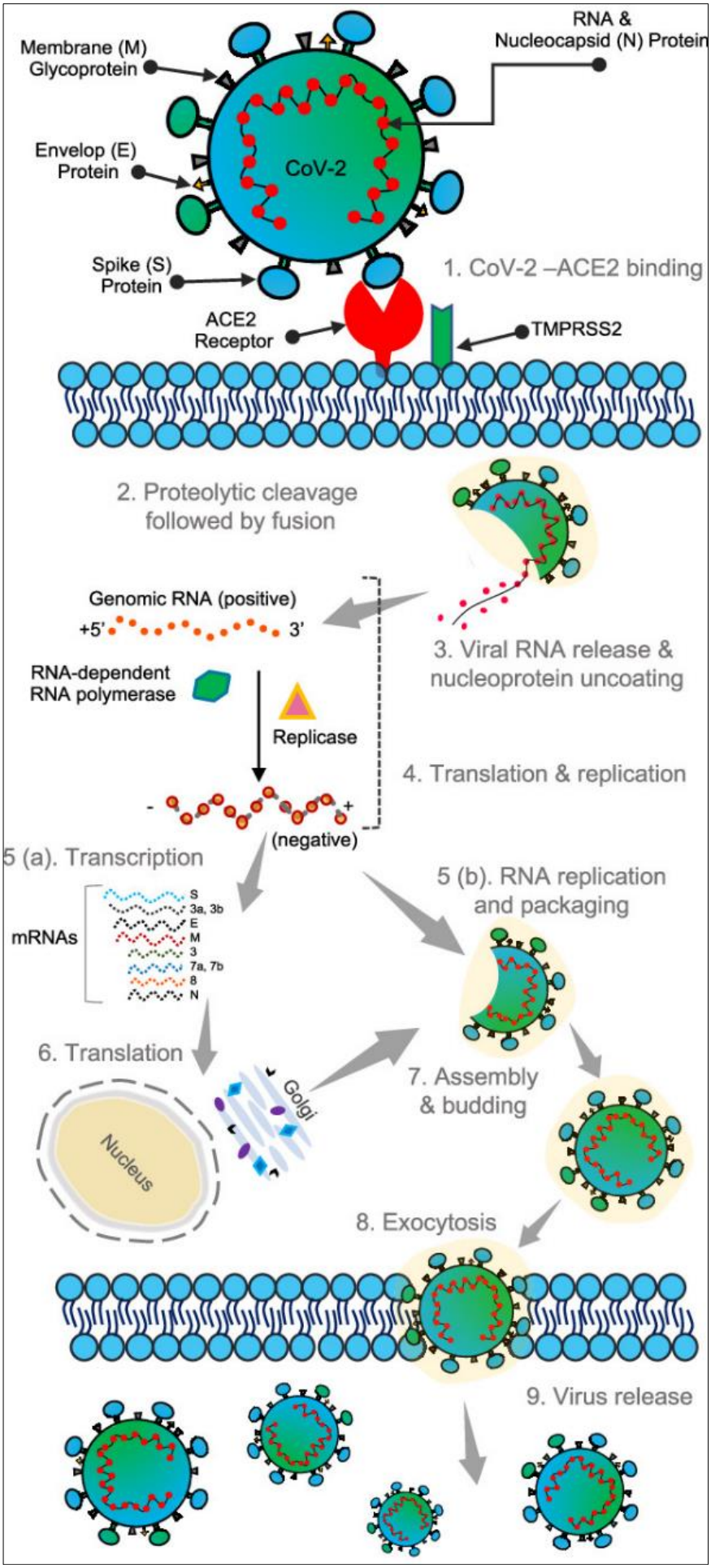

Fig 1: Life cycle of SARS-CoV-2

While S1 directly attaches to the peptidase domain of the ACE2, S2 subunits assist in the membrane fusion that is important for viral infection. S2 contains cleavage sites and is digested through host proteases. ACE2 is a dimer of the 2 units and holds the RBD in its peptidase domain. The contact between the ACE2 and SARS-CoV-2 is facilitated through polar interactions. An arch-shaped helix of the peptidase domain of ACE2 links with the loop area of the RBD of the spike protein (Fig. 2). The other helix and loops combine the antiparallel strands and coordinate the peptidase domain to the RBD [6]. The amino acid interactions that are examined in RBD of SARS-CoV-2 and the peptidase domain of ACE2 are concluded significant features for the blocker design. Investigation of the SARS-CoV-2 vision design via TEM discloses a roughly spherical or moderately pleiomorphic morphology. The vision diameter is investigated to have a wide distribution of 80-160 nm and a dense mass of nucleic acid and nucleocapsid protein under a well-defined lipid bilayer. TEM also shows the nail-like shape of the SARS-CoV-2 spikes a broad head (7 nm) and a long body (23 nm) [7].

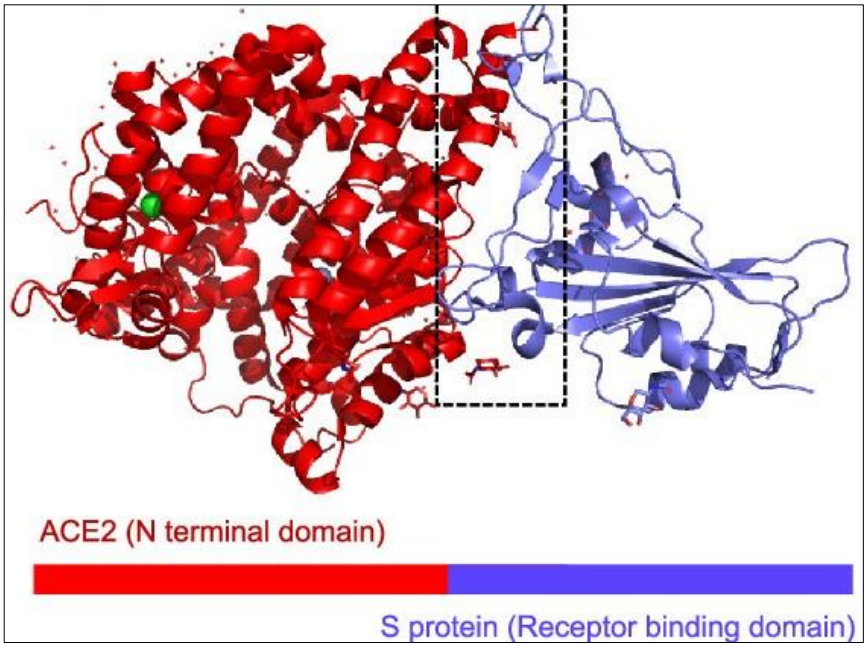

Fig 2: Structurally interaction of ACE2-RBD

After the separation of the S1 subunit from the spike protein, a conformational change was examined in the S2 subunit. This change from a compressed form to a nail-like shape was confirmed through different scientists and is called a post-fusion state. A 3D map and 2D projection images of S2 protein at the post-fusion state with negative staining EM as well as biophysical tests and Cryo-EM structure evaluation that SARS-CoV-2 spike protein binds tightly to ACE2 host cell receptors (>10 times) when compared to the spike protein of SARS-CoV-2 [8].

Innate and adaptive immune response

Both innate and adaptive immunity are initiated through the SARS-CoV-2 infection. Humoral and cell-mediated immunity is further recorded to play a defensive role to the infection. While inflammation and dysfunctional immune responses lead in both local and systemic tissue harm. Pathogen-associated molecular patterns (PAMPs) recognition activates the innate immune response, further triggering signaling pathways and nuclear translocation of transcription factors (NF-κB, IRF3, IRF7). These transcription factors further lead in the initiation of tumor necrosis factors (TNF), chemokine-dependent inflammatory responses (by NF-κB), and type-I interferon (IFN-α and β) dependent antiviral innate immune responses to terminate the viral infection [9]. Furthermore, adaptive immune responses are particular (for virus or virally cells infected) and become detectable after 1 week of the disease onset. The defensive role of humoral (B-cell) immune response is mainly carried through antibody secretion to neutralize the SARS-CoV-2 after particularly inhibiting the virus-host interaction. $CD8^+$ T-cell response against viral infection is beneficial for the direct killing of the infected cells, whereas $CD4^+$ T-cells help in cytokine production and priming of B-cells and $CD8^+$ T-cells (Fig. 3) [10].

Organ systems and viral infection

SARS-CoV-2 generally affects the respiratory system first and then spreads systemically to the heart, liver, and kidneys, although it is still uncertain whether the viral infection directly results in organ or tissue injury as observed in COVID-19 patients. It is important to mention that ACE2 is highly expressed in the respiratory tract and other organs and tissues, encompassing the cardiovascular system (CVS), CNS, GIT, and female reproductive systems. In the pulmonary system, higher ACE2 expression leads the alveolar epithelial cells more reachable for SARS-CoV-2 and is clinically presented through the quick progress of pneumonia, proceeding to the acute respiratory distress syndrome (ARDS) and multiple organ failure [11]. In the CVS, cells (heart, endothelial cells) are report a high ACE2 expression, which balance blood pressure and myocardial contractility. SARS-CoV-2 binding to ACE2 can lead in the activation and up regulation of ACE2 downstream signal transduction mechanisms. This includes the activation of the Ras-ERK-AP-1 pathway, which further may activate the C-C motif chemokine ligand 2 (CCL2), which is a pro-fibrosis

factor, resulting in the development of cardiac inflammation and fibrosis [12].

A rise in the levels of myocardial markers (specific and nonspecific) has been recorded in patients and may act as significant tools for examining the level of viral progression to the heart as well as other vital organs. In the CNS, virus may infect the CNS by direct infection injury (blood circulatory and neuronal pathway), hypoxia injury (alveolar, interstitial region, pulmonary edema, and related disorders), immune system (macrophages, microglia, and astrocytes), and ACE2 (capillary endothelium and vascular system). A rise in alveolar gas exchange disorders expresses hypoxia in the CNS which leading to raised anaerobic metabolism in the mitochondria of brain cells [13]. This hypoxia causes to headaches, drowsiness, loss of taste and may cause severe damage to CNS. The extent expression of ACE2 and TMPRSS2 in intestinal epithelial cells involving several organs (duodenum, small intestine, pancreas, and liver) of the gastrointestinal tract chances these cells and organs possible targets of SARS-CoV-2. ACE2 is also much showed in reproductive organs, including in placenta, uterus, and fetal interface of pregnant women, for resist preeclampsia. The presence of ACE2 in fetal tissue may also provide target sites for SARS-CoV-2 binding, leading further morbidity and mortality [14].

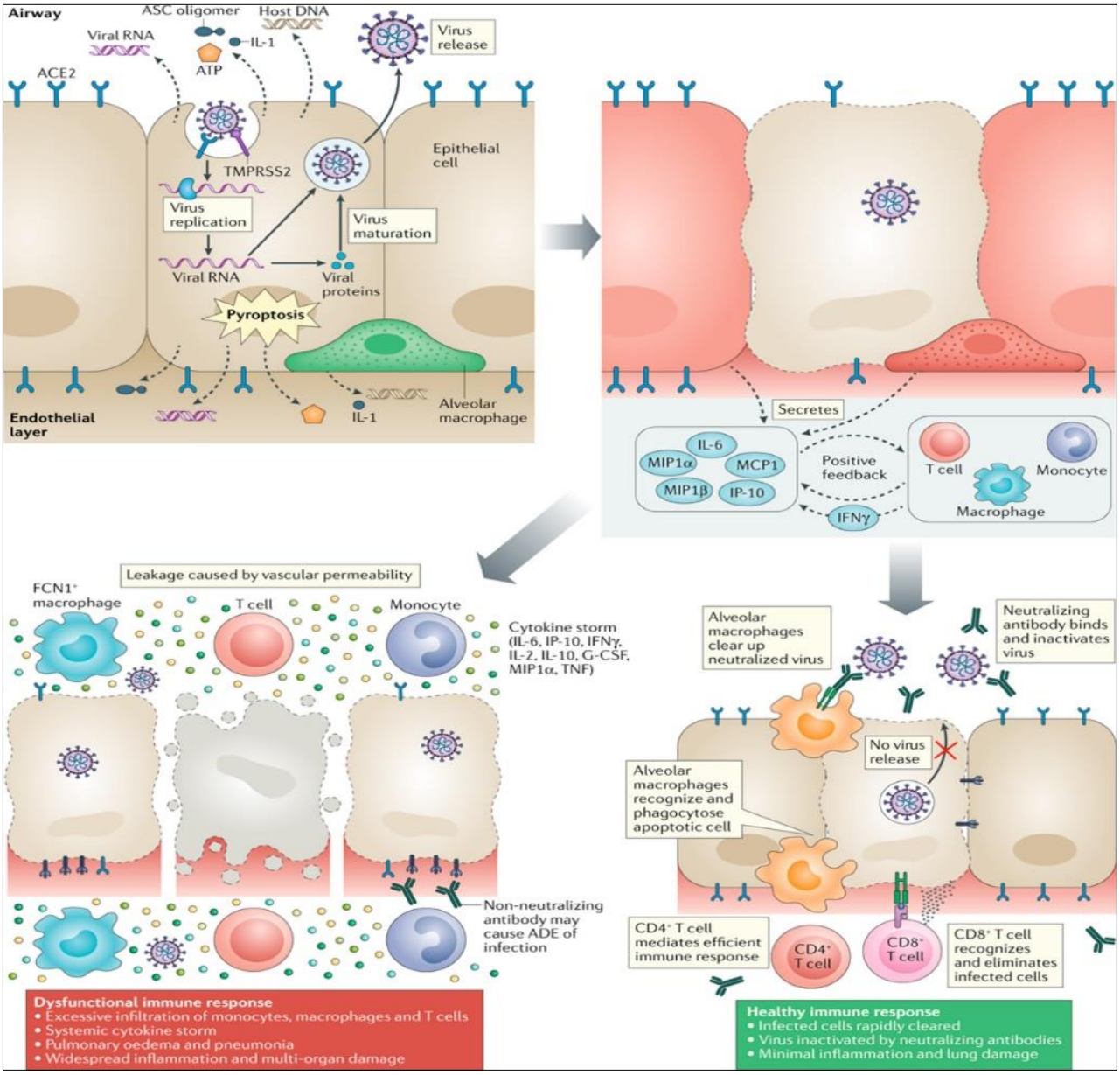

Fig 3: Dysfunctional and healthy immune response during viral infection

Therapeutics production and discovery

The symptomatic treatment path is currently attended in the absence of absolute antiviral treatment against SARS-CoV-2. Artificial intelligence and several computation tools are presently in implement to help the long process of drug discovery and development. Through recently available genetic information and protein structure modeling, different therapeutic options based on drug repurposing are predicted for the immediate treatment of infected patients. Target recognition to stop the pathogenesis of the viral infection holds the key in this production [15]. Viral protease, TMPRSS2, RNA polymerase, and the interaction location of viral spike protein to host receptor ACE2 are among the key targets recognized for repurposing already existing antiviral and advance small molecules under production (Fig. 4). Targeting the SARS-CoV-2 surface spike protein using

neutralizing antibody is another strategy proposed. The focus is basically toward at exploiting recently accessible genetic information to synthesize immunogenic segments against spike protein involving its RBD. Different conventional and new lead screening and lab or animal testing procedures are accounted to boost up this generally slow and challenging [16].

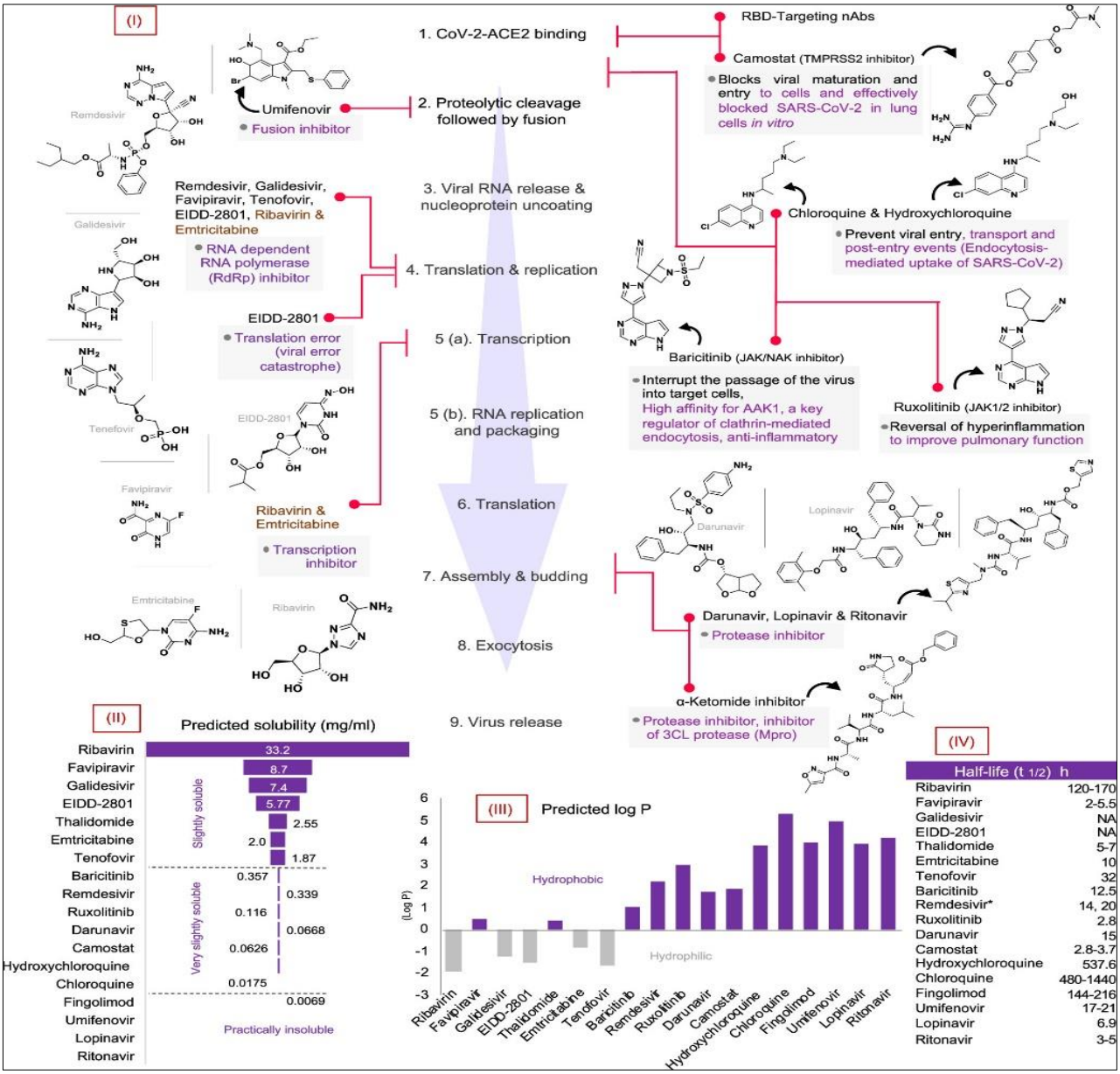

Fig 4: Current antiviral molecules under production for SARS-CoV-2 therapeutics

It is also recommended that a combined neutralizing antibodies can be needed to guarantee prophylaxis. Several targets that are accounted for neutralizing antibody production are based on the information associated to the already known SARS and MERS viral infections. Cytokine therapy (Chemokines and interferons) is also suggested payable to its possible to stop viral replication and since its use in treating SARS viral infections. Targeting the SARS-CoV-2 viral RNA genome by RNA interference (RNAi) or antisense oligonucleotides is further interesting achievement to identify [17]. It is recorded that RNAi like small interfering RNAs (siRNAs), RNA aptamers, and antisense oligonucleotides are may be used in treatment of SARS infection. In some siRNA therapy, various regions are monitored as targets to stop the infection. Another siRNA targets recorded involve RNA polymerase and replicase areas of coronavirus blocking its infection and replication. Antisense oligonucleotides and RNA aptamers are recorded to target the pseudoknot structure and unwinding of the SARS-CoV-2 RNA [18].

SARS-CoV-2 vaccine production

The COVID-19 pandemic has seriously affected human lives, and desperate efforts are being implemented across the world to develop effective vaccines. The primarily vaccine candidate has accounted to human clinical tests as an outcome of fast-tracked production ways and new vaccine methodological platforms. Similarly, for prior therapeutic enhancement, the important genomic match of SARS-CoV-2 with further coronaviruses is helping the vaccine producers to facilitate plans toward the most favorable vaccine candidates [19]. The target strategy for several vaccine candidates is to introduce neutralizing antibodies against the viral spike protein, avoiding the

ACE2-mediated host uptake. In the case of SARS-CoV-2 vaccine production, higher neutralizing antibodies titers and possible safety were recorded with spike protein subunit vaccines when compared to several strategies. Previous coronaviruses vaccine production investigation recommends spike protein subunits, RBD of the S1 subunit, and spike protein or gene as the much suitable target sites. But now, understanding of SARS-CoV-2 particular antigen for ongoing trial vaccine candidates is insufficient [20].

The production of COVID-19 vaccine candidates is depending on further high-tech platforms involving live and killed viruses, replicating or non-replicating viral vectors, DNA and mRNA, virus-like particles, and recombinant based resembles. Several objectives offer major significances like viral vectors with their possible immune response, better protein expression, and extended stability, and DNA or mRNA provides antigen manipulation flexibility, although the recombinant protein-based production destination is helpful to scale-up via existing development capabilities (Table 1) [21]. Boosting the immunogenicity via vaccine adjuvants is also under observation to reduce the feasible dose and to strengthen the therapeutic and safety door. Balanced immune systems and rising disease risk in the elderly population also demand adjuvant options to enhance efficiency of vaccines [22].

Table 1: The SARS-CoV-2 vaccine candidates currently progressed to clinical production

Vaccine and producers	Status	Characteristics
mRNA-1273 (Moderna)	Open label, phase I	Novel LNP-encapsulated mRNA-based vaccine, perfusion stabilized spike protein of SARS-CoV-2
Ad5-nCoV (CanSino Biologicals)	Dose-escalating phase-I	Recombinant novel coronavirus vaccine
INO-4800 (Inovio pharma)	Open-label study, phase-I	DNA plasmid encoding S protein
ChAdOx1 nCoV-19 (COV001) University of Oxford, England	Multicenter study, phase I/II	Adenovirus vaccine vector, vaccine administered intramuscularly
BNT162 BioNTech/ Fosun pharma/ Pfizer	Vaccine candidate selection study, phase I/II	LNP formulation-based mRNA vaccine, 1 candidate utilizes self-amplifying mRNA (saRNA)

Nanomedicine role in COVID-19

The COVID-19 calamities demand a quick investigation of several available nanomedicine techniques. While nanomedicine options are in implementation for the outline of the vaccine carriers, there are insufficient further nanomedicine approaches being examined to trapping the recent epidemic. Therapeutic improvement and challenges against SARS-CoV-2 infection are similar from further infectious diseases as well as cancer immunology investigation [23]. Similarly, the vaccine production break important commonalities with options concluded against earlier known SARS and MERS coronaviruses. Hence, it is worth revisiting these closely related therapeutic or vaccine strategies and associated nanomedicine use, and this way we may design "repurposed nanotechnology" to fast-track the current research (Fig. 5) [24].

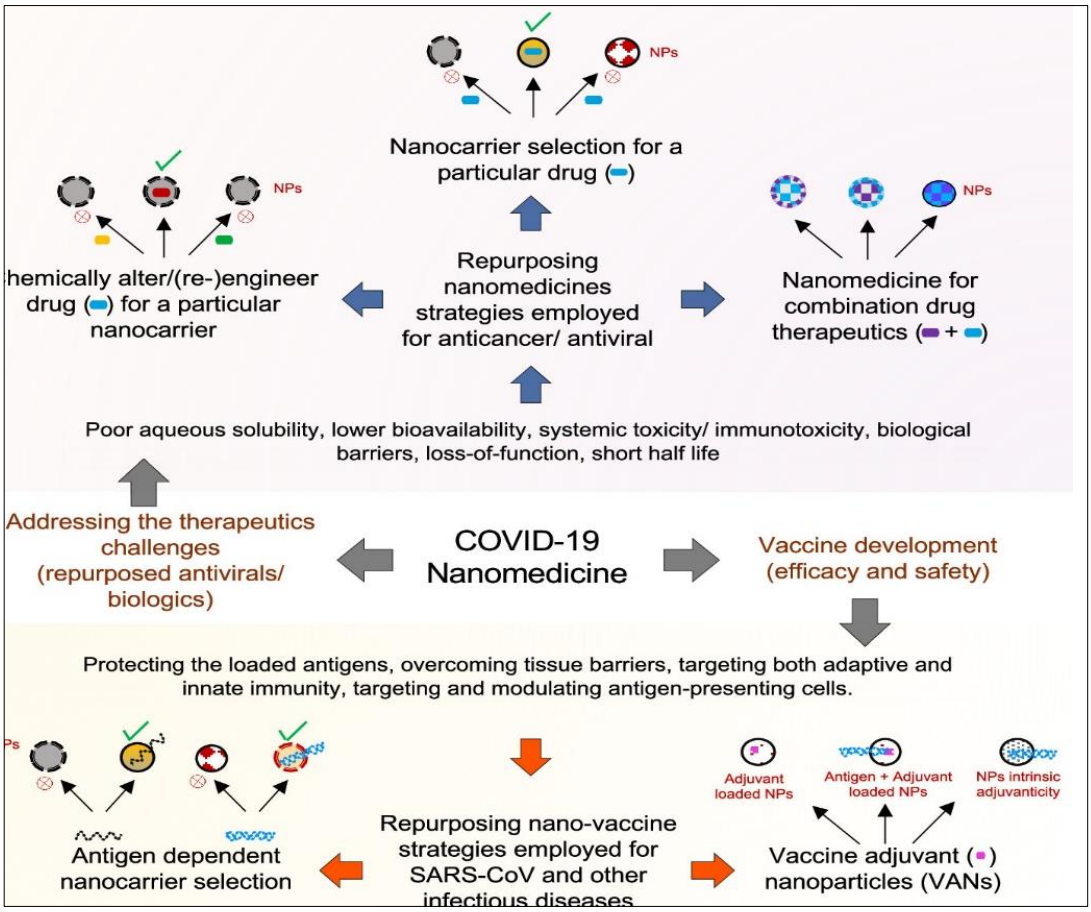

Fig 5: Nanomedicine approaches for COVID-19 therapeutics and vaccine production

Bio molecular and antiviral delivery

Nanoparticle-based therapeutics offers various chances to mark the drawbacks of present antiviral treatment. Further general problems like poor aqueous solubility and low bioavailability may be elucidated through nanocarriers-based antiviral drugs delivery, improving its pharmacokinetics or pharmacodynamics characterizations and leading in dose decrease, lowered toxicity, and enhanced drug bioavailability and conserve prevention of viral spread. Despite viral suppression in the plasma, other challenge including, is the presence of sub-therapeutic concentrations of an antiviral drug in conserve locations [25]. Active targeted nanoparticles offer the chance to cross biological obstacles and maintain therapeutic concentrations in shaded viral reservoirs. It is most feasible to target a particular organ and cellular and intercellular locations included in the pathophysiology of SARS-CoV-2 (ACE2 expressing cells, domains of viral spike protein, *Cathepsin* binding sites). Controlled drug-releasing nanoparticles are the better option to diminish the risk effects of poor patient consent and viral rebound during the time of medication of viral infections [26]. A nanomedicine is thus an important strategy to transform the antivirals repurposing and enhancing the COVID-19 therapeutic management. The role of nanoparticles is conclusive in the improvement of RNAi, neutralizing antibodies, protein, and peptides. An important requirement with such drug candidates is the safety against degradation "loss-of-function" in structural circulation and intracellular delivery. Nanoparticles based delivery (involving prodrug) ensures enhanced half-life of the biologicals through blocking premature drug release and degradation, besides avoidance of renal and hepatic clearance [27]. Engineered nanoparticles offer stealth properties to elude immune recognition and preferable cellular uptake. Targeted nanoparticles give a boosted rate of endocytosis which beneficial delivery of a nanoparticle dose to the target cell. Capability to handle a greater drug load entails the delivery of possible nanoparticles and is much carried with a controlled drug release towards the cells ensuring lowered side effects [28].

Nanomedicine strategies for SARS-CoV-2 therapeutics

A wide range of active moieties involving antivirals, biologics, and nucleic acids may be loaded and delivered through nanoparticles. Securing the suitable therapeutic candidate with nanoparticle, focused for a particular disease situation, is important for the commercial outcome of nanomedicine against the SARS-CoV-2. This approach requires to assign with reformulating authorized as well as under clinical trial drug candidates to boost the Therapeutic Index (TI), primarily through forwarding the obstacles related with the drug molecule and common toxicity or side effects [29]. Preferable perception of drug-specific side effects is the development process and to investigate with select a general strategy to maximize the effect of nanomedicine on the drug's TI. A rational development and interpretation of nanomedicine will need more strategic track progress addressing the right translational obstacle and encouraging further nanomedicine research. Strategic rules suggested for the production of antiviral nanomedicine are of great significance, highlighting the specific field and mechanisms to fast-track the COVID-19 nanomedicine research [30].

Nanomedicine for combined drug therapeutics

Combine drug therapy is further option for treatment of COVID-19, offering various advantages like lower dosages of the individual drugs leading fewer side effects, attaining several and complimenting therapeutic targets, and lowering the likelihood of resistance development. Numerous combinations for novel coronavirus treatment are reported in the WHO landscape description (Table 2). Nanocarriers are intrinsically very functional for the delivery of several drugs with various physicochemical properties favorable the full probable of combine therapies [31]. The flexibility presented through a variation of nanomaterials and fabrication methods allows the outline of drug combinations loaded in nanocarriers with perfect control in protecting synergistic drug ratios, overlapping pharmacokinetics, and lowering combination allied side-effects. Different nanocarrier strategies are described for the co-encapsulation of both hydrophobic and hydrophilic drugs (Fig. 6), performing the sequential release of 2 drugs ratio-metric loading and controlled release of 3 drug candidates, code livery of RNAi/plasmid DNA plus chemotherapeutics, and code livery of siRNA plus miRNA [32].

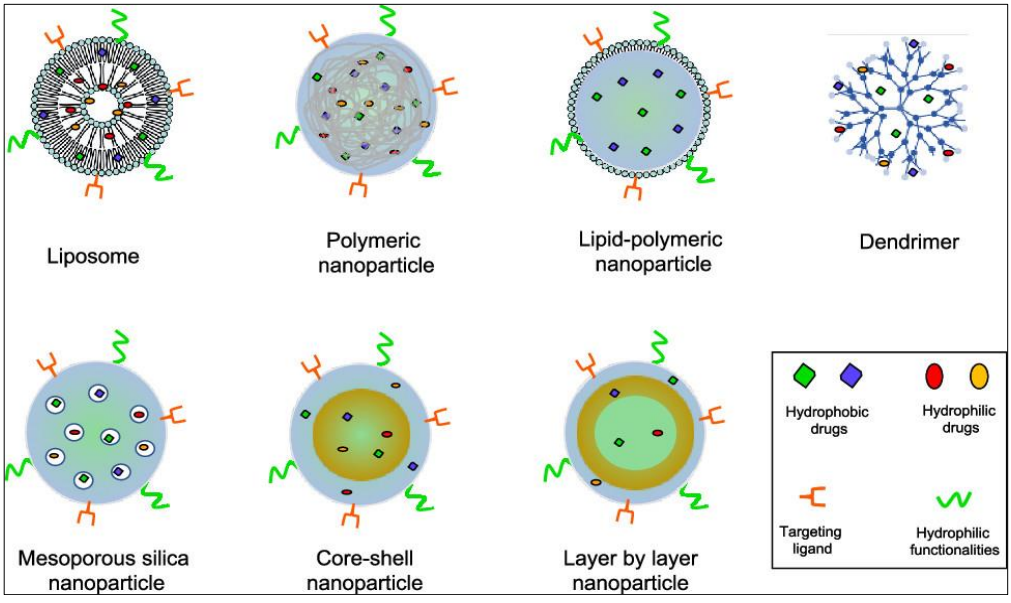

Fig 6: Nanocarrier platforms exploited for combined drug therapeutics

Table 2: Combined drug treatments proposed for SARS-CoV-2

Combined description	Candidates	Status
Protease inhibitors	Ritonavir + lopinavir	Under trial of SARS-CoV-2
(Non-nucleoside + nucleoside) RTase inhibitor	Emtricitabine + tenofovir	Under trial of SARS-CoV-2
(Nucleoside + protease**)** inhibitor	Ribavirin + ritonavir/ lopinavir	Clinical study of SARS
Antiretroviral protease inhibitor + cobicistat	Darunavir + cobicistat	Under trial of SARS-CoV-2
Antiviral + type I interferons	IFN + ribavirin	Clinical study of SARS, MERS
Interferons + antiviral + steroid hormones	IFN + ribavirin + steroids	Clinical study of SARS

Vaccine delivery for SARS-CoV-2

Nanoparticles may be loaded with a variety range of antigenic moieties (physical entrapment or chemical conjugation), and a possible antigenic show makes it a highly preferable substitute in vaccinology when compared to standard approaches. Additionally, protecting the native structure of the antigen, nanoparticles enhance the delivery and presentation of antigens to the antigen presenting cells (APCs) [33]. The major advantages of vaccine nanocarriers are their nanosize, hence several biological systems like viruses (involving SARS-CoV-2) and proteins are nanosized. Nanoparticles may be directed through oral and intranasal routes and subcutaneous and intramuscular injections, allowing a basic significance through overcoming tissue barriers and targeting major areas like lymph nodes, penetrate mucosal, and epithelial barriers (Airway, nasal, and gastrointestinal) [34].

Nanoparticles have seen their capability to target adaptive (T-cells and B-cells) and innate immune systems (macrophages, monocytes, and neutrophils) at the cellular level. Regulating APCs via nanoparticles could be very significant, specifically for COVID-19 vaccine strategies. The capability of nanoparticles to bring antigen to dendritic cells (DCs) through boosting antigen presentation and various mechanisms may enhance T-cell immunity. There are several different nanoparticle-based mechanisms to change the immune response are described (Fig. 7) [35]. To enhance the efficiency and protection of the vaccine approach, a possible significance displayed through nanoparticles is their capability to carry molecular adjuvants or sometimes nanomaterials themselves holds an intrinsic adjuvant property for the loaded antigens. The WHO records the different preclinical stages nanoparticle-based vaccine candidates (Table 3) [36].

Table 3: Nanoparticle-based vaccine candidates in preclinical analysis

Platform	Candidate vaccine type	Producers
Protein subunit	Nanoparticle vaccine + matrix M	Novavax
Protein subunit	Nanoparticle vaccine	LakePharma, Inc.
RNA	LNPs formulation of mRNA	Sanofi Pasteur
RNA	LNPs-encapsulated mRNA	University of Tokyo
RNA	Liposome-encapsulated mRNA	BIOCAD

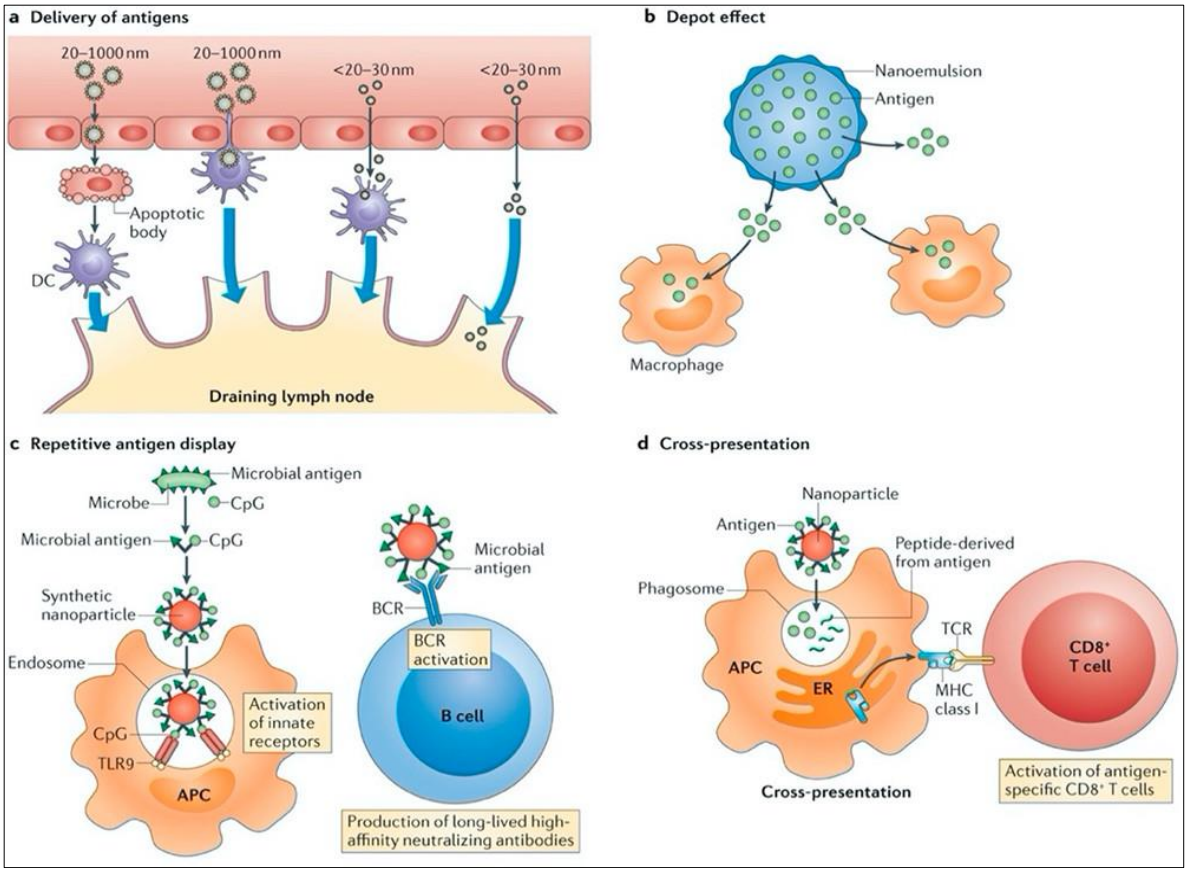

Fig 7: Nanoparticle-based immune response regulation

Challenges and strategy of COVID-19 vaccine

Historically, vaccine shows key successes against acute infectious diseases, where naturally produced immunity (through neutralizing antibodies) gives enduring safety in a patient's section. Primarily, bigger problems in the COVID-19 vaccine research are to diagnostic approaches that regulate the T-cell and B-cell immunity to this virus. Further challenge is the priority of accelerating the production of precise "next-generation" vaccine strategies that can assist particular population subgroups or individuals with committed immunity [37]. Advance strategies to produce nanocarrier-based COVID-19 vaccines are mainly significant and sometimes overlapping when coordinated to nanocarrier-based therapeutics. The Nano vaccine strategy needs a strong attraction towards the cellular expression of the selected antigen, beside with the selection of correspond nanoparticles to introduce complimenting immunomodulatory effects [38].

Selection of antigen-dependent nanocarrier

Loading antigens inside or on the surface of nanocarriers is dependent on various factors involving the biological strength, antigen's physicochemical characteristics, target locations, and needed immunogenic release rate. Physical adsorption of antigens on nanoparticles is depending on its surface charge and no covalent hydrophobic interactions. Antigens with an amphoteric nature are more satisfactory for adsorption or surface immobilization on nanoparticles like chitosan and dextran sulfate-based polymeric nanoparticles, inorganic nanoparticles, and carbon nanotubes [39]. Antigen release in sometimes is predesigned based on the properties of the bio-environment such as pH, ionic strength, and temperature. Encapsulation and matrix entrapment of the antigens in a nanocarrier is different technique used to prevent its biological degradation. Polylactide-coglycolide (PLGA) nanoparticles are ideal for encapsulating antigens and provide controlled or extended biological release [40].

These nanoparticles are successful preclinically in holding antigens like HBsAg, malaria antigens, tetanus toxoid, Listeria monocytogenes antigens, and Bacillus anthracis spores, initiating prolonged cellular and humoral immune response. LNPs are virus-sized (80-200 nm) particles synthesized through the self-assembly of an ionizable cationic lipid. Sustained release kinetics of mRNA expression (Fig. 8) [41] and hence protein translation may be achieved through selecting for intramuscular and intradermal routes, giving high antibody titers, and lymphocytes (B-cells and T-cells) immune responses. Various nanoparticles of these cationic lipids (like DOTAP or DOPE) are formulated with indistinct alterations (like cationic lipids plus cholesterol, cationic lipids plus cholesterol and PEG), where cholesterol is im0plemented to rise strength and also PEG-lipid to rises the formulation half-life [42].

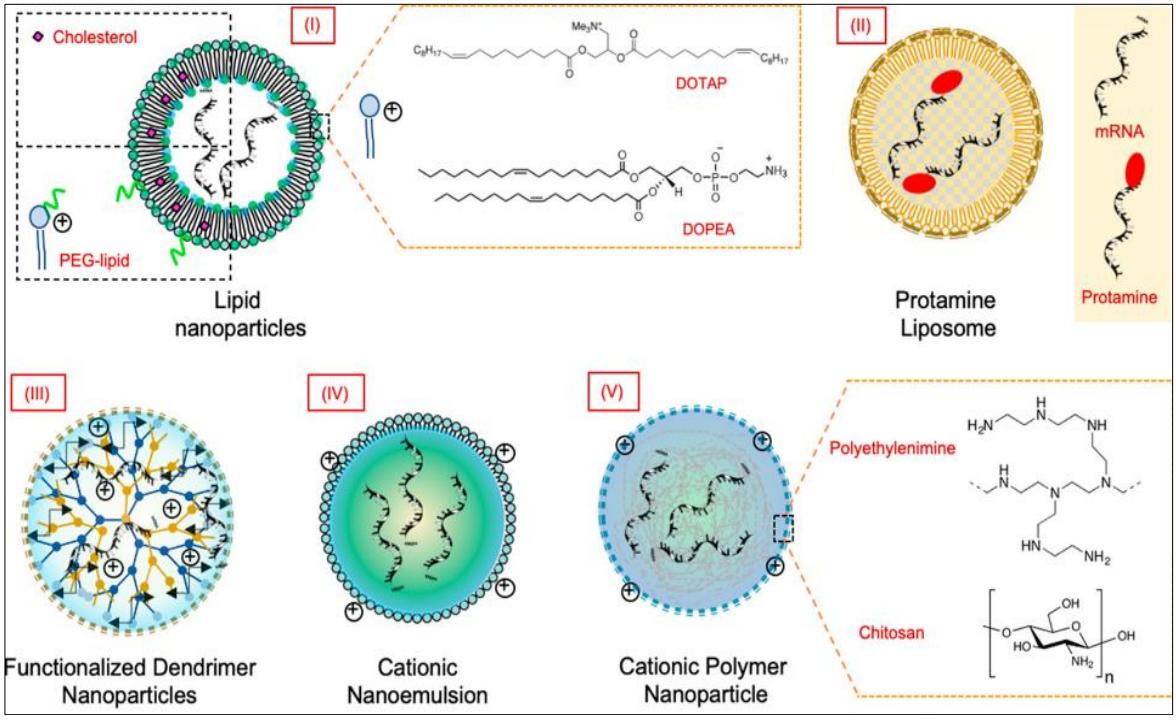

Fig 8: Significant nanocarrier and delivery methods for mRNA delivery

Nanocarriers based on cationic lipids, synthetic and natural polymers, and inorganic particles are presented for DNA-based vaccine formulations. Polymeric nanocarriers encapsulating DNA protect biological inactivation and give controlled release and targeted cell delivery. PLGA nanocarriers are the mostly investigated polymeric platform for DNA vaccine production, expressing enhanced systemic antigen-specific antibody responses [43]. To boost the efficacy of DNA loading and systemic safety, functional or composite PLGA nanoparticles (like cationic glycol-chitosan plus PLGA, PLGA plus PEI) are investigated (Fig. 9). Further suitable documented cationic polymer-based nanocarriers for DNA vaccine outline are chitosan and PEI nanoparticles. Use of PEG functionalization on nanoparticle surfaces is thoroughly usual to introduce stealth characteristics (exhibit undetectable to phagocytes and block reticuloendothelial system clearance), arrest nonspecific protein interaction, lower systemic toxicity, and enhance stability [44].

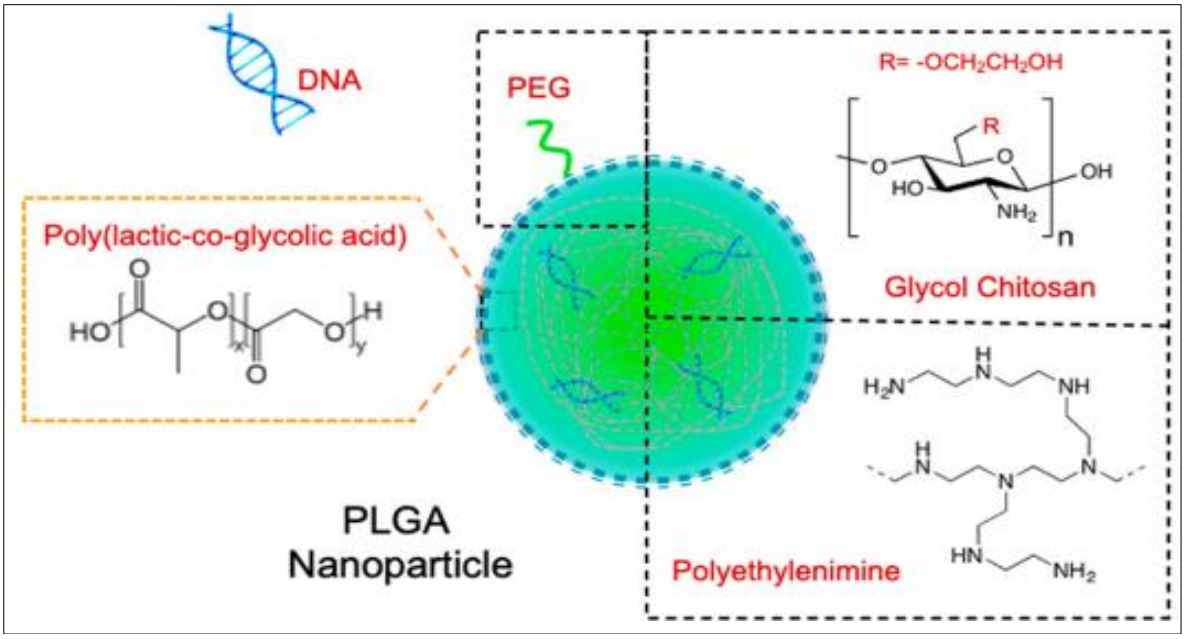

Fig 9: Delivery methods and nanocarriers for DNA vaccines

Vaccine adjuvant nanoparticles

Vaccine adjuvants nanoparticles (VANs) are considered to enhance the overall efficiency and protection of the initiated immune response. Specifically, in COVID-19 pandemic, vaccine adjuvants are particular to lowering the needed antigen dose (dose-sparing), allowing the creation of more units and making it available to major population. Beside many preclinical COVID-19 vaccine candidates, 5 protein subunit vaccine candidates are recorded by a combined antigen and adjuvant [45]. NVX-CoV2373 vaccine (recombinant SARS-CoV-2 glycoprotein) with an adjuvant (matrix M) is currently predicted to move toward clinical tests. Thus, it is beneficial to consider the feasible strategies implemented through VANs in several research investigations that could help to enhance current COVID-19 vaccine platforms. Notifying particular immune cells to board a defensive immune response against a particular antigen is the general mechanism of VANs outlined to enhance efficiency [46].

Adjuvants enhancing protection give a kind of counter-regulatory signal commanding the immune system to evolve a tolerance for incoming antigens. VANs may either act as a nanocarrier for molecular adjuvants or have an inherent physicochemical property to revitalizing pro or anti-immunity pathway. VANs are planned to tackle the restrictions linked to the standard delivery of molecular vaccine adjuvants like rapid bloodstream clearance, systemic distribution, and lack of immune cell targeting or lack of antigen-adjuvant colocalization [47]. Lymph node targeting of VANs is a secured option to reach a beneficially high-dose-sparing effect, while DCs targeting VANs can improve its adjuvanticity. *In-vivo* investigation outcomes against infectious challenge have seen PLGA and calcium phosphate nanoparticles co-encapsulating the antigen and adjuvants to enhance efficiency through boosting antigen uptake, APC activation, and higher antibody titers [48].

Beside of this, co-encapsulation option permits the colocalization of antigen and adjuvant in endosomal or phagosomal compartments promoting the activation of DCs and activates strong cross-presentation and T-cell priming. Synergized activation of APCs and prolonged antibody response was reported with the codelivery of TLR4 and TLR7 small molecule adjuvants by PLGA nanoparticles. VANs are implemented to co-deliver self-antigens or immunoregulatory drugs as adjuvants to actuate antigen particular peripheral tolerance of auto reactive T-cells and prevent any consequential autoimmune response [49]. Nanoparticles because of their intrinsic adjuvanticity (through activating complement system, inducing autophagy and inflammasome activation) are evaluated as VANs. Surface chemistry and nanoparticles hydrophobicity beside with several physicochemical properties are able of selecting these adjuvanticity mechanisms intrinsically [50].

Gold and PLG nanoparticles are recorded to activate NALP3 inflammasome in DCs, leading in enhanced adjuvanticity similar to an alum-mediated adjuvanticity mechanism. Vaccine adjuvants have been implemented to rise the efficacy and the antibody responses of vaccines in the older. O/W emulsion, immune regulating complexes, cationic and anionic liposomes, virosomes, and micro particles are the different adjuvant's techniques produced to enhance the influenza vaccination in the elderly population [51]. For instance, A liposome-based adjuvant AS01 is an important approved technology developed for the herpes zoster subunit vaccine aiming old age population (70 or above). Introduction of adjuvants has seen a lowered risk of pneumonia and influenza in clinical tests and may thus play a key role in stimulating the immune system responses of the older, which other may be modulated for COVID-19 vaccine progress [52].

Conclusion

Nanomedicine can play a pivotal role in advancing COVID-19 treatment and vaccine development. In the absence of a particular antiviral against SARS-CoV-2, current therapeutics target the multifaceted molecular interactions included in viral infections and severely deals repurposing already existing antiviral molecules employed for further RNA viruses. Presently, it is alike significant to view for a preferable nanocarrier delivery to make these repurposed therapeutics secure and more potent. The expedition of COVID-19 vaccine production is very spectacular and

includes advance technological platforms like antigen carriers, viral vectors, and delivery methods. Since most of the COVID-19 vaccine candidates are sophisticated biological moieties, the range of nanocarrier delivery becomes highly pertinent. Some of these opportunities involve nanocarrier-based effective or targeted delivery, better antigen presentation, and the induction of complimenting immunomodulatory effect. An exceptional significance is given to VANs, which either behave as a carrier for molecular adjuvants or produce an anti-immunity effect through their individuals. In this age of advanced nanomedicine, the strategies to implement these technologies and create a frontline role in tackling this outbreak or pandemic [53].

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Author Contribution
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Conflict of interest
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