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Exploring the therapeutic role of nanomedicine in COVID-19 disease

M.D. Imad Uddin◆, B. Teja, A. Sowmya, D. Mounika, Tippu Arif Hussain and Faizan Sayeed*

Department of Pharmacology, Pulla Reddy Institute of Pharmacy, Hyderabad-502313, Telangana State, India.

**Department of Pharmaceutics, Mesco College of Pharmacy, Hyderabad-500006, Telangana State, India.*

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Abstract

COVID-19 or the Coronavirus disease 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a great pandemic. At the time of writing this (29th March 2021), more than 127 M people had affected and 2.78 M had died across the world. Due to the lack of specific treatment against COVID-19, antiviral agents and effective medicines are critically needed to prevent the COVID-19 pandemic. Revised drugs such as remdesivir have revealed a favourable clinical efficacy against COVID-19. This review provides an overview of the origin of coronavirus, the role of nanomedicine in coronavirus, nanomedicine vaccines, diagnosis, and therapy against coronavirus. This information may cause any effect in the disease outbreak. Taking all this under consideration, an effort has been made to teach readers the easiest method of the role of nanomedicine, which may play a pivotal role in the management of diseases.

1. Introduction

Coronaviruses are enveloped positive sense RNA viruses starting from 60 nm to 140 nm in diameter with sharp nail-like projections on their plane and it looks like a crown when observed under the microscope; soit got the name coronavirus. Four types of coronaviruses are there namely; HKU1, NL63, 229E, and OC43 are in transmission in humans, and usually cause mild respiratory diseases (Singhal, 2020). Coronaviruses infect many species of animals, including humans. Some of the animal viruses, such as porcine transmissible gastroenteritis virus (TGEV), and avian infectious bronchitis viruses (IBV), bovine coronavirus (BCoV), have veterinary importance. The murine coronavirus mouse hepatitis virus (MHV) is studied as a model for human disease (Weiss and Martin, 2005).

Nanomedicine is multidisciplinary field, where nanoscience, nanoengineering, and nanotechnology interrelate with the biosciences. Given the extensive scope of nanomedicine, we expect it eventually to involve all aspects of drugs. Also, nanomedicine, such as medicine, can enter the clinics and may be a part of standard medical practice assuming all aspects of the relocation are satisfied, including safety, regulatory, and ethical requirements. It is predicted that nanomedicine will cause the event of higher devices, drugs, and other applications for early diagnoses or treatment of a good range of diseases with high specificity, efficacy, and personalization, with the target being to reinforce patients' quality of life.

Corresponding author: Mr. M.D. Imad Uddin

Associate Professor, Department of Pharmacology, Pulla Reddy Institute of Pharmacy, Hyderabad-502313, Telangana State, India

E-mail: imadpharma111@gmail.com

Tel.: +91-8374175556

Inspite of the necessity to systematize characterization methods, nanoparticles are expected to enhance the detection and diagnosis of diseases. First, smart nanoparticles are often designed to supply differences in the area of interest and report details about the local environment after administration into the body. This information can assist in portraying the fine anatomical structures of organs and labeling tissues with certain markers and enables local read-out of the concentrations of molecules of interest, which helps to research diseases directly inside the human body. Second, nanoparticles are very important constituents of many high-throughput diagnostics machines which will analyze extracted samples (such as blood, tissue, *etc.*) outside of the body for rapidly detecting biological markers and molecular alterations. The capability to examine multiple biomarkers at the same time, it may improve diagnostic accuracy. Furthermore, multifunctional or theranostic nanoparticles which will simultaneously diagnose, treat, and even monitor therapeutic efficacy are being engineered.

Nanoparticles are also being developed for the treatment of disease; NPs are used as delivery vehicles for pharmaceutical agents, as bioactive materials, or as essential components in implants. In the case of delivery, nanoparticle-based carrier systems have a particular ability to cross biological barriers. Thus, nanoparticles can get into tumors through their localized leaky vasculature and are retained because of poor lymphatic drainage in the tumor micro-environment. This passive targeting is called the improved permeation and retention (EPR) effect.There is an current debate in the literature concerning the effectiveness of active, *i.e.*, ligand/receptor-mediated targeting,*versus* passive targeting, but any carrier has to be delivered to the given site before it bind to cell surface receptors or else be retained by other effects. (Pelaz *et al.*, 2017).

Nanomedicine affects all fields of medicine, and it has been considered a crucial instrument for novel diagnostics, medical imaging, nanotherapeutics, vaccines and to evolve biomaterials for regenerative

medicine. Soft nanomaterials obtained from polymers (polymeric nanoparticles), lipids (lipid-solid nanoparticles, nanostructured lipid carriers, liposomes), surfactants (microemulsion, nano-emulsions, liquid crystals), and proteins (protein nanoparticles) have been applied in nanomedicine, especially for drug delivery. The immensity of interactions between nanomaterials and tissues/biological molecules is the base for their use for various medical applications. Drug-based nanoparticles have been developed for many years, and several others are under clinical trials for cancer, neurodegenerative, inflammatory, cardiovascular and infectious diseases, although only a few of them are approved for human use (Mainardes and Diedrich, 2020).

Applications of nanotechnologies in medicine are particularly favorable, and areas like disease diagnosis, drug delivery targeted at specific sites within the body, and molecular imaging are being effectively investigated and a few products are undergoing clinical trials. Nanotechnology is comparatively new. Inspite of the fact that the complete scope of contributions these technological advances will make in medicine is undetected, recent advances suggested nanotechnology will have an intense impact on disease prevention, diagnosis, and treatment. The present generation of medicines is principally based on small molecules with a mass of 1000 Da or less that circulate systemically. Usual detrimental result of systemic biodistribution include toxicity to non-target tissues, difficulty in maintaining drug concentrations within therapeutic windows, and metabolism and excretion of drugs, all of which may minimie efficacy. Nanotechnology-based delivery systems could alleviate these difficulties by merging tissue-or organ-specific targeting with therapeutic action. Multifaceted nanodelivery systems could also combine targeting, diagnostic, and therapeutic actions. More than 90 years ago, Nobel laureate German immunologist, Paul Ehrlich proposed the so-called magic bullets artificial biochemical agents that would carry and release drugs at only preferred sites in the body. Targeting the delivery of drugs to diseased lesions is one of the necessary features of the drug delivery systems. To carry an adequate dose of the drug to the lesion, suitable carriers of drugs are required. Although, chances to develop nanotechnology-based efficient drug delivery systems increase into all therapeutic classes of pharmaceuticals, the development of effective treatment procedures for the respiratory, central nervous system, and cardio respiratory disorders remains a financially and therapeutically important need. Many therapeutic agents have not been victorious because of their limited capability to reach the target tissue.

Moreover, quicker growth opportunities are anticipated in developing delivery systems for anticancer agents, hormones, and vaccines owing to safety and efficacy limitations in their standard administration procedures. For instance, in cancer chemotherapy, cytostatic drugs damage both malignant and normal cells alike. Thus, a drug delivery strategy that selectively targets the malignant tumor is very much necessary. Additional problems include drug instability in the biological environment and premature drug loss through expeditious clearance and metabolism. Similarly, high protein binding of several drugs such as protease inhibitors limits their diffusion to the brain and also other organs. Moreover, nanotechnology for drug delivery applications may not be suitable for all drugs, most likely those drugs that are less potent because the higher dose of the drug would make the drug delivery system more gigantic, which would be difficult to administer. Drug bioavailability is a interconnected problem with potential nanotechnology solutions. Nanotechnology is opening up new therapeutic chance for a large number of agents that cannot be used effectively as conventional oral formulations, because of poor bioavailability. Sometimes, reformulation of a drug with a smaller particle size may improve oral bioavailability. Nanoparticles formulations supply shielding for agents vulnerable to degradation or denaturation in regions of harsh pH, and also prolong the duration of display of a drug by increasing retention of the formulation through bio-adhesion. Additional wide application of nanotechnology is the transport of antigens for vaccination. Mucosal immunity is most important in disease prevention but continues to be limited by both degradations of the vaccine and limited uptake. Recent advances in encapsulation and development of suitable animal models have demonstrated that micro and nanoparticles are able to increase immunization. It has been shown that M cells in the Peyer's Patches of the distal small intestine are able to engulf large microparticles and recent studies have explored the benefits of nanoencapsulation (Sahoo, 2005). Therefore this review is focused mainly on exploring the role of nanomedicine in the treatment of COVID-19 disease.

2. What is coronavirus?

There is a new replacement of public health crises frightening the planet with the emergence and spread of the 2019 novel coronavirus (2019-nCoV) or the serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus originated in bats and was communicated to humans through yet unspecified intermediary animals in Wuhan, Hubei province, China in December 2019. The disease is transmitted by inhalation or contact with infected droplets and, therefore, the incubation period ranges from 2 to 14 days.

2.1 History

There are two events in the past 20 years wherein intersecting of animal betacoronaviruses to humans has resulted in critical disease. The first such example was in 2002-2003 when a new coronavirus of the β genera and with beginning in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong Department of China. This virus nominated as severe acute respiratory syndrome coronavirus affected 8422 people mostly in China and Hong Kong, and gives rise to 916 deaths (mortality rate 11%) before being contained. Nearly after a decade in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, appeared in Saudi Arabia with dromedary camels as the intermediate host and afflicted 2494 people and caused 858 deaths (mortality rate 34%).

2.2 Origin

On February 11, 2020, the WHO Director-General, Dr.Tedros Adhanom Ghebreyesus, revealed that the disease that gave rise to this new CoV was a "COVID-19," which is the synonym of "coronavirus disease 2019".Coronavirus biological vectors are unknown. However, serological and genetic evidence from several studies supports a zoonotic origin of SARS-CoV (Abdellah *et al.*, 2021). This conjecture was first based on epidemiological reports exhibiting that early patients with SARS in the Guangdong department were displayed to live wild game animals held in markets helping the restaurant trade.

2.3 Structure

Coronaviruses are encircled positive-sense RNA viruses starting from 60 nm to 140 nm in diameter with spike-like projections superficially showing them a crown-like appearance under the electron microscope; therefore the name coronavirus. Coronaviruses have positive-strand RNA, with significant RNA genome (approximately 30 kb) reported to date. The genome RNA is complexed with the important nucleocapsid (N) protein to form a helical capsid present within the viral membrane. The membranes of all coronaviruses contain at least 3 viral proteins. These are spike (S), the sort I glycoprotein that gives the peplomers on the virion surface, giving the virus its crown-like morphology within the electron microscope; the membrane (M) protein, a protein that reach the membrane 3 times and gives a short N-terminal ectodomain and a cytoplasmic tail; and little membrane protein (E), a highly hydrophobic protein (Figure 1).

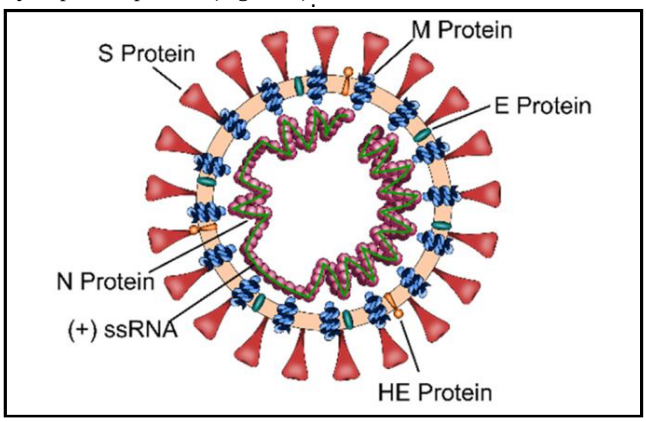

Figure 1: Structure of coronaviruses explaining structural proteins and the viral genome. Virus has characteristic crown-like surface. Photo is credited to Valencia (2020).

The first human coronavirus, which belongs to the Corona-viridae family, and was identified in the 1960s and is up till now, seven α- and β-CoVs have been identified. Coronavirus is named for its crown-like surface appearence (corona) of spike proteins. CoV particles (80-120 nm) are spherically enwrapped, positive-sense ssRNA genomes encoding 8-10 open-reading frames (ORFs). In the case of SARS-CoV-2, the genome (~30,000 nucleotides) has around 79.5% sequence identity with SARS-CoV (Yang, 2021). Two-thirds of the viral genome (ORF1a/b) convert to two polyproteins, pp1a and pp1ab, and encode 16 nonstructural proteins (NSP1–NSP16), while the remaining ORFs, located near 3-terminus, encode secondary and structural proteins. The structural proteins, which are converted from sub-genomic mRNAs, include envelope (E), nucleocapsid (N), membrane (M) and spike (S) proteins.

2.4 Types of CoVs

Common human CoVs with less pathogenicity are 229E (α-CoV), NL63 (α-CoV), OC43 (β-CoV), and HKU1 (β-CoV), these cause less effective diseases. Nevertheless, serious effects, which can be life-threatening, are seen with SARS-CoV, MERS-CoV and the recently emerging CoV (SARS-CoV-2). In late 2002, a spillover of SARS-CoV from bats to humans started in China, causing SARS, which is disappeared by 2004. After managing the SARS-CoV epidemic, MERS-CoV emerged in late 2012 started from camels in the Middle East region. The seventh identified CoV (SARS-CoV-2) was discovered for the first time in December 2019 in Wuhan (China) (Liu, *et al*., 2021).

It infects humans, causing COVID-19 disease, and is currently is responsible for the worldwide health emergency. The overall structure of SARS-CoV-2 is similar to that of other CoVs with the phylogenetic similarity (79.5%) with SARS-CoV gives rise to the name SARS-CoV-2.

2.5 Mode of transmission of CoVs

CoVs are spread *via* person-to-person transmission. The virus spreads mainly *via* sneezing and coughing as saliva droplets or nasal discharge, additionally, to direct contact with infected people and indirect contact with surfaces immediately used by infected persons. Airborne transmission may also be possible in appropriate conditions. Latestly, SARS-CoV-2 was isolated from fecal swabs and the possibility, of fecal-oral transmission has been reported. Interestingly, stool samples continue to show positive results even after persons show negative results in respiratory samples (Figure 2).

2.6 Epidemiology

Bunches of COVID-19, first reported from the Wuhan Metropolitan in the People's Republic of China, in December 2019, have quickly assumed a worldwide form. All ages are defenseless against coronavirus. COVID-19 stays a highly contagious disease, with the reproductive number (R_0) approximately ranging from 1.4 to 3.5. The recent WHO estimate of R_0 was 1.4 to 2.5. The basic reproduction number (R_0) is the expected number of secondary cases that could arise from one case in a susceptible population. Reproduction number is the essence of infectious disease epidemiology and indicates the risk of an epidemic spread. Preliminary studies, conducted at the starting of the outbreak, reported more estimates of R_0, in the range of 2.24-3.58 (Chatterjee *et al*., 2020).

However, by the top of January 2020, the number of individuals who encouraged the disease without exposure to the market or another individual with respiratory symptoms increased. The transmission of the disease among individuals who did not visit Wuhan and among healthcare workers suggested a person-to-person spread of the virus (Chowdhury *et al.*, 2020). Infection is transmitted through large droplets arisen during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before the onset of symptoms.

The differences might be accounted for by missed cases within the initial days, and therefore the effectiveness of critical care protocols and aggressive management techniques utilized outside China. In any case, as epidemiologic experience from outbreak research shows, as long as the epidemic is ongoing, CFR is probably going to vary, especially as case detection becomes more accurate, and less severe cases are also accounted for.

The mean incubation period was 5.2 days (95% CI 4.1-7.0 days) during a study supporting 425 cases, and therefore the median incubation period was 3.0 days (range 0-24 days) in another study based on 1,324 cases. It would be possible that the only case, with an outlying incubation period of 24 days, was a second exposure, instead of a single infection incubation period. The incubation period for COVID-19 remains equivalent to other recent epidemic viral diseases - SARS (2-7 days).

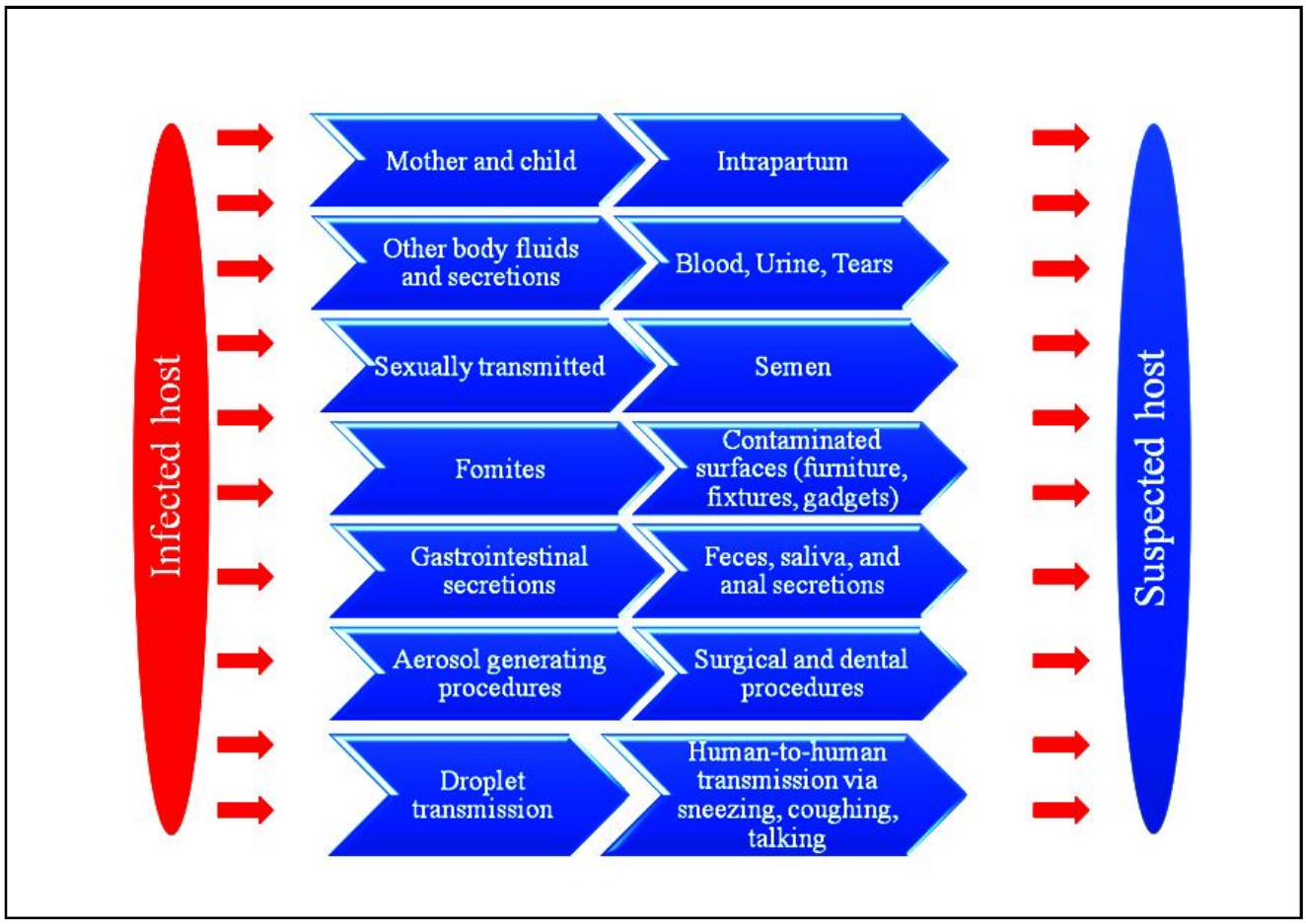

Figure 2: Transmission of coronavirus from infected to suspected person

2.7 Symptoms

The clinical features of COVID-19 are different, starting from an asymptomatic state to acute respiratory distress syndrome and multiorgan dysfunction. The common clinical features include fever (not in all), cough, pharyngitis, headache, fatigue, headache, myalgia, and breathlessness. Symptoms like pharyngeal pain, dyspnoea, dizziness, abdominal pain and anorexia are more likely to be present in patients with severe illnesses. Moreover, patients who are elderly, have underlying co-morbidities including hypertension, diabetes, cardiovascular disease and cerebrovascular disorder are more likely to possesses adverse outcomes. The foremost common complications of COVID-19 are acute respiratory distress syndrome, arrhythmias, acute cardiac injury, shock, and acute kidney injury.

The clinical course of the disease varies widely. In the study of Wang and his team the median time from the primary symptom to dyspnea was 5 days, to hospitalization 7 days, and acute respiratory distress syndrome (ARDS) 8 days. ICU admission was required for patients who developed ARDS (61%), arrhythmia (44%), or shock (30%). Patients treated in ICU are older (median age 66 years) and are most likely to have comorbidities (72.2%).

2.8 Pathophysiology

The mechanism of injury caused by SARS-CoV infection remains unspecified. A SARS disease model was proposed, comprising of 3 phases: viral replication, immune hyperactivity, and pulmonary destruction. Coronaviruses cause acute and chronic respiratory, enteric, and central nervous system (CNS) diseases in different species of animals, including humans.

The recently identified SARS-CoV, which was shown to cause severe acute respiratory syndrome, was the first example of severe illness in humans caused by a coronavirus. Since the recognition of SARS-CoV, there have been reports of two new human coronaviruses correlated with respiratory disease. HKUI is a group II coronavirus came from an elderly patient with pneumonia. This virus has been difficult to generate in cell culture, and there is small information available about the biology of this virus. HCoV-NL63 is a group I coronavirus isolated from a 7-month-old child in the Netherlands who was suffering from bronchiolitis and conjunctivitis. HCoV-NL63 is related to serious respiratory symptoms, including upper respiratory infection, bronchiolitis, and pneumonia. While firstly associated with infections of children, NL63 has been also been noticed in immuno compromised adults with respiratory tract infections (Figure 3)

Among the structural elements of CoVs, there are spike like glycoproteins composed of two subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors, in SARS-CoV-2, the S2 subunit - containing a fusion peptide, a transmembrane domain, and a cytoplasmic domain is highly protected. Thus, it can be a aim for antiviral (anti-S2) compounds or vaccines (Cascella *et al*., 2021).

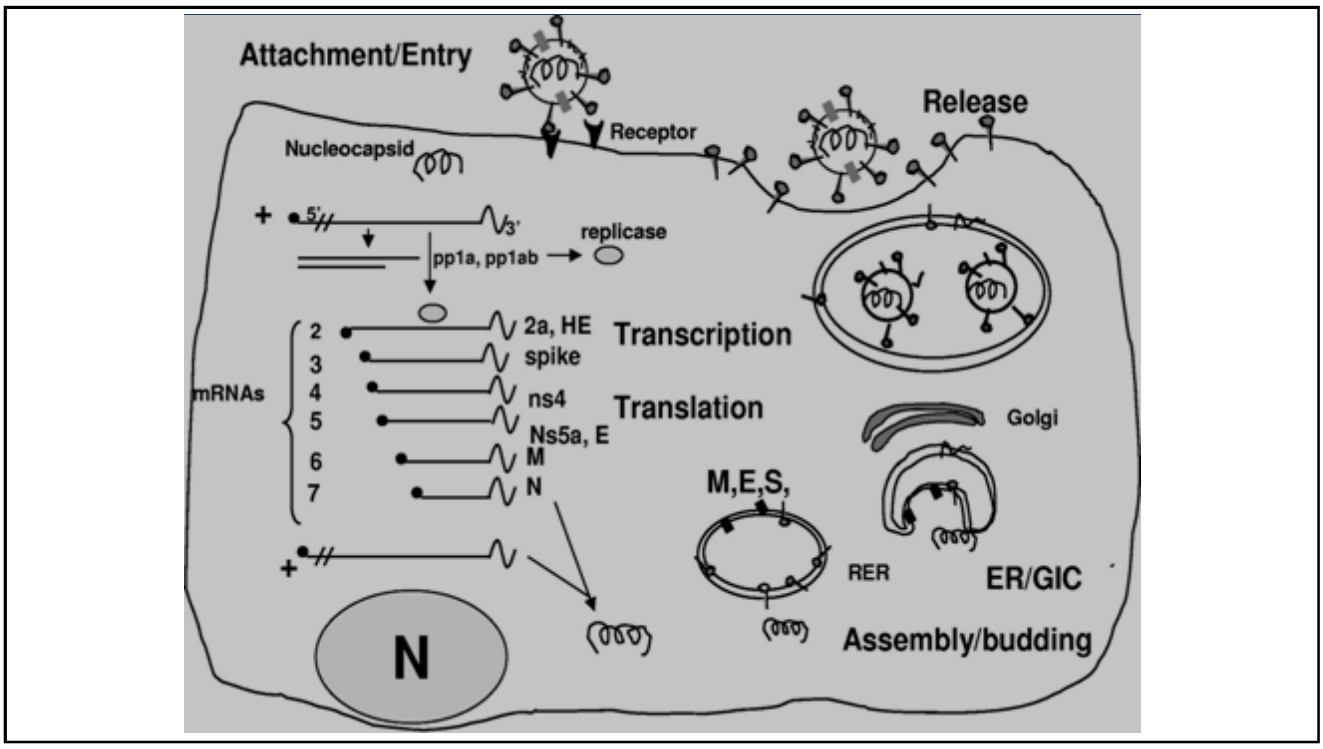

Figure 3: Pathophysiology of coronavirus. Reproduced from Mainardes and Diedrich (2020).

3. Different methods of treatment

Treatment is essentially supportive and symptomatic.The first step is to make sure sufficient isolation to prevent communication to other contacts, patients, and healthcare workers. The casusual principles are maintaining hydration and nutrition and decreasing fever and cough. In hypoxic patients, providing oxygen through nasal prongs, face masks, high flow nasal cannula (HFNC), or non-invasive ventilation is designated Detailed instructions for critical care management for COVID-19 have been published by the WHO. There is, formerly, no accepted treatment for COVID-19.

3.1 O_2 fast challenge

In a patient with a oxygen saturation less than 93-94% (< 88-90% if COPD) or a respiratory rate more than 28-30 / min, or dyspnoea, the administration of oxygen by a 40% Venturi mask must be performed. After a 5 to 10 minutes re-evaluation, if the clinical and instrumental picture has improved the patient un-interruption to treatment and undergoes rejudging with in 6 hours. In case of failure amelioration, the patient undergoes a non-invasive treatment, if not contraindicated.

3.2 HFNO and non-invasive ventilation

In regards to HFNO or NIV, the experts' panel, identifies that these approaches performed by systems with good network fitting do not produce broad spread dissemination of exhaled air, and their use can be considered at lessening the risk of airborne transmission.

3.3 High-flow nasal oxygen (HFNO)

Administration is a relatively new technique that is used in the intensive care unit (ICU), and equally in the operating room (OR). Because this procedure has a considerable risk of aerosolization, it had to be used in negative pressure rooms.

3.4 Non-invasive ventilation and continuous positive airway pressure therapy

NIV/CPAP has a key role in controlling COVID-19-associated respiratory failure.

3.5 Intubation and protective mechanical ventilation

Mechanical ventilation is life-renewing in severe respiratory failure, and few medical therapies equal its potentiality. While some COVID-19 patients are often managed with accessorial oxygen, patients with the foremost serious respiratory failure demand installing of a catheter. A catheter facilitates control over an unsteady airway, and enables precise regulation of oxygen, pressure and volume.

But the catheter brings in its wake a slew of complications. Each day of mechanical ventilation exposes patients to obstacles and increases mortality. The impact of mechanical ventilation in COVID-19 is unknown. It depends on whether intubated patients truly required mechanical ventilation or whether or not they could have been sustained with oxygen supplied by less drastic methods (Tobin *et al.*, 2020). Additional intensive care therapies like corticosteroids, antiviral therapy, serotherapy, anticoagulant, plasma therapy, inflammation inhibitors may be needed while managing SARS-COV-2 infections (Cascella *et al.*, 2021).

3.6 Corticosteroids

A recent large-size RCT (the Recovery trial) demonstrated that dexamethasone alleviates deaths by one-third among critically ill COVID-19 patients. Patients with severe COVID-19 can develop a systemic inflammatory response that can be promoting to lung injury and multisystem organ dysfunction. It has been put forward

that the strong anti-inflammatory effects of corticosteroids may prevent or reduce these deleterious effects. The evaluation of COVID-19 therapy (RECOVERY) trial, a multicenter, randomized, open-label trial in hospitalized patients with COVID-19, showed that the mortality from COVID-19 was lesser among patients who were randomized to take dexamethasone than among those who took the standard of care. The safety and efficacy of combination therapy of corticosteroids and an antiviral agent targeting serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the treatment of COVID-19 have not been extremely severe studied in clinical trials. However, there are conceptual reasons that such combination therapy may be beneficial in patients with severe disease.

3.7 Antiviral therapy

Because of serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2), replication produce many of the clinical manifestations of COVID-19, antiviral therapies are investigated for the treatment of COVID-19. These drugs hold back viral entry (*via* the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3 CLpro) and the RNA-dependent RNA polymerase. Because viral replication might be particularly active early in the course of COVID-19, antiviral therapy might have the highest impact before the illness progresses to the hyper inflammatory state that can characterize the further stages of the disease, including critical illness. For this reason, it is essential to understand the role of antiviral medications in treating mild, moderate, severe, and critical illness to enhance treatment for people with COVID-19. Remdesivir, Chloroquine or Hydroxychloroquine with or without Azithromycin, Lopinavir/Ritonavir, and other HIV protease inhibitors, ivermectin are some of the drugs used in antiviral therapy.

3.8 Serotherapy

Antibodies taken from the blood of healed individuals show a therapeutic option currently under study. It is calculated that the dose of antibodies important for the treatment of a single patient with SARS-CoV-2, needs the removal of antibodies transferred by at least 3 patients recovered from the SARS-CoV-2 infection. A clinical trial has been inaugurated (June 11, 2020) for investigating an antibody cocktail for the prevention and treatment of COVID-19.

3.9 Anticoagulant

Because COVID-19 patients have a greater incidence of venous thromboembolism and anticoagulant therapy is connected with alleviated ICU mortality, it is suggested that patients should receive thromboprophylaxis. Furthermore, in the case of known hypercoagulability or thrombosis, full therapeutic-intensity anticoagulation (*e.g*., enoxaparin 1 mg/kg twice daily) is indicated.

3.10 Plasma therapy

Plasma contributed from patients who had recovered from SARS has been administered as immunotherapy to SARS patients. Human convalescent-phase plasma had a great effect, if administered prior in the course of SARS infection. The new rise of coronavirus disease 2019 (COVID-19) widespread has reevaluated the usefulness of historic convalescent plasma transfusion (CPT).

The important points from available data are as follows: (a) Convalescent plasma mightcontrol mortality in critically ill patients, (b) Increase in neutralizing antibody titers and vanishing of SARS-CoV-2 RNA was observed in most of the patients after convalescent plasma transfusion therapy, and (c) Aidful on clinical symptoms after administration of convalescent plasma. Based on the available scientific data, convalescent plasma transfusion therapy in COVID-19 patients looks safe, clinically effective, and mortality reduction (Rajendran *et al*., 2020).

4. Nanomedicine and coronavirus

4.1 Role of nanomedicine in coronavirus

Various nanocarriers are utilized for drug delivery to solve the difficulties concerned with drug molecules. These can be classified into two categories, polymeric and inorganic nanocarriers. In many research laboratories around the world, scientists are working on nanoparticle-based vaccine products which are still in consideration such as Novavax developing a protein subunit of a nanoparticle vaccine + matrix M. Soft nanomaterials obtained from polymers (polymeric nanoparticles), lipids (lipid-solid nanoparticles, nanostructured lipid carriers, liposomes), surfactants (microemulsion, nano_emulsions, liquid crystals), and proteins (protein nanoparticles) have been applied in nanomedicine, mainly for drug delivery (Figure 4) (Mainardes and Diedrich, 2020).

4.2 Nanomedicines to understand CoV's mechanisms

Remarkable for all the efforts of finding an efficient treatment or vaccine against the novel SARS-CoV-2 or the related disease COVID-19 is that the inconvertible fact that most drugs currently in clinical trials are reassigned from other disease targets including other viral infections, such Ebola or HIV, but also cancer or rheumatoid arthritis. With the increasing number of cases and related deaths, a quick treatment was crucial and therapeutics already effective against known pathways or already evaluated for safety in clinical trials are the foremost rapid strategy to find a treatment against SARS-CoV-2 infections. Nonetheless, SARS-CoV, and MERS-CoV are knew for nearly 20 years, and so far, no efficient treatment against these diseases is out there and memorable for the present outbreak. As SARS-CoV, and MERS-CoV only had limited case numbers, which led to the outbreaks being controlled comparably fast, funding for locating a vaccine or treatment against these viruses was limited and efforts to seek out a vaccine were shelved after governmental funding was stopped. Nonetheless, the very fact that after nearly 2 decades no efficient treatment is available, also demonstrates that it is also crucial to further investigate and understand the virus, and therefore the related processes involving cellular uptake and replication, to style an efficient treatment directly targeted to SARS-CoV-2, and potentially other CoVs. Recently, a wide range study analyzing protein interactions involved in host cell-virus responses has identified 332 possible protein-protein interactions of which 66 demonstrated a drug profile. These interactions are often targeted by 69 known drugs that are either already FDA-approved for various diseases or in clinical trials especially, therapeutics targeting mRNA translation and predicted regulators of the Sigma 1 and Sigma 2 receptors presented effective profiles for the treatment of SARS-CoV-2 infections. The detailed analysis of the protein interactions of SARS-CoV-2 and host cells is crucial step towards a more specialized and directed treatment of SARS-CoV-2 and highlights promising candidates which may find their application within the treatment of those viral infections soon.

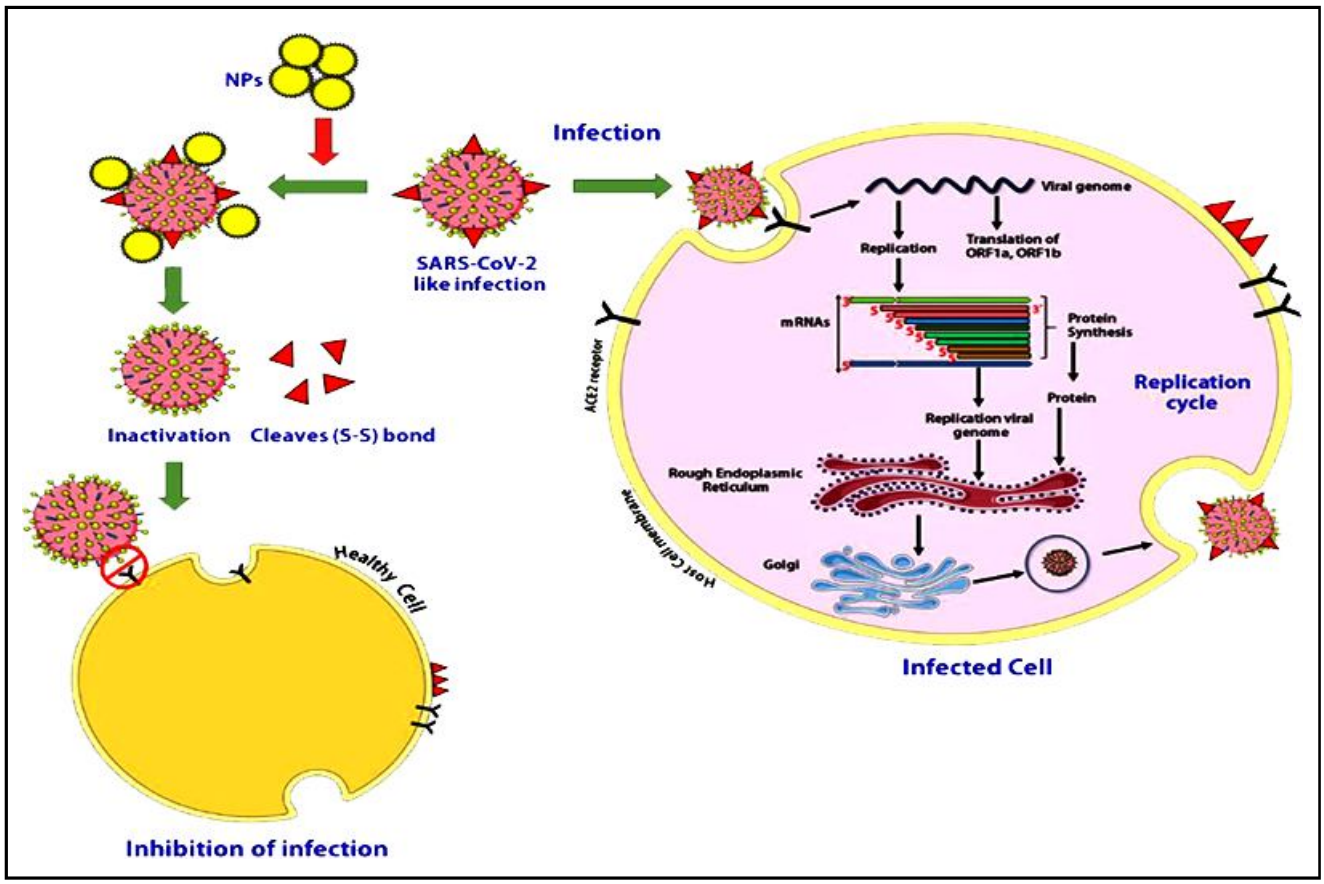

Figure 4: Replication cycle and role of nanomedicine in neutralizing the virus infection such as SARS-CoV-2. Reprinted from Wankar *et al.* (2020).

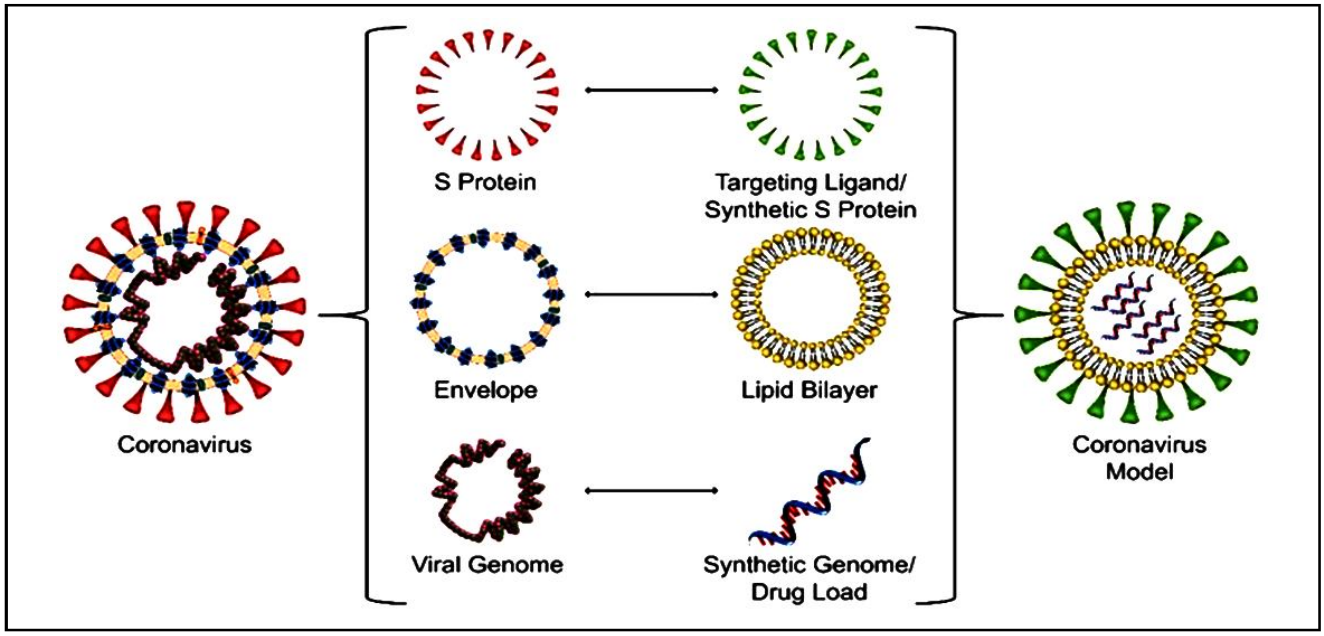

Figure 5: Design of a virus model using nanoparticles. Strategy to mimic a virus for the investigation of biological processes and virus behaviour using nanomedicine strategies displaying the use of targeting ligands or synthetic proteins to mimic the S protein of a coronavirus, a lipid bilayer to mimic the viral envelope and synthetic RNA/ DNA or a drug to mimic the encapsulated viral genome. Reprinted from Heinrich *et al.* (2020).

As beforementioned, different nanocarriers are often used as NPbVs or drug delivery systems, whereas viral proteins, VLPs and liposomes are exclusively ready to mimic the infection pattern and mechanics almost like actual viruses like CoVs. These nanocarriers have been demonstrated for the utilization within the vaccine or therapeutic delivery towards CoV-infected cells presenting tunable characteristics and properties like size, surface charge, and surface modifications. However, compared to liposomes, viral proteins and VLPs on the one hand display more limitations regarding their composition and architecture thanks to the pre-defined proteins from the viral source. Liposomes, on the opposite hand, are often generated employing a sort of lipids where the precise composition allowed for the particular tuning of liposome characteristics and behavior as well as the encapsulation of several agents ranging from RNA/ DNA towards therapeutics, and others.Moreover, liposomes can easily be modified by surface conjugation of peptide sequences like PEG, or targeting ligands to permit immune escape, mucus penetration or drug delivery to specific target cells.

The characteristics of liposomes also facilitate a singular use of those systems in investigating viral infections. Liposomes can be designed to imitate the viral composition, eventually furnishing their characteristics and behavior. The use of liposomes as a model virus in CoV is astimulating approach in particular due to higher safety in handling compared to measure live viruses permitting laboratories that they do not own facilities to handle SARS-CoV, MERS-CoV, or SARS- CoV-2 to research potential treatment during a realistic fashion as well as due to the high tunability of the model properties and characteristics. Generally, a liposome imitating a CoV comprises of: (i) a liposomal bilayer that mimics the viral envelope, (ii) peptides or purified protein conjugated onto the liposome surface mimicking the viral S protein, and (iii) an encapsulated agent likea drug or gene mimicking the viral genome. (Figure 5) (Heinrich *et al*., 2020).

4.3 Polymeric solid colloidal nanoparticles

Polymeric nanoparticles allow the safe and effective *in vivo* administration of the drug molecules with their unique properties such as greater safety, and efficacy, controlled drug release and targeted drug delivery. It also alleviates the high dose-related side effects and permeability across the cellular membrane due to its nano-size properties. This beneficial effect of the polymeric nanoparticle can be utilized for drug delivery to bring back the known drug to treat the SARS-CoV-2 infection have developed the poly (lactic-co-glycolic acid) (PLGA) polymer-based nano-sponge to tackle SARS-CoV-2 infectivity. Essentially, human lung epithelial type II cells and human macrophages membrane-coated nano-sponge was composed with PLGA as the inner core material which shares the same cellular physiology necessary for the entry of SARS-CoV-2 into host cells. This artificial cellular nano-sponge acts as a receiving target for SARSCoV-2 during incubation where it becomes neutralized and not capable to infect the host cells. In this way, the polymeric nanoparticle is a potential nanocarrier system to transport drugs to treat SARS-CoV-2 infection (Wankar *et al.*, 2020).

4.4 Liposomal targeted delivery to treat COVID-19 disease

The liposome is a lipid bilayer vesicle and is broadly utilized for the delivery of hydrophobic and hydrophilic drugs. The liposome can functionalize as a "stealth liposome" that exhibit long systemic circulation, targeted and stimulus-responsive drug delivery. Due to its biocompatible and biodegradable nature, it is one of the preferred carriers for drug formulation and can be a powerful platform for developing the novel formulation to treat COVID-19 infection. Ohno *et al.* (2009) have studied synthetic peptides-based liposomes to treat SARS coronavirus infection. The chemically conjugated peptideliposome is effective for the initiation of cytotoxic T lymphocytes that clears the virus load and can be a potential treatment strategy against SERS (Verma *et al*., 2018). Tai *et al.* (2020), examined the liposome-based novel formulation of hydroxychloroquine in Sprague-Dawley (SD) rats as a potential treatment for COVID-19. This inhalable formulation has found a greater drug concentration in the lungs (~30-fold) with a longer half-life in the lung and lesser exposure to another organ such as the heart compared to intravenous injection. Thus, the liposome as a carrier system might rely characteristic advantages for drug delivery to treat the COVID-19 infection.

4.5 Inorganic and metallic based nanocarrier for COVID-19 treatment

Several metal nanoparticles such as gold, silver, platinum, gadolinium, silica, and it is hybrid nanostructure can be used to formulate inorganic nanocarrier for drug delivery (Jadhav *et al*., 2018). The silver nanoparticle is known for its broad-spectrum antimicrobial activity and is an active component in pharmaceutical products such as silver-sulfasalazine where silver ion increases the antimicrobial property of sulfasalazine drug. It is used in the treatment of wound dressing and burns care products. Furthermore, silver has recorded anticancer, anti-inflammatory, antiplatelet, anti-angiogenesis antifungal, and antibacterial activities. Besides, silver nanoparticles are under research for viricidal effects. Coronavirus has been found to adhere to planes and remains there for around 12 h where the silver-based anti-infective coating can stabilize the virus.

Scientists in the field of nanomedicine have steadily researched on linking the gene delivery capability of various nano-systems and viral vectors to high infectivity. Nanomedical scientists have studied the molecular mechanisms of vectors to increase delivery systems that could be used in a types of fields. Nanoparticles and viruses act at asimilar scale, which makes the nanotechnology approach very powerful in vaccine development and immuneengineering. Nanoparticles are weapons that can produce the structural and functional properties of viruses, and nanomedicine can be the great alternative to new interesting vaccine development, the present time, wherein SARS-CoV-2 is a major threat worldwide, is the most essential, and nanotechnology and nanomedicine are represented as new therapeutic technologies and approaches that can have a clinical impact.

4.6 Versatile and multivalent nanobodies efficiently neutralize SARS-CoV-2

The still critical situation regarding the COVID-19 pandemic needs extensive research efforts in the field of diagnostics and therapy. There is a readiness to take uncommon approaches to develop safer therapies, especially for serious courses of the disease. A promising concept is based on the application of so-called nanobodies as neutralizing antibodies, which effectively alleviate the viruses from binding to the host cells. Nanobodies are originated from a single strain of antibodies produced in Camelidae species in the immune response to various pathogens. In the study held by

Xiang and his team, llamas were immunized with a recombinant protein representing the receptor binding domain (RBD) of SARS-CoV-2. The animals showed a potent and specific immune response in the form of a high antibody titer of 1.75 × 106. The obtained serum had the ability to effectively neutralize pseudo-typed SARS-CoV-2, with half-maximal neutralization titer (NT50) of ~310,000,which was orders of magnitude more effective than serum from human convalescents that has maximum neutralization levels around 5,000. For further characterization, single-chain VHH antibodies were isolated from this serum, which was shown to have high binding affinities against the RBD of the virus (IC50 = 509 pM). In an extensive proteomic analysis, 109 highly diverse nanobody sequences were selected from thousands of various VHH antibodies and submitted to *E. coli* expression. The resulting recombinant proteins were further researched in binding studies using ELISA and SARS-CoV-2-GFP pseudo-virus neutralization assays. Among them, 6% had neutralization activities below 0.5 nM. Eventually, the capability of these candidates to stabilize the SARS-CoV-2 Munich strain was investigated. The three best nanobodies had values of 2.1 ng/ml (0.133 nM), 1.6 ng/ml (0.102 nM) and 0.7 ng/ml (0.045 nM), with a stable binding to the target structure. The affine candidate was also checked for on-shelf stability and remained soluble after ~6 weeks of storage at room temperature after purification. No multimeric forms or aggregations were determined by size-exclusion chromatography. It can be concluded that the described nanobodies exhibit excellent physicochemical properties and could help as safe therapeutic tool in the context of SARS-CoV-2 infections. These nanobodies represent the most strong SARS-CoV-2 neutralizers to date. Future developments should focus on the application technique to allow a safe administration in the most effective form. (Lyer *et al*., 2020).

4.7 Nanoparticulate mRNA vaccine against COVID-19

Zhang *et al*. (2020) describe the development of ARCoV, one of the mRNA vaccines against the SARS-CoV-2-virus that is presently on its way to being or already approved for human use in few countries. New vaccines can be developed and produced very fastly by using mRNA. The authors describe the synthesis of the lipid nanoparticles (LNP) that are used for encapsulation of the mRNA, which was modified from an existing protocol for little interfering RNAs, followed by a tangential flow filtration and purification. They used a part of the SARS-CoV-2 spike protein, the receptor-binding domain (RBD), as an immunization antigen. Transfecting this mRNA into four cell lines led to high production of the respective protein fragment, which was recognized by various antibodies, and interacted with three positive patient sera. In Balb/c-mice, the injection of LNPs loaded with that of a luciferase non-Covid-mRNA-construct preceded in a photon flux in the muscle tissue around the injection site and in the liver. In muscle tissue, the LNPs triggered a great infiltration of monocytes, macrophages and dendritic cells, acting as immune response adjuvants, as has been previously suggested.

At the same time, after injection of the final mRNA construct, RBD-staining was seen in these tissues that colocalized to macrophages in muscle, lymph nodes and liver tissue, showing that ARCoV-LNPs were able to recruit antigen-presenting cells. Consequently, immunocompetent female Balb/c mice were immunized with single doses of 2 and 30 µg, or with doses of 2 and 10 µg, and a booster injection of the similar doses at day 14. All injections induced production of SARS-CoV-2-specific IgGs and neutralizing antibodies with the double dosing of 10 µg. ARCoV being the most effective regimen. Consequently the authors evaluated the *in vivo* protection efficacy of the vaccination 40 days after the second injection of 2 and 10 µg, respectively with 6000 plaque forming units of an adapted virus strain MASCp6. RNA measurement and immuno-staining of the lungs and the upper respiratory tract showed full protection after vaccination or treatment and no clinical symptoms or tissue alterations were appeared, whereas both the virus and clinical alterations were found in the placebo groups. As a second *in vivo* model, a placebo-controlled vaccination study with doses of 100 or 1000 µg of ARCoV was carried out in cynomolgus monkeys. Also in this model, efficient vaccination results were shown, albeit one of ten animals failed to produce detectable neutralizing antibodies and in comparison to other mRNA vaccines the doses were relatively high. In the end, the authors investigated the influence of different storage temperatures on the efficacy of the vaccine, demonstrating good stability at room temperature within 7 days. This could be of high significance when the vaccines have to be distributed to the population of underdeveloped regions far away from larger cities. Currently, the vaccine is being examined in a phase I placebo-controlled clinical study.

4.8 Bionanotechnology toward nanotherapies for COVID-19 management

Since the COVID-19 pandemic was announced as an international health emergency, remarkable efforts are made to design and develop novel therapeutic agents to acknowledge and exterminate the SARS-CoV-2 virus. Such agents are urgently required to conflict against COVID-19. Reasearchers are, therefore, exploring all the possible structures and strains of SARS-COV-2 virus protein. These details are necessary in order to investigate active sites of the SARS-CoV-2 virus, and this is a requirement when trying to develop a safe drug, vaccine, and therapeutic agent to conflict against COVID-19 selectively. Based on recent investigations (Kaushik *et al*., 2020), genuine efforts are made to explore SARS-CoV-2 virus-related pathogenesis and its effected effect on human systems. It has been found that the SARS-CoV-2 virus can stay in the human body for as long as 21 days, and it could affect the respiratory system, which in turn can destroy other organs and change functional systems within the human body. Such challenging consequences have raised the demand for effective and efficient therapeutic agents. It is recommended that such new agents carry out targeted and long-term efficacy with minor side effects (Hu *et al*., 2020). The design and development of such therapeutic delivery are possible through the exploration of an optimized bionanotechnology, *i.e*., nanomedicine to conflict the COVID-19 pandemic.

Nanomedicine (size ranging from 10 to 200 nm), pharmacologically relevant therapeutic delivery, has shown an important achievement in the management of targeted diseases, like, for example, cancer and viral infections (Nair *et al*., 2010). It has been suggested that if scientists can investigate a therapeutic agent against the SARS-CoV-2 virus then it is the site-specific delivery that will be agreat challenge. This site-specific delivery of an advanced therapeutic agent and controlled release and maintenance of the therapeutic agent has an important role in the possible management of COVID-19 (Vashist *et al*., 2018).

Advancing bionanotechnology is significant to the development of nanomedicine against SARS-CoV-2 to manage the COVID-19 pandemic. As we know, the SARS-CoV-2 virus strain variation is dependent on several categories, mainly personal medical history, which makes the optimization of a therapy challenging. Exploring precision nanomedicine may be another way to control COVID-19 infection in a personalized fashion and it is possible *via* investigating bio-nanotechnology and nanomedicine, designed and developed for personalized health wellness (Paliwal *et al*.,2020).

4.9 Nanotechnologies strategies for disinfection and PPE

COVID-19 is known to be very communicable and has various routes of transmission. Latest studies have shown that SARS-CoV-2 spread through micro-droplets transmitted from person-to-person or through touching contaminated surfaces. It is in this context (WHO) recommends the use of physical and chemical factors to reduce contamination by the use of masks and hygiene personal care procedures, as well as disinfection of surfaces, especially for frequently touched surfaces, such as door handles, tables, chairs, hand nails, and switches. Various disinfectant agents are described in the literature, including sodium hypochlorite, hydrogen peroxide, alcohols, soaps/surfactants, *etc*. (Campos *et al*., 2020).

4.10 Nanomaterials for surface decontamination

This is where nanotechnology offers a lot of opportunities for the development of various efficient and encouraging disinfectant systems. Studies based on nanotechnology for the development of new materials, open vie points for surfaces with self-cleaning properties. Those systems can have an antimicrobial activity or be able to release chemical disinfectants unhurriedly, expanding their time of action (Figure 6).

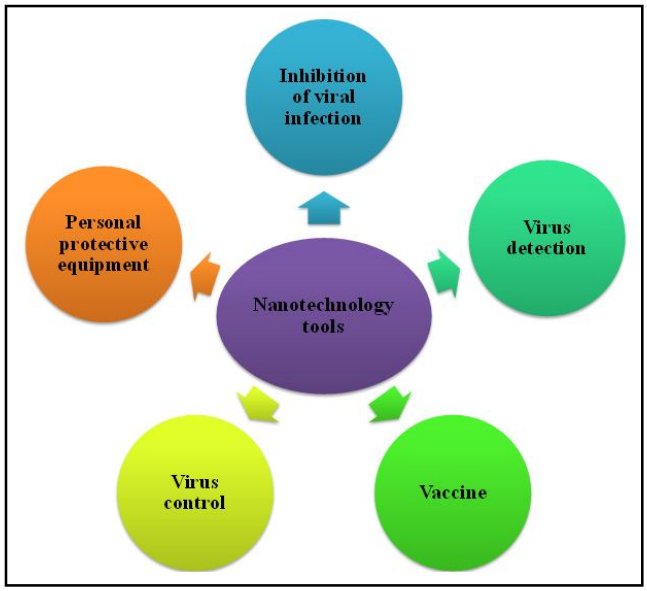

Figure 6: Schematic representation of nanotechnologies tools to prevent and control COVID-19. Nano-based materials could help in: (i) enhanced the speed and sensitivity of virus detection; (ii) help in the development of more efficient and safer treatment and vaccines and (iii) improve the safety of healthcare workers through the development of nano-based personal protective equipment (PPE).

4.11 Nanotechnology-based surface disinfectant in coronavirus infection

As another exposure-reducing strategy toward CoVs and concerning the significance of the polluted surfaces in the spread of the coronavirus, particular observation has also paid to decontamination of surfaces using 70-85% ethanol, NaClO, and iodine-based disinfectants. On the other hand, findings have confirmed the antiviral activity of nanoparticles, resulting in their usage as surface disinfectants with cell membrane entrance virus replication inhibition as well as surface attachment impede of the virus into cells. Moreover, the nanotech surface company has recently evolved a self-sterilizing formulation based upon titanium dioxide and silver ions to disinfect buildings. Generally, nanotechnology-based filters (face masks) and disinfectants are promising products for personal and public protections against Coronavirus which need further investigation (Alimardani *et al*.,2021).

4.12 Development of nanomaterials for PPE

As per the United States Centers for Disease Control and Prevention (CDC), the main factors for the spread of COVID-19 are close contact (person-to-person) and respiratory droplets produced by infected persons. The proper use of PPE, such as masks and gloves, is also important to conflict with the spread of the coronavirus. Furthermore, there are many issues regarding the availability and usefulness of PPE products, for example facemasks not fitting properly or not suitable for limiting airborne viral particles. Nanotechnology is offering new materials that are more pleasant, resistant, and safer means for protection against biological and chemical risks. Facemasks, lab or medical aprons and others have been nanoengineered to furnish new functions, for example, hydrophobicity and antimicrobial activity without affecting the material's appearance or breathability. The hydrophobicity of PPE products can provide an effective barrier on its self against airborne droplets emitted during coughing or sneezing.

This usage of nanomaterial for facemasks has 2 positive points. First, facemask protection works as a filter and microbicidal agent, resulting in restricting and inactivating/killing the pathogens. Second, the management of this material after its use becomes safer once the biggest part of pathogens is damaged in contact with the masks mitigating the expectations of contamination during the undressing process. The technology patents also leave this technology open for the production of other types of PPE, such as visitor aprons, surgical aprons, medical and lab coats, foot protection and bedsheets, whichmay further help in avoiding the spread of pathogens.

4.13 Nanomedicine strategies to target the immune system

Besides facilitating targeting of the infected cells in Coronavirus to avert the virus from spreading throughout the body, nanocarriers also show hopeful abilities to deliver anti-inflammatory drugs towards immune cells to prevent CRS. Various from the nanocarriers discussed before that targeted to reach the NALT and arouse an immune response towards presented antigens causing immunity, such nanocarriers are targeted to deliver anti-inflammatory agents towards inflammatory macrophages and T cells, which are mainly involved in CRS and restrict the production of IL-6, IL-1, TNFα, and other cytokines. In particular, the targeting of macrophages has been recently in focus of thenumber of studies, due to the involvement of macrophages in inflammatory diseases such as

rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis or diabetes, cardiovascular diseases, cardiac diseases as well as cancer as summarized somewhere else. Same as therapeutics targeted for the treatment of CoV infected cells, different studies have been described in the past that combined currently evaluated anti-inflammatory therapeutics with nanocarriers to increase their stability and resistance to degradation, prolong drug exposure or permit targeted delivery of those therapeutics. For example, tocilizumab, an IL-6 antagonist, was combined with hyaluronate-gold nanoparticles for the treatment of rheumatoid arthritis, dexamethasone acetate was packed into SLNs for the delivery to the lung, or colchicine-loaded lipid bilayer-coated mesoporous nanoparticles for the treatment of cancer.

Inspite of various strategies to target macrophages are emerged over the decades, directed targeting of pro-inflammatory macrophages remains challenging and studies that target macrophages with circumstances of the CRS are infrequent. Nevertheless, a few approaches have demonstrated the use of nanocarriers designed to target pro-inflammatory immune cells. Anencouraging target for specific delivery towards macrophages in the presence of mannose receptor (also known as CD206) on the surface of such macrophages. For example, nanoparticles were produced containing mannosylated bioreducible cationic polymers facilitating the presence of mannose receptors for cellular uptake. These nanocarriers were designed to transfer siRNA against TNFα expression in macrophages, which eventually decreased the pro-inflammatory response in inflammatory bowel disease. Moreover, mannose receptor is not only displayed on pro-inflammatory macrophages, and also, displays over expression in anti-inflammatory macrophages as well. This foregrounds a challenge in the specific targeted delivery of therapeutics towards macrophages - macrophage specific markers might be shared by both, pro-and anti-inflammatory markers, making the design of specifically targeted nanocarriers particularly challenging. Various potential surface markers for the targeting of inflammatory macrophages and preventing CRS are CD80 or CD86, also being reported as surface markers for inflammatory macrophages.

Generally, nanocarriers that are targeted for the delivery of anti-inflammatory therapeutics for averting CRS face the same barriers as NPb-Vs and other lung-targeted nanocarriers described in detail prior including the mucus layer of the top of the pulmonary lining as well as the necessity to cross the pulmonary barrier to reach the capillaries and occasionally inhibit the secretion of pro-inflammatory cytokines from macrophages and T cells (Heinrich *et al*.,2020).

5. Challenges and limitations

Nanomedicine offers a number of opportunities against coronaviral infections in the field of vaccination, molecular diagnosis and treatment. Moreover, instead of those interferences, it is still greatly challenging to safely convey Nanoparticles from laboratory invention to the clinic. The important challenges and obstacles are experienced at various stages, starting from understanding viral genomic and proteomic composition to clinical translation. While genomic and proteomic compositions of SARS-CoV-2 were quickly identified to help in the design and development of NP-based approaches against the virus, a high mutation rate and the consequent genetic diversity is still a crucial obstacle for successful therapy. This is clear in the case of NP-based RBD vaccines, where RBD is a variable sequence in the CoV genome. Besides, reversion and pathogenesis is a critical safety issue such as eosinophilic immunopathology in lungs and full-length S protein antigen-related liver damage. Viruses do not have sufficient therapeutic targets, which can be easily targeted without affecting host cells. Correspon-dingly, studying the weak points of the virus and accessibilities of infected cells will allow us to design specific ligands, which can be used to surface functionalize nanoparticles and target the lifecycle of the virus. Also, scaling up nanoparticle production is very challenging, Thus, we have to give more awareness to adjust scale up procedures and infuse more in the translation of bench-top research to clinical practice. SARS-CoV-2 as an emerging pathogen has not enough animal models, which are required for preclinical studies.

Moreover, each virus behaves variably from one host to another, and host response to SARS-CoV-2 is still under study, Thus, broadening the spectrum for NP-based vaccination, diagnosis, or treatment against various viruses is still very hard.

Iron oxide particles are also found to display dangerous characteristics both *in vitro* and *in vivo*, essentially due to the production of ROS. A polymer shielding on the surface of iron oxide nanoparticles dramatically improved cell viability. Surface modifications another approach to decrease the damaging effect of nanoparticles. As anassumption, the addition of hydroxyl groups to gadolinium fullerene particles alleviated the generation of ROS, thereby mitigating toxicity (Varahachalam *et al.*,2021).

6. Future possible srategies

Advances in nanotechnology design and manufacture set the foundation for various creative solutions many of which have been regenerating in response to SARS-CoV-2 which highlights the potential that nanotechnology hold for different applications (Shin *et al*., 2020). Faster translation of those technologies into the clinic and breaking barriers of regulatory authorities shows a build of trust in this growing field. The use of lipid nanoparticles, viral-based vaccines, viral-like nanoparticles, and other hard nanomaterials for important detection and fabrication of personal protection instrumentshas been at the spearhead in the COVID-19 pandemic. While those technologies are all very favorable, it is understandable that some may take many months prior to proving their potential and may not realize their true impact on COVID-19 pandemic. Moreover, this will place the basis for these platform technologies to adapt to other currently existing health challenges and future health crises. We believe that this will be a big push for nanomedical applications and become amotive for the scientific and industrial communities, stakeholders, funding, and regulatory bodies to infuse more effort in this ever-growing field.

An interesting feature of nanomedicine is the capability to provide a generic platform that can be easily adapted to suit the application in necessity. For instance, just by altering the therapeutic molecule encapsulated inside natural or synthetic nanoparticles different examples of the COVID-19 vaccine have been developed (Al-Ahmady *et al*., 2020).

7. Manipulative magnetic nanomedicine: The future of COVID-19 therapy

Nanobiotechnology is developing very promising to investigate novel methodologies for managing COVID-19 pandemic/endemic

successfully. In this way, researchers have explored the Opto-electro-magnetic nano-system to detect the SARS-CoV-2 virus using a biosensing approach. Such optical, electrical, or magnetic biosensors function based on gene-sensing and immune-sensing has detected the SARS-CoV-2 virus selectively at a very low level. These structured-miniaturized biosensors could be managed using a smartphone and promoted for clinical application for early-stage diagnostics of coronavirus infection. The successful integration of these SARS-CoV-2 virus sensors with AI and IoMT promotes virus detection at point-of-location and sharing of bioinformatics with the medical center at the the similar time for timely therapeutics decision. This approach is also useful for following tasks and managing COVID-19 infection according to patient infection profiling. To prevent person-to-person coronavirus transmission, researchers have developed stimuli-responsive nanotechnology enable which can not only trap aerosol of virus size but can eliminate viruses on applying external stimulation for instance nano-enable photo-sensitive virus degradation. Different types of clothes containing nanoparticles have demonstrated SARS-CoV-2 virus trapping and elimination successfully. Moreover, essential attention is required to increase the production and distribution of these masks for public use (Vahedifard *et al*., 2021).

8. Conclusion

Nanomedicine has already proven its value through its application drug delivery and nano-sensors in sars-like diseases. Nanomedicine and its components can play an essential role in many stages of prevention, diagnosis, treatment, vaccination, and research related to COVID-19. Nano-based antimicrobial technology can be unified into the personal instruments for the higher safety of healthcare workers and people. Different nanomaterials, such as quantum dots, can be used as biosensors to diagnose COVID-19. Nanotechnology offers benefits with the use of nano-systems, such as liposomes, polymeric, lipid and metallic nanoparticles, and micelles for drug encapsulation, and it expedites the overall improvement of pharmacological drug properties. Antiviral functions for nanoparticles can aim at the binding, entry, replication, and budding of COVID-19. The toxicity-related inorganic nanoparticles are one of the restricting factors of its use that should be further investigated and modified. Biogenic nanoparticles are eco-friendly, quickly manufactured in more quantities, biocompatible, and of well-defined size and morphology. The close morphological and physicochemical similarity of SARS-CoV-2 with synthetic nanoparticles also makes nanoparticles an effective intervention method. To execute particular functions, nanoparticles may be enormously functionalized with various polymers and functional groups.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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