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Review article

Repurpose but also (nano)-reformulate! The potential role of nanomedicine in the battle against SARS-CoV2

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ABSTRACT

The coronavirus disease-19 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has taken the world by surprise. To date, a worldwide approved treatment remains lacking and hence in the context of rapid viral spread and the growing need for rapid action, drug repurposing has emerged as one of the frontline strategies in the battle against SARS-CoV2. Repurposed drugs currently being evaluated against COVID-19 either tackle the replication and spread of SARS-CoV2 or they aim at controlling hyper-inflammation and the rampaged immune response in severe disease. In both cases, the target for such drugs resides in the lungs, at least during the period where treatment could still provide substantial clinical benefit to the patient. Yet, most of these drugs are administered systemically, questioning the percentage of administered drug that actually reaches the lung and as a consequence, the distribution of the remainder of the dose to off target sites. Inhalation therapy should allow higher concentrations of the drug in the lungs and lower concentrations systemically, hence providing a stronger, more localized action, with reduced adverse effects. Therefore, the nano-reformulation of the repurposed drugs for inhalation is a promising approach for targeted drug delivery to lungs. In this review, we critically analyze, what nanomedicine could and ought to do in the battle against SARS-CoV2. We start by a brief description of SARS-CoV2 structure and pathogenicity and move on to discuss the current limitations of repurposed antiviral and immune-modulating drugs that are being clinically investigated against COVID-19. This account focuses on how nanomedicine could address limitations of current therapeutics, enhancing the efficacy, specificity and safety of such drugs. With the appearance of new variants of SARS-CoV2 and the potential implication on the efficacy of vaccines and diagnostics, the presence of an effective therapeutic solution is inevitable and could be potentially achieved via nano-reformulation. The presence of an inhaled nano-platform capable of delivering antiviral or immunomodulatory drugs should be available as part of the repertoire in the fight against current and future outbreaks.

1. Introduction

Increased human–animal contact, massive animal farming and globalization have facilitated conditions for virus spillover to humans [1,2] and indeed man-kind has received a number of warnings. The 1918 Spanish Flu (H1N1 virus), severe acute respiratory syndrome coronavirus (SARS-CoV), swine influenza virus and Middle East Respiratory Syndrome (MERS-CoV) all represent viruses of animal origins that have crossed over to humans and represented very formidable foes [3–5]. Despite multiple warnings, the sequence of events that have started in late 2019 and resulted in the worldwide spread of SARS-CoV2 and its unfortunate multifaceted impact, has taken the world by surprise [6,7]. A number of cases of "unknown viral pneumonia" related to a local seafood market were reported in Wuhan City, Hubei, China in December 2019 [8]. The underlying reason was rapidly identified as a novel coronavirus (SARS-CoV2) and the resultant respiratory diseases has been named coronavirus disease 2019 (COVID-19) [9]. In March 2020, the COVID-19 outbreak received recognition as a pandemic by the World Health Organization (WHO).

As with other respiratory viruses, transmission is believed to

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predominantly occur through respiratory droplets (aerosols) [10], resulting in a plethora of very diverse symptoms. While the main symptoms include fever, a dry cough, dyspnea, myalgia and pneumonia, some patients also reported sore throats, rhinorrhea, headache and hyposomea [11]. Additionally, rectal swabs from infected patients have also tested positive for SARS-CoV2, questioning the possibility of fecal-oral transmission [1,12] and adding nausea, diarrhea, abdominal pain and hypogeusia to the long list of COVID-19 related symptoms [11,13]. The diverse nature of symptoms has made it rather difficult to conduct a clinical diagnosis, at least without computer tomography or a specific diagnostic test [14]. Several patients confused COVID-19 for other forms of less serious respiratory [14] or gastrointestinal tract (GIT) illnesses, delaying attempts to seek medical assistance and increasing the risk of diseases transmission. Additionally, a large number of patients remain asymptomatic, despite carrying the virus and hence posing as risk of infection [15]. Coupled with the relatively long incubation periods [15], the limited availability of approved vaccines [16] and "effective" treatment [14,17], it becomes obvious how the current COVID-19 dilemma has come into shape.

With the diseases spreading around the globe, number of infections and related deaths soaring, governments were obliged to enforce border shutdowns, travel restrictions and quarantine [18]. While such measures have significantly dampened the spread of the diseases and temporarily reduced the burden on health systems [19,20], prolonged lockdowns are not sustainable and are certainly not a long term solution from both social and economic viewpoints [21]. The measures applied to control the COVID-19 outbreak have already resulted in major socio-economic losses [18,22] and with the curve of infection rates not flattening, the expected negative impact could be humongous as enforced by lessons learned from the 1918 influenza pandemic [21,23]. Thus, scientists and researchers all over the world are racing to find cost-effective solutions for early diagnosis and effective treatment of COVID-19 infections. The development and testing of vaccines is still ongoing and the typical timeline for approval of novel drugs can (depending on the substance class) exceed 10 years [24]. An alternative solution is the repurposing of currently approved drugs. Drug repurposing has therefore been on the frontline of strategies used in the battle against COVID-19 [25]. Nanotechnology could be leveraged to provide assistance in the fight against SARS-CoV2, on several levels and one of them is the nano-reformulation of repurposed drugs. The use of nanoparticles (NPs) in drug delivery has reshaped the drug development landscape over the past decades [26]. NPs have been credited for their ability to improve drug solubility, change undesirable pharmacokinetics, allow for the realization of the benefits of new macromolecular therapeutics arising from genomic and proteomic research, and increasing drug localization in target organs and tissues and thus, lowering the systemic toxicity and side effects, i.e., drug targeting [26]. Furthermore, NP size, shape, surface charge and surface chemistry can be modified, facilitating the synthesis of particles with tailored biological properties. For instance, Lammers *et al* have recently highlighted [27] the promising potential of the reformulation of dexamethasone using nanocarriers. In a similar manner, the reformulation of other drugs that are currently being clinically investigated in COVID-19 is likely to provide new pathways for drug administrations and improved therapeutic outcomes.

Inspired by Professor Kostas Kostarelos plea "Where have all the (nano)scientists gone?" in Nanoscale nights in COVID-19 [4], in this review, we attempt to show what nanomedicine could and ought to do in the battle against SARS-CoV2. In COVID-19, it has become rather obvious at this point that controlling the diseases requires a cessation of viral progression and control over the rampage immune response that is believed to result in a trail of collateral damage often being indicted for the disease related mortality [28]. We start by a brief description of SARS-CoV2 structure and pathogenicity and move on to discuss the current limitations of repurposed antiviral and immune-modulating drugs that are being clinically investigated in COVID-19. Focus will be shed on how nanomedicine could address limitations of current therapeutics, enhancing the efficacy, specificity and safety of such drugs.

2. SARS-CoV2 structure & pathogenicity

Similar to other coronaviruses the SARS-CoV2 is an enveloped non-segmented positive-sense single-stranded RNA virus. In general, coronaviruses show a broad distribution in humans, other mammals and birds and are divided into four genera (α, β, γ, and δ) [29–31]. Although most human coronavirus infections are mild, three coronaviruses of animal origins have crossed the species barrier causing fatal pneumonia. SARS-CoV, MERS-CoV, and the COVID-19 causative agent SARS-CoV2 all share common structural attributes and belong to the beta-coronavirus genus [8,22,29,32]. The beta-coronavirus genome encodes several structural proteins and non-structural proteins [22]. Structural proteins include, the spike (S) protein, the envelope (E) protein, the membrane (M) protein, and the nucleocapsid (N) protein [30] (Fig. 1). The S, M and E proteins are involved in viral coat formation, whereas the N protein is mainly involved in RNA genome packing [31].

The S protein is a transmembrane, homotrimeric, class I fusion glycoprotein that is credited for the crown like appearance of the viral particles [33,34]. Given its surface exposure, the S protein is recognized by the host immune system, serving as an interesting target for vaccine development [35,36]. Additionally, the S protein mediates coronavirus entry into host cells [8,35,37]. The SARS-CoV2 S protein shares a sequence identity of more than 72% with SARS-CoV, where both viruses utilize their S proteins to gain entry into the host cell via the Angiotensin Converting Enzyme 2 (ACE2) receptors [38]. The S protein is composed of two functional subunits; the S1 subunit which is responsible for binding to the host cell receptor and the S2 subunit to which viral fusion to host cellular membranes is attributed [8,37]. For successful viral entry, these subunits require cleavage also known as "priming" by host proteases [37,39]. Host protease activation is therefore a significant determinant of SARS-CoV2 infection and pathogenesis. SARS-CoV2 similar to SARS-CoV utilize the transmembrane protease, serine 2 (TMPRSS2) and lysosomal cathepsins for S protein priming [40,41]. However, despite sharing several common attributes, the S protein of SARS-CoV2 contains a furin-like cleavage site that is absent in the SARS-CoV [38,39,41]. This furin-like cleavage site may have significant functional implications for virus entry [39]. Furin, is a proprotein convertases; a serine secretory proteases regulating various biological processes by forming active products from precursor proteins and has been implicated in viral infections [39,42]. Furin has the potential to cleave viral envelope glycoproteins, enhancing viral fusion with cell membranes of host cells. Since furin is highly expressed in lungs, it might be leveraged by SARS-CoV2 for efficient spreading in the human population, resulting in the higher infectivity observed with SARS-CoV2 virus in comparison to other coronaviruses [39]. Indeed, Shang *et al.* elegantly demonstrated that furin contribute to SARS-CoV2 but not to SARS-CoV host cell entry [41]. Furin activation would hence allow SARS-CoV2 entry into cells with relatively low expressions of TMPRSS2 and/or lysosomal cathepsins [41]. More recently Peacock *et. al* demonstrated that SARS-CoV2 virions lacking the furin cleavage site show lower infectivity in ferrets. This indicated the important role of furin in SARS-CoV2 transmission [43], which is in line with the recent discovery of the SARS-CoV2 VOC 202012/01 that is a recent variant strain predicted to be more rapidly transmissible than other circulating strains of SARS-CoV2 [44]. SARS-CoV2 VOC 202012/01 has 14 non-synonymous mutations, 6 synonymous mutations and 3 deletions. The P681H mutation occurs near the S1/S2 furin cleavage site [44], although the significance of this mutation is yet to be determined, it could potentially play role in the increased transmission rates observed.

Once inside the host cells, viral RNA is then released and using host cell translational machinery it is translated into viral polyproteins, which are subsequently cleaved into functional proteins. Such cleavage is facilitated by viral proteases including; coronavirus main protease (3CLpro or Mpro), and papain-like protease (PLpro). The latter also

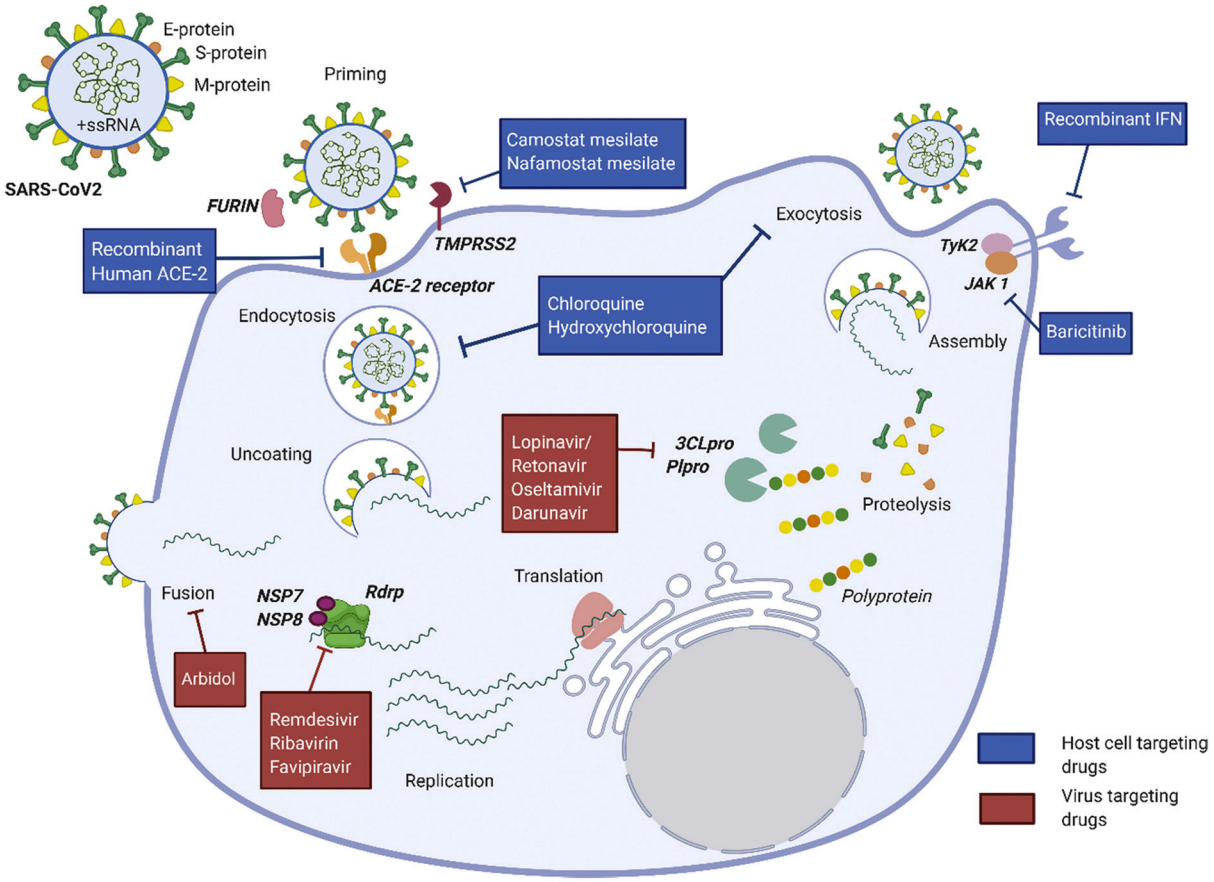

Fig. 1. SARS-Cov2 -host cell interaction and possible drug targets. Abbreviations: ACE2: Angiotensin Converting Enzyme 2 receptor, TMPRSS2: Transmembrane protease, serine 2, NSP7 and NSP8: Non-structural proteins, Rdrp: RNA-dependent RNA polymerase, 3CLpro: Coronavirus main protease, PLpro: Papain-like protease, TyK-2 and JAK-1: Kinases of the Janus family.

functions as a deubiquitinase that acts on certain host cell proteins, including interferon factor 3 and NF-κB, consequently resulting in immune suppression [22,45]. A third non-structural protein; RNA-dependent RNA polymerase (RdRp) catalyzes the synthesis of new viral RNA, hence playing a central role in the replication and transcription cycle of SARS-CoV2. RdRp is believed to function with assistance of other non-structural proteins (nsp7 and nsp8) [46]. Given their pivotal role in the SARS-CoV2 lifespan, these non-structural proteins all serve as suitable targets for antiviral therapy.

3. Reformulation of repurposed drugs

3.1. Tackling SARS-CoV2

Several drugs are currently being clinically evaluated against SARS-CoV2, these drugs could be divided into two broad classes; drugs acting on viral components and drugs acting on host cell components. Table 1 provides a list of antiviral drugs that are being clinically evaluated in COVID-19. It is well established that SARS-CoV2 infects respiratory cells in the lungs [12], making such cells or the associated virions in the lung suitable targets for most of the drugs listed in Table 1. Up until July 2020, with the exception of ribavirin [47] and recombinant interferons (IFN) [48], all evaluated drugs were administered systemically. In fact, it is only very recently that inhalation was considered for remdesivir (NCT04480333- July 2020 and NCT045392262-September 2020) and hydroxychloroquine (NCT04497519-August 2020 and NCT04461353-July 2020). The systemic administration therefore stirs up two very pressing points of discussion; how much of the administered drug actually reaches the lung and more specifically the host infected cell and as a consequence, where does the remainder of the dose go? Additionally, where does the drug distribute and what are the resultant off target effects? The answers to these questions become rather obvious by considering the adverse effects observed with these drugs (Table 1). For instance, GIT side effects are observed with most of the orally administered drugs [49–54], in some cases these GIT side effects were severe, leading to the early termination of treatment [49]. In addition to GIT adverse effects, lopinavir/ritonavir also induce hepatic injury given their distribution to the liver following oral administration for instance. The latter is underpinned by lopinavir's low oral bioavailability and its metabolism by the CYP3A4. In fact, one of the main reason for co-administration of ritonavir is to achieve drug concentrations that are high enough to inhibit viral replication while allowing less frequent dosing in HIV patients [55] and in COVID-19 clinical trials (NCT04252885, NCT04255017, NCT04321174). Additionally, lopinavir/ritonavir induce hepatic activity of cytochrome P450 enzymes; CYP2C9, CYP2C19, and CYP1A2 [56] also resulting in multiple drug interactions [49,57–59]. The latter becomes rather critical when taking into consideration that patients with severe cases of COVID-19, requiring antiviral therapy, are those with other pre-existing conditions that require treatment with other medications. Similarly, when considering oral versus nebulized ribavirin, nebulized ribavirin is less likely to induce systemic side effects including hemolytic anemia and GIT discomfort [60]. However, other route related adverse effects were reported with nebulized ribavirin such as cough, nasal congestion, and dyspnea [60].

While systemic side effects were observed with antiviral drugs targeting viral components **(**Table 1**),** drugs that target host proteins may cause, (depending on administration route and dose) even more

Table 1
Anti-viral drugs clinically evaluated in COVID-19.

Drug	Target/MOA*	Route of administration	Clinical Trials	Side effects
Drugs targeting viral components				
Remdesivir	RdRp inhibitor [61,62]	IV [61]	**Monotherapy:** NCT04365725, NCT04280705, NCT04582266, NCT04431453, NCT04539262, NCT04501952, NCT04345419 **In Combination:** NCT04409262 + Tocilizumab, NCT04401579 + Baricitinib, NCT04492475 + Interferon beta-1a, NCT04583969 + Lenzilumab, NCT04583956 + Risankizumab, NCT04480333+ NA-831. NCT04410354+ Merimepodib, NCT04315948+SoC, NCT04292899+SoC, NCT04292730+SoC, NCT04330690+ standard supportive care	Abnormal liver function, diarrhea, rashes, renal impairment, and hypotension [61]
Arbidol	Viral fusion [11]	Oral [51]	**Monotherpay:**, NCT04255017, ChiCTR2000030254 **In Combination:** NCT04252885+ standard treatment, NCT04260594 + basic treatment, NCT04350684+ Interferon-β 1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine	Minimal; Abnormal LFT, GIT reactions [51,63]
Lopinavir/ ritonavir	3CLpro and/or Plpro. inhibitor [62,64]	Oral [49]	**Monotherapy:** NCT04372628 NCT04255017, NCT04321174 **In Combination:** NCT04276688+ IFNβ-1B + Ribavirin NCT04303299+ Chloroquine or darunavir or Oseltamivir or Favipiravir, NCT04320277+ Baricitinib, NCT04499677+ Favipiravir, NCT04403100+ Hydroxychloroquine, NCT04346147+ Hydroxychloroquine, NCT04252885+ standard treatment	Anorexia, nausea, abdominal discomfort, diarrhea, hepatic injury, pancreatitis, cutaneous eruptions, QT prolongation. [49]
Favipiravir	RdRp inhibitor [11,62]	Oral [63]	**Monotherapy:** ChiCTR2000030254, NCT04349241, NCT04333589, NCT04542694 NCT04351295, NCT04448119 **In combination:** ChiCTR2000029600 + IFNα, NCT04359615+ hydroxychloroquine, NCT04303299+ lopinavir + ritonavir or chloroquine or darunavir, NCT04310228 + tocilizumab, NCT04558463+ standard therapy, NCT04532931+ Nitazoxanide, NCT04376814+ hydroxychloroquine, NCT04358549+SoC, NCT04346628+SoC	Minimal side effects; raised serum uric acid, abnormal LFT, GIT reactions [50,63]
Ribavirin	RdRp inhibitor [62]	IV, Oral [17], Inhalation [47]	**Monotherapy:** NCT04356677, NCT04551768 **In combination**: NCT04276688+ Lopinavir/ ritonavir+ IFNβ, NCT04563208+ Nitazoxanide, NCT04494399+ IFN β-1b + SoC, NCT04392427+ Nitazoxanide+ Ivermectin	Teratogenic Hemolytic anemia [65], mild lymphopenia, hyperuricemia, itching, rash, cough and nasal stuffiness [66]
Darunavir	3CLpro inhibitor [62]	Oral [67]	**In combination:** NCT04252274+Cobicistat, NCT04303299+ritonavir+ lopinavir or oseltamivir or favipiravir or chloroquine.	Skin rash [67]
Oseltamivir	Neuraminidase inhibitor [68]	Oral [69]	**Monotherapy:** NCT04255017 **In combination:** NCT04303299+ lopinavir+ ritonavir or chloroquine or darunavir, NCT04516915 + Vidofludimus calcium, NCT04338698 + Hydroxychloroquine + Azithromycin, NCT04261270+Ritonavir+ ASC09F, NCT04558463+standard therapy	Nausea and vomiting [70]
Drugs targeting host cell components				
Hydroxychloroquine*	Preventing viral entry and transport [53]	Oral [52]	**Monotherapy:** NCT04497519, NCT04466540, NCT04435808, NCT04429867, NCT04461353 **In combination:** NCT04336332 + Azithromycin, NCT04355026 + Bromhexine, NCT04338906+ Camostat mesilate NCT04355052+ Camostat mesylate or Azithromycin, NCT04391127+ Ivermectin, NCT04261517+conventional treatment, NCT04477083+supportive treatment, NCT04458948+ Azithromycin	Pruritus, headaches, dizziness, GIT disturbances, psychiatric effects, retinal toxicity, cardiotoxicity including cardiomyopathy and rhythm disorders QT prolongation and arrhythmias [54,71]
Chloroquine*		Oral and IV [72]	**Monotherapy:** NCT04303507, NCT04351724, NCT04323527, NCT04344951, NCT04345419 **In combination:** NCT04428268+Losartan, NCT04351191+SoC, NCT04328493+SoC	
Baricitinib*	Inhibition of viral endocytosis [73]	Oral [74]	**Monotherapy:** NCT04321993, NCT04340232, NCT04421027 **In combination:** NCT04320277 +Lopinavir+Ritonavir, NCT04346147+hydroxychloroquine, NCT04373044+ Hydroxychloroquine	Impairment of IFN mediated antiviral response increasing risk of other viral infections [73]
Camostat mesilate	TMPRSS2 inhibitor [75]	Oral [75]	**Monotherapy**: NCT04321096, NCT04353284, NCT04455815, NCT04374019, NCT04530617	Thrombocytopenia, hyperkaliemia, hepatotoxicity, anaphylactic shock,

(*continued on next page*)

Table 1 (*continued*)

Drug	Target/MOA*	Route of administration	Clinical Trials	Side effects
			In combination: NCT04338906+ hydroxychloroquine, NCT04355052+hydroxychloroquine, NCT04583592+SoC, NCT04470544+SoC	nausea, abdominal discomfort, abdominal fullness, diarrhea, rash, pruritus [76]
Nafamostat mesilate	protease TMPRSS2 inhibitor [77]	IV [77]	**Monotherapy:** NCT04473053 **In combination:** NCT04352400+SoC, NCT04390594+SoC	Agranulocytosis, hyperkalemia, hypotension, dyspnea, anaphylactic shock, abdominal pain, nausea, vomiting, anorexia, myalgia and arthralgia. [78–80]
Recombinant Human Angiotensin-converting Enzyme 2 (APN01)	Blocking cell entry via ACE2 [81]	IV [82]	**Monotherapy:** NCT04335136	Diarrhea, rash, hypernatremia [82]
Recombinat IFN# IFN-α2β IFN-β1	Direct inhibition of viral replication and supporting an immune response for viral clearance [83]	Inhalation, oral [84] Subcutaneous injection [48]	**Monotherapy:** **In combination:** NCT04276688 +Lopinavir/ Ritonavir+ Ribavirin, NCT04465695+ Clofazimine, NCT04350281+ Hydroxychloroquine, NCT04494399+ Ribavirin, NCT04293887+standard therapy, NCT04469491+SoC	Neuropsychiatric adverse effects [85]

LFT: Liver function tests, PLpro: Papain-like protease, 3CLpro: 3-chymotrypsin-like protease (Coronavirus main proteinase), RdRp: RNA-dependent RNA polymerase, TMPRSS2: Transmembrane serine protease 2, IFN-β1: Interferon beta-1, SoC: Standard of care.

* reported immunomodulatory properties and ability to dampen cytokine storm and hyperinflammation [86–88].

undesired side effects, given the wider availability of their target in non-targeted organs [77]. The latter is for instance, rather obvious from the adverse effect profile of chloroquine, hydroxychloroquine and camostat mesliate [53,54,76]. In addition to the systemic adverse effects, the low amount of effective drug in the lung might render the use of most systemically administered antivirals in COVID-19 treatment non-conclusive. This is also emphasized by the lack of disease relevant pharmacokinetic trials [89]. Although, currently little is known about the effective drug concentration required to inhibit SARS-CoV2 replication, the exposure of the virus to a low drug concentration *in-vivo* is a plausible reason for the clinical ineffectiveness observed with antiviral drugs [49,64]. In fact, following the intravenous administration of remdesivir in two COVID-19 patients, the drug was not detected in bronchoalveolar aspirate [90]. Within the same context, data obtained from MERS patients indicated that the relative concentrations required to inhibit viral replication was higher than actual concentrations detected in sera of patients treated with lopinavir/ritonavir [91,92]. In a similar manner, camostat mesilate is currently being clinically investigated in COVID-19, where patients are receiving two 100 mg pills, 3 times a day for 5 days (NCT04321096). While investigators are optimistic about the outcomes, based on previous positive *in-vitro* experiments [40] and results from animal trials [93], at this point it cannot be guaranteed that enough drug will be distributed to the lungs [94]. Animal trials investigating the efficiency of systemic and inhaled antiviral drugs in influenza have reported similar results [95]. In such cases, the local delivery of drugs directly to the lung would provide a promising approach to deliver higher drug concentrations to the site of action while at the same time, minimize toxicity due to off-target distribution and possibly reducing the administered dose [26,96], all of which could be potentially achieved with the use of nano and microparticles (MPs).

Upon inhalation of NPs or MPs, their lung deposition and clearance profile depends on their physicochemical properties, as well as the patient's lung anatomy and health state [26,97]. In the lungs, the airways and the alveoli are lined with pseudostratified epithelium, which is protected by a ciliated mucus layer in the tracheobronchial area [26]. A particle's geometric diameter, density and shape all contribute to its aerodynamic diameter (AD) which greatly decides where the NP deposits in the lung [97]. When inhaled through the mouth, particles with ADs larger than 5 μm deposit in the oropharynx and large airways, where they fall prey to mucociliary clearance rather than reaching the lung [98]. Particles with smaller ADs (1–5 μm) deposit deep into the lungs by gravitational sedimentation due to lower air velocity in this region [97,98]. Finally, smaller NPs tend to be exhaled as they mostly remain suspended in inhaled air [26,99,100] (Fig. 2). However, if

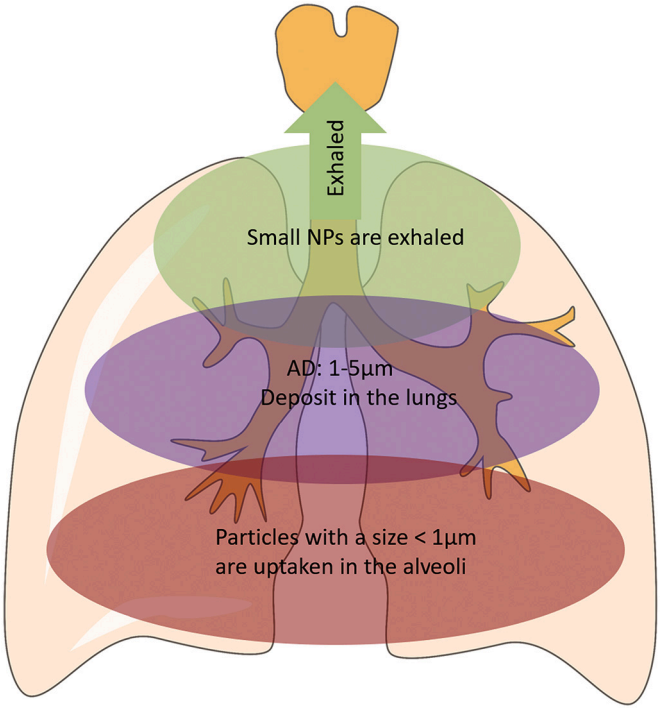

Fig. 2. Inhaled NP deposition in the lung as function of particle diameter. AD: Aerodynamic diameter.

particles do escape exhalation, they may be deposited in all regions of the respiratory tract by diffusion [98]. In case their lung delivery is required, attempts to enhance NP lung deposition include nebulization or incorporation into larger particles [26,101]. While targeting of most lung regions seems possible with NPs and/or MPs, the important questions is; where is the NP/MP deposition required for treatment of COVID-19? Are there any specific disease related changes in the lung physiology that could be exploited for better drug targeting to the needed site?

Mild forms of COVID-19 are usually confined to the conducting airways. Conversely, severe forms of the disease will more likely involve deeper lung portions and the alveoli [102]. COVID-19 progression has been divided into three stages (Fig. 3). Stage 1, is mostly asymptotic and involves the binding and replication of SARS-CoV2 in epithelial cells in

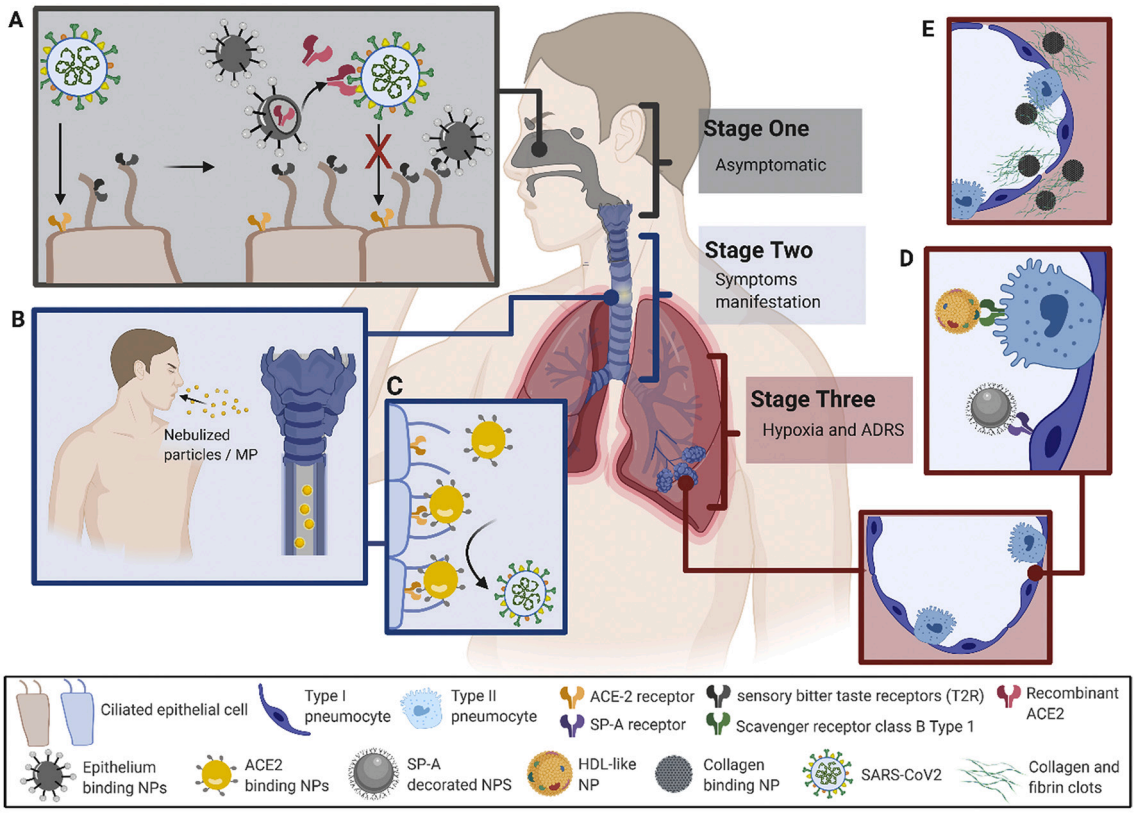

Fig. 3. Stages of COVID-19 and relevant drug targeting approaches (A) Cilia binding nanoparticles loaded with recombinant ACE2 as prophylactic for SARS-CoV2 cell entry (B) Enhancement of NP deposition in the lung by nebulization or incorporation into larger particles (C) Competition of ACE2 binding NPs with SARS-CoV2 in the airways and alveoli (D) Active targeting of NPs to infected alveolar cells (E) Collagen binding NPs for increased NP residence in severe cases of COVID-19.

the nasal cavity [102,103]. In the second stage, the disease is usually clinically manifested and SARS-CoV2 migrates along the respiratory tract down the conducting airways [102]. For most patients, the disease is restricted to the upper and conducting airways and will resolve before reaching lower portions of the lung. However, a small percentage of unfortunate patients progress to the third stage, in which SARS-CoV2 infects the alveoli leading to hypoxia and progression to acute respiratory distress syndrome (ARDS) [102]. So where should the drug be delivered? Intranasal administration of drugs would in this case be highly effective in limiting viral spread [103], but given the short nature of this phase (usually 1–2 days) and in most cases its asymptomatic nature [102], it seems that intranasal delivery would be more suited to the administration of vaccines or other prophylactic measures as opposed to delivery of antivirals *per se*. While the use of nanotechnology in COVID-19 vaccines is out of the scope of this review, here, a discussion of a prophylactic option might be of interest, particularly since it would involve "nano-reformulation". It is well established that SARS-CoV2 employs the ACE2 receptor for cellular entry [40] and ACE2 receptor expression has been detected in the nasal epithelium [104], along with a plentiful supply of proteases required for S protein priming [104]. Hence, blocking such interaction in the nose might provide a prophylactic advantage by limiting viral entry in the first place. Recombinant soluble ACE2 receptor has shown potential in SARS patients by acting as a competitive binder to the virus S protein, preventing its binding to host cells [38,105]. In fact, intravenous APN01 (recombinant human Angiotensin-converting Enzyme 2) is currently being clinically investigated in COVID-19 (NCT00886353). In this trial, the recombinant protein is being administered intravenously, which with no doubt does not serve as the optimal route for administration of such a bulky, sensitive macromolecule, limiting its ability to reach the respiratory tract in intact form and sufficient concentration [106,107]. Its intranasal application would at least ensure its local presence in sufficient concentrations. However, if administered in free from, this would render it prone to enzymatic degradation and rapid clearance, requiring repeated frequent treatments [106,108,109]. By anchoring the protein or loading it into NPs its life-time could be possibly enhanced [110]. Literature includes numerous reports describing the formulation of mucoadhesive NPs [109,111–113]. While muco-adhesion has been claimed to increase NP/MP residence time [109,111–113], it has also on other occasions been reported to result in rapid elimination by muco-ciliary clearance [114]. In fact, because of such clearance an approximate half-life of 21 min has been reported for intranasal applied drugs [108,109]. With disregard to its ability to increase or decrease NP residence time, it is plausible that mucus presents a formidable barrier hindering NP access to epithelial cells. Within the same context, mucus should theoretically limit viral access to the same cells, practically the latter does not always happen. Several studies have demonstrated that factors including surface charge, hydrophilicity and size influences the penetration of viruses through the mucus [115–117]. These studies should serve as guidelines for the formulation of mucus penetrating NPs [118,119]. CoVs heavily glycolyzed S proteins endow mucus penetrating properties, which indicates that PEGylation of NPs; the conjugation of polyethylene glycol onto the surface of the NP could endow similar favorable attributes [118–120].

Another possible approach to increase the NP residence time in the nose would be binding to cilia. This would be rather interesting in COVID-19 since the virus is believed to gain access through ciliated cells attributed to their very high expression of ACE2 receptors [103]. In such case, the NP would require functionalization with a cilia binding ligand and loading with APN01 (Fig. 3A). Several receptors have been reported to exist on cilia of the differentiated human airway and nasal epithelium [109,121–124] and hence could be used to facilitate NP active binding to cilia. An interesting observation is that most of these receptors when stimulated with appropriate ligands, trigger a response that could result in pathogen clearance. For instance, upon the stimulation of the sensory

bitter taste receptors (T2R) an increase in concentration of intracellular calcium occurs, which culminates in increased ciliary beat frequency, providing a defensive mechanism for the elimination of potential pathogens [125]. More specifically, Lee *et al.* demonstrated that stimulation of T2R38 (one of the T2R receptors which is expressed in motile cilia lining the sino-nasal cavity) results in nitric oxide production [126], which demonstrated antiviral effects towards SARS-CoV [127]. The latter reveals a possible synergistic action of APN01 loaded cilia targeted NPs in the SARS-CoV2 prophylaxis. To the best of our knowledge, to date, the formulation of NPs capable of actively binding to motile cilia in the nasal cavity or the respiratory system has not been reported. However, Pala *et al.* synthesized nano-drug delivery systems loaded with fenoldopam capable of binding to primary cilia for the treatment of ciliopathy related vascular hypertension [128]. Dopamine-receptor type-5 (DR-5) is largely expressed in cilia. Hence, the authors speculated and elegantly demonstrated that DR-5 labelled NPs could be used to functionalize NPs for cilia targeting [128]. In the case of motile cilia, cilia beating movement might make it harder for the NPs to actually make sufficient contact with the receptors. Viral particles are bioengineered NPs [4]. If these naturally engineered nano-pathogens could deposit onto beating cilia, why would not the man-made nano-medicines behave similarly? On this note, irrespective to the active interaction with cilia, NP deposition on motile cilia might also offer an added advantage. By adjusting the physicochemical properties of the NPs, an increase in cilia beat frequency could also be obtained; anionic NPs with diameters larger than 300 nm have shown to increase cilia beat frequency upon their deposition, also possibly resulting in enhanced viral clearance [129]. This relatively large particle size, would also limit NP absorption and their translocation to the brain through the olfactory pathways [109] limiting systemic toxicity and increasing residence time in the nasal cavity.

In the symptomatic phases of the diseases, from a drug delivery perspective, delivering the drugs to the upper and conducting airways or deep into the alveolar region would help prevent disease progression and deterioration of patient health, hence reducing mortality rates. To do so, antiviral drug encapsulation into particles with suitable ADs (1–5 μM) would be necessary [130]. In addition to the suitable AD, these particles should be suited to drug physicochemical properties to allow for a high encapsulation efficiency (EE) of drug, a suitable drug release profile and more importantly the preservation of drug functionality [26]. Since most of the drugs that are currently being clinically investigated in COVID-19 therapy are repurposed drugs, a number of nano-formulations although not for therapy of COVID-19, have been reported (Table 2) and meet most of the aforementioned perquisites of a suitable carrier system. To date, nano-formulations containing recombinant human ACE2 (APN01) have not been reported. APN01 is a water soluble bulky molecule [131] and hence would be best encapsulated into hydrophilic polymeric systems via formulation methods that are devoid of heat and the use of organic solvents [106,132]. Alternatively, silica NPs could also be utilized for the encapsulation of APN01 or other

Table 2
Anti-viral drug properties and reported nano-formulations.

Drug	Solubility	Molecular weight	Particle Type	Particle Diameter (nm)	EE%
Remdesivir	Low [135]	602.58 g/mol	PEGylated dendrimer [134]	–	–
Arbidol	Low [140]	477.4 g/mol	Selenium NP [141]	70	–
Lopinavir	Low [142]	628.8 g/mol	Pullulan acetate NP [143]	197	77
			SLN [144]	230	99
			SLN [145]	223	83
			PCL NP [146]	195	93.9
Ritonavir	Low [147]	720.9 g/mol	SLN [148]	170–250	53
			SLN [149]	≈ 300	53–73
			SLN [150]	127–146	94–98
			Eudragit RL100 [151]	150–328	40–94
			PLA NP [152]	~300	90
			Eudragit-PCL NP [153]	120 and 559	100
			Alginate NPs [154]	220 ± 2	15.2*
Favipiravir	Low [155]	157.1 g/mol	Silicon-doped C60 fullerenes [156]	–	–
Ribavirin	Soluble [157]	244.2 g/mol	Poly-L-lysine-PLA NP [158]	103	1.6*
Darunavir	Low [159]	547.7 g/mol	Lipid NP [159]	200	90
			SLN [160]	100,200,500	42–90
Hydroxychloroquine	Low [161]	434 g/mol	Eudragit RL-100 NP [162]	344	63
			Liposomes [163]	100–150	100
			Liposomes [164]	122	>90
Chloroquine	Low [165]	319.9 g/mol	PLA [166]	<300	64
			Dextran NP [167]	≈58	81
			SLN [168]	≈375	78–90
			Gelatin NP [169]	100–400	15–19*
			SLN [170]	≈113	≈94
			Chitosan NP [171]	150–300	> 54
			Polymeric iron NP [172]	≈ 10 nm	–
			Silver NP [173]	254 nm	–
			Chitosan NP [174]	150–500	≈93
Baricitinib	Low [175]	371.4 g/mol	PLGA [175]	≈91	88
Camostat mesilate	Low [176]	494.52 g/mol	Chitosan NP [177]	250–320	70
Nafamostat mesilate	Low [178]	539.6 g/mol	PLGA NP [179]	150–300, 400–600	60–70
Recombinant Human Angiotensin-converting Enzyme 2 (APN01)	Soluble [180]	85.9 KDa	–	–	–
Recombinant IFN IFN-α2β	Soluble [181]	19.271 KDa	–	–	–
Oseltamivir phosphate	Soluble [178]	410.4 g/mol	Liposomes [182]	≈106	≈89
			Gold NP [183]	2–14	–
			Selenium NP [184]	10	–
			Silver NP [185]	2	18#

calculated as % from total mass based on Energy Dispersive X-Ray (EDX) analysis.
NP: Nanoparticle, PCL: poly caprolactone, PLA: poly lactic acid, PLGA: poly lactic co-glycolic acid, SLN: solid lipid nanoparticles,
* Drug content *w*/w%.

hydrophilic drugs. In this case, APN01 is allowed to diffuse into prefabricated silica NPs under non-denaturing conditions [133]. Only very recently (September 2020), has remdesivir been nano-reformulated [134]. This nano-formulation is a PEGylated dendrimer that allows a sustained release of remdesivir allowing less frequent dosing [134]. Remdesivir is a low molecular weight compound with low water solubility and higher solubility in ethanol [135] and dimethyl sulfoxide (DMSO) [136]. Accordingly, when considering alternative options for its encapsulation into nanocarriers, formulation of polymeric NPs by nanoprecipitation using ethanol soluble biodegradable polymers could offer a suitable encapsulation approach [132,137], or mesoporous silica capsules [138]. Alternatively, other drugs have been encapsulated into chitosan NPs by a modified form of the inotropic gelation method, where the drugs were incorporated through the use of DMSO [139], also offering a possible means for the nanoencapsulation of remdesivir.

While most of the particles listed in Table 2 show a decent ability to encapsulate antiviral drugs, their relatively small size would render them not suitable for deposition in the lung following inhalation [26,100] at least without breath coordination [26]. Notwithstanding, if they do deposit in the conducting airways or deeper in the lung, this small size would increase their interaction with epithelial cells allowing for the delivery of higher drug concentrations in the target cell cytosol [26,186]. This smaller size would also reduce particle phagocytosis which is significant for particles of geometric diameter ranging between 1 μm −2 μm and decreases for smaller particles [100,130,186,187]. But is evading phagocytosis by pulmonary macrophages really beneficial? Early on at the beginning of the pandemic, the ability of SARS-CoV2 to infect macrophages was debatable. With time it has been speculated [188], then demonstrated by autopsy and pathological postmortem investigation of two patients [189]. More recently, it has become rather obvious that SARS-CoV2 infects monocytes and macrophages stimulating cytokine release and the up-regulation of M2-type molecules [190]. However, the ability of the virus to replicate inside these phagocytic cells remains elusive [190].With this information on hand, it seems that the deposition of larger NPs deep into the lung would be preferred. The latter could be achieved through nebulization [191]. The use of nebulizers is common in hospital setting for the treatment of respiratory diseases and is feasible for elderly patients [111] that are more prone to serious cases of COVID-19. When NP suspensions are nebulized, NPs deposit in the lung as a function of the AD of the atomized suspension droplets. It is however important to ensure that the NP size and surface properties do not change upon storage in solution, nor does a significant drug release occur before administration. Additionally, it would be necessary to optimize NP suspension concentration to avoid particle aggregation [192]. Another possible approach is the incorporation of NPs in larger MPs that dissolve releasing smaller NPs once in contact with fluids at the site of deposition, or similarly adsorb them onto water soluble carriers of suitable ADs (Fig. 3B) [101,193]. In such case, the NPs would be stored in dry state and hence ensure that the concerns observed with nebulization are somewhat limited [194]. The use of dry powder inhalers (DPI) has been in deed utilized for the delivery of NPs [195]. Notwithstanding, MPs have also been used for drug delivery to the lung following inhalation [196]. Table 3 provides examples form literature by which small NP lung deposition was enhanced by nebulization or through the incorporation into larger particles for administration in dry form for local drug delivery to the lung.

Once deposited in the lungs, approaches to enhance interaction with target cells would be desirable. ACE2 receptor is expressed on ciliated bronchial cells, among others [50]. Concomitantly, SARS-CoV2 has been reported to infect bronchial and bronchiolar mucosa [215]. In such case,

Table 3
Aerosolization of NPs by nebulization or incorporation into larger MPs-examples from literature.

Diseases	Particle type	Therapeutic agent	GD (μm)	AD (μm)	AD obtained by
Asthma / COPD/airway inflammation	SLN and NLC [197]	Beclomethasone dipropionate	0.16–0.23	3–4	Nebulization
	LNC [198]	Fluticasone propionate	0.03–0.1	–	Nebulization
	PLA [199]	Theophylline and budesonide	0.2–0.4	<5	Nebulization
	MSP [200]	Dexamethasone	large MSP 1.5 small MSP 0.230	4–6*	Nebulization
	Chitosan coated PLGA NP [201]	Budesonide	≈ 0.2	–	–
	Sterically stabilized phospholipid nano-micelles [202]	Beclomethasone dipropionate	≈ 0.02	≈ 3	Nebulization
	DPPC-HA MP [203]	Dexamethasone palmitate	≈12–14	–	–
	Nanoemulsion [204]	Budesonide	≈ 0.01	≈4–8	Nebulization
Lung Cancer	PACA NP [205]	Doxorubicin	0.137	3.41	Incorporation in MP
	Magnetic-nanocomposite-MP [206]	–	NP 0.144–0.159 MP 0.701–0.851	4.5	Incorporation into MP
	NLC [207]	Celecoxib	0.217	≈1.6	Nebulization
	Functionalized gelatin NP [208]	–	0.2	0.5–5	Nebulization
	Magnetic/chitosan NP [101]	Fluorescein	<0.15	5–6	Incorporation in MP
Bacterial infections of the lung	Liposomes [209]	Amikacin	–	4.7	Nebulization
	Multilamellar liposomes [210]	Rifampicin and isoniazid	–	0.96	Nebulization
	SLN [211]	Rifampicin, isoniazid and pyrazinamide	–	1.7	Nebulization
	WGA modified PLGA NP [212]	Rifampicin, isoniazid and pyrazinamide	0.35–0.4	2.8	Nebulization
	PLGA NP [191]	Rifampicin, isoniazid and pyrazinamide	0.186–0.29	1.88	Nebulization
Others	PLGA NPs [100]	siRNA	0.262	≈ 5	Incorporation into MPs
	DLPC liposome [213]	Cyclosporine A	–	0.82	Nebulization
	PEG400-HPMCP nanospheres [214]	Beclomethasone dipropionate	≈0.2	–	Nebulization

AD: Aerodynamic diameter, DPPC:Dipalmitoyl-snglycero-3-phosphatidylcholine, DLPC: dilauroylphosphatidylcholine, GD: Geometric diameter HA: hyaluronic acid, HPMCP: hydroxypropyl methylcellulose phthalate, LNC: lipid nanocapsule, MSP: mesoporous silica particles, MP: microparticles, NP: nanoparticle, NLC: nanostructured lipid carriers, PACA: poly alkyl cyanoacrylate, PEG: poly ethylene glycol PLA: poly lactic acid, PLGA: poly lactic co-glycolic acid, SLN: solid lipid nanoparticles, WGA: wheat germ agglutinin.

* aerosolized droplets diameter.

if NPs that have been designed to deposit in the conducting airways were actively modified to bind to ACE2 receptor, theoretically a more specific drug delivery could be achieved. Not dependent on the loaded drug, these particles would also compete with the virions over the available ACE2 receptors (Fig. 3C). The functionalization of NPs with angiotensin II has been previously reported [216] and would be expected to increase NP interaction with ACE2 receptors and enhance NP internalization. The latter is based on the reported ability of angiotensin II to induce ACE2 internalization and degradation into lysosome [217]. While there is currently no data available indicating whether NP bound angiotensin II could be metabolized by ACE2 or type 1 angiotensin II receptor (AT1R), care has to be taken however with the exogenous administration of angiotensin II in any form, since the enhancement of angiotensin II signaling and the attenuation of ACE2 activity are believed to be a primary driver of COVID-19 ARDS [218,219]. Hence, other ACE2 binding ligands might more appropriately serve the task, or the co-administration of AT1R blockers such as losartan [220]. Within this context, losartan is currently being clinically investigated in COVID-19 (NCT04335123). Alternatively, cationic polyamidoamine dendrimer NPs have also been shown to bind to ACE2 receptors in the lung. However, these particles have also been reported to induce lung injury via deregulation of the renin-angiotensin system [221].

Drug delivery to the alveoli would also be required in severe cases of COVID-19. SARS-CoV2 was detected in type I and II pneumocytes in infected macaques [215] and in humans is believed to mainly infect type II cells [222]. Type II pneumocytes are responsible for the generation of pulmonary surfactant which is crucial for reduction of surface tension in the lung [223]. SARS-CoV2 mediated damage to type II cells drastically reduces pulmonary surfactant production and its secretion to the alveolar space [224]. As a consequence, atelectasis and the perturbation of the air-liquid-interphase occur [224]. On top of being critical to one's survival, these changes to the lung structure and function also complicate NP delivery to infected pneumocytes. Thorely *et al.* demonstrated the ability of human alveolar type I cells to internalize 50–100 nm NPs [186]. More importantly, the authors reported that prior to cell internalization these NPs were opsonized by surfactant proteins and such opsonization mediated their cellular internalization [186]. The alterations that occur in surfactant quantity and make-up may therefore complicate NP uptake by alveolar cells in COVID-19 lungs. In ARDS, relative to healthy surfactant, an 80% reduction in the total phospholipid content is observed in addition to massive reduction in surfactant protein A (SP-A) content [225–227]. Both phospholipids and pulmonary surfactant proteins, including SP-A, present a significant portion of the inhaled NP corona and are believed to mediate NP uptake by macrophages and/or alveolar cells [186,228,229]. In this context, utilizing a combination of NP coating with pulmonary surfactant in addition to active targeting would enhance NP delivery to infected cells. Backer *et al.* elegantly demonstrated that while the presence of a pulmonary surfactant on the outer shell of RNA loaded NPs significantly lowered their cellular internalization, it surprisingly increased RNA expression levels. The authors speculated that this increase in RNA expression was the result of reduced RNA leakage and modulation of intracellular trafficking by the surfactant coat. Interestingly, upon incorporation of folate on the outer surfactant shell, a massive increase in NP internalization by folate receptor expressing cells was observed, which was also complimented by a further increase in RNA expression [230]. Particle tagging with SP-A should also facilitate NP internalization. A number of SP-A binding receptors have been identified on the pneumocyte membrane [231–234]. Among which CKAP4/P63 and BP55 facilities SP-A derived receptor-mediated endocytosis in type II cells [234–237]. Indeed, SP-A mediated liposome uptake in freshly isolated type II pneumocytes via a receptor-mediated endocytosis process involving BP55 has been reported [234]. Type II pneumocytes also express the scavenger receptor class B type 1 (SR-B1), which is specific to high-density lipoprotein (HDL) [238]. Luthi *et al.* synthesized HDL-like NPs using gold NPs as a core template which was then decorated with phospholipids and apolipoprotein A-I [239]. Although not in pneumocytes, but these HDL like NPs demonstrated high functional ability to bind SR-B1 [240,241]. Also not for pneumocyte targeting HDL-mimetic poly lactic co-glycolic acid (PLGA) nanoparticles have also been synthesized [242] and could be similarly employed for targeted drug delivery to infected type II cells (Fig. 3D). But is drug delivery into infected alveoli really necessary? Or is drug delivery with-in their vicinity sufficient? Especially if coupled to approaches that would increase their resident time in the lungs and also if antiviral delivery to phagocytic cells is required. This enhanced residence would provide ample time for drug release, providing local high concentrations of antiviral drugs. Similar to SARS-CoV, the diffused alveolar damage observed in COVID-19 patients is accompanied with fibrin rich hyaline membranes [243]. Fibrin clots in the alveoli are also prominent, this is in addition to collagen accumulation which all contribute to the development of a fibrotic lung state [223,224,243–245]. Approaches to enhance NP residence would either exploit the intrinsic ability of the NP building materials to bind one of the aforementioned targets or their active modification with binding ligands. To exemplify the former, we have recently demonstrated the intrinsic collagen binding ability of chitosan NPs and have in fact utilized these NPs for drug delivery to fibrotic livers as function of such binding [246,247]. Analogously, chitosan NPs possessing the required physicochemical properties to deposit deep into the lung should bind to fibrotic regions of the lung showing lower clearance and prolonged residence time as a function of collagen binding (Fig. 3E). Fibrin and/or fibrinogen binding NPs have been explored for tumor targeting [248]. The leaky vessels to which “enhanced permeation” (EP in EPR) is attributed to in NP cancer targeting, are also responsible for the blood clotting products that bedeck the walls of tumor vessels and the interstitial spaces [248]. Within this context, CREKA (Cys-Arg-Glu-Lys-Ala) coated iron oxide NPs have shown specific affinity for tumor vessels endowed by the fibrin-fibrinogen binding properties of the CREKA peptide [249]. Other fibrin-fibrinogen binding peptides have been reported in literature [250,251] and could in fact be utilized for similar purposes in COVID-19 patients following inhalation. While not related to antiviral effects, these clot targeting particles could also be loaded with thrombolytic agents and hence help mitigate one of the very significant reasons for COVID-19 associated mortality.

While it is logical to question the suitability of inhalation therapy in COVID-19, particularly for patients with severe diseases and those on mechanical ventilation, the use of aerosol therapy during mechanical ventilation is expanding. Delivery of therapeutic agents by inhalation has seen increasing applications for many respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), allergies, and influenza [98]. Pressurized metered-dose inhalers (pMDIs) and nebulizers are commonly employed in intensive care units even in mechanically ventilated patients [252].

3.2. Tackling the immune system

Activation of the innate and adaptive immune responses occurs in reaction to SARS-CoV2 infection. A well-coordinated immune response is indeed required for defense against viral infection and has proven efficient in SARS-CoV2 eradication in the majority of COVID-19 patients. In a small subset of unfortunate patients, excessive and deregulated host immune defenses have resulted in harmful tissue damage [219]. Recent data from clinical trials demonstrate that at around one week post infection, patient health state is mainly incapacitated by immunopathological events as opposed to the virus itself (NCT04381936) [27]. To address the enraged host immune defenses, a number of immune-modulating drugs are currently being clinically investigated. Table 4 provides a list of these drugs, their molecular targets and reported side effects. Before addressing the possible advantages endowed by the nano-reformulation of these drugs, a description of SARS-CoV2 induced immunopathology is warranted. Based on current data from COVID-19 patients and based on lessons learned from

Table 4
Immunomodulatory drugs clinically evaluated in COVID-19.

Drug	MOA	Route of administration	Clinical Trials	Side effects
Direct suppression of inflammatory cytokines/chemokines or their receptors				
Sarilumab	Soluble and membrane IL-6 receptors mAb [258–260]	SC [258,259]	**Monotherapy:** NCT04357808, NCT04359901, NCT04324073, NCT04322773, NCT04315298(Completed), NCT04327388 (Completed), NCT04357860 + SOC **In Combination:** NCT04386239 + antiviral agents	Increased risk of infections, reaction at injection site, elevated liver enzymes, neutropenia [258,259]
Tocilizumab	Soluble and membrane IL-6 receptor mAb [261]	IV, S.C [262] [263]	**Monotherapy:** NCT04317092, NCT04345445, NCT04445272, NCT04412772 NCT04435717, NCT04363853 NCT04560205, NCT04315480 NCT04519385, NCT04331795, NCT04377750, NCT04377659, NCT04359667, NCT04320615, NCT04339712, NCT04577534, NCT04356937, NCT04372186, NCT04363736, NCT04479358+SOC, NCT04412291+SOC, NCT04306705+SOC **In Combination:** NCT04332094+Hydroxychloroquine+Azithromycin NCT04310228+Favipiravir NCT04409262+Remdesivir NCT04335305+ Pembrolizumab NCT04476979+Dexamethasone NCT04330638+ Anakinra	Upper respiratory tract infection, hypercholesterolemia, nasopharyngitis, hypertension, elevated liver enzymes, generalized erythema, rash, urticaria, reaction at injection site [262,263]
Sirukumab	IL-6 mAb [264]	SC [264]	**In Combination:** NCT04380961 + SOC	Cardiovascular abnormalities, increased risk of infections, injection-site hypersensitivity, gastrointestinal perforations, elevated liver enzymes, decrease in leukocytes, neutrophils and platelets count. [264]
Siltuximab	IL-6 mAb [265,266]	I.V [265,266]	**Monotherapy:** NCT04322188(Completed), NCT04329650 **In Combination:** NCT04330638+ Anakinra, NCT04486521+ tocilizumab and corticosteroids	Itching, weight gain, hyperuricemia, rash, upper respiratory tract infection, headache, fatigue, diarrhea, increased risk of infections, gastrointestinal perforation [265,266]
Olokizumab	IL-6 mAb [267]	S.C & I.V [267,268]	NCT04380519, NCT04452474	chest pain, back pain, gastrointestinal disorders, pneumonia, abnormal liver function test, perineal abscess, mania [268]
Adalimumab	TNF-α mAb [269]	S.C. [270]	None	Increased risk of rare infections, cytopenia, headache, rash, abdominal pain and injection site reaction. [270,271]
Anakinra	IL-1 α/ β receptor antagonist [272]	SC, I.V. [272]	**Monotherapy:** NCT04362111, NCT04339712, NCT04324021, NCT04443881, NCT04408326, NCT02735707, NCT04364009, NCT04412291 **In combination:** NCT04357366 + trimethoprim/sulfamethoxazole, NCT04330638 + Siltuximab or Tocilizumab, NCT04366232 +/− Ruxolitinib (i.e alone or associated with Ruxolitinib)	Reaction at injection site, progression of arthritis, upper respiratory tract infection, sinusitis, headache, arthralgia, nausea, diarrhea [273]
Canakinumab	IL-1β mAb [274]	S.C, IV [275]	**Monotherapy:** NCT04348448, NCT04362813, NCT04510493	Reaction at injection site, nasopharyngitis, gastrointestinal disorders [274,275]
Mavrilimumab	GM-CSF receptor mAb [276]	S.C, IV [276]	**Monotherapy:** NCT04447469, NCT04463004, NCT04492514, NCT04399980	Mild [277]
Gimsilumab (MORAb 022)	GM-CSF mAb [278]	IV, SC [278]	**Monotherapy:** NCT04351243	N/A
TJ003234	GM-CSF mAb [279]	I.V. [280]	**Monotherapy:** NCT04341116	N/A
Emapalumab	IFN-γ mAb [281]	IV [282]	**Monotherapy:** NCT04324021	Cytomegalovirus infections, hypertension, pyrexia. Gastrointestinal hemorrhage, abdominal pain, tachycardia, diarrhea and constipation [281,282]
Leronlimab	CCR5 mAb [283]	S.C. [283]	**Monotherapy:** NCT04343651, NCT04347239	Diarrhea, headache, swollen lymph nodes, and high blood

(*continued on next page*)

Table 4 (*continued*)

Drug	MOA	Route of administration	Clinical Trials	Side effects
				pressure, irritation at site of injection (NCT00642707) [284]
Direct suppression of compliment components or their receptors				
Ravulizumab	C5 mAb [285]	IV [285]	**Monotherapy:** NCT04390464+SOC, NCT04369469+ SOC, NCT04570397+SOC	Respiratory tract infection, headache pyrexia and hemolysis [286]
Eculizumab	C5 mAb [287]	IV [288,289]	**Monotherapy:** NCT04346797, NCT04355494, NCT04288713	Headache, meningococcal infection, urinary, respiratory and gastrointestinal infections. [287,290]
Avdoralimab	C5a receptor mAb [291]	IV, SC [292]	**Monotherapy:** NCT04371367	Diahrrea, fatigue, back pain, reduced WBC, skin rashes. [292]
Indirect suppression of inflammatory cytokine/chemokine				
(CD24Fc) - CD24 extracellular domain-IgG1 Fc domain recombinant fusion protein	Binds to DAMPs preventing their interaction with TLRs hence inhibiting nuclear NF-kB activation and secretion of inflammatory cytokines, particularly, the release of IL1β, IL6 and TNFα release [293,294]	IV (NCT04317040)	**Monotherapy**: NCT04317040	N/A
Selinexor*	Inflammatory cytokine suppression via inhibition of NF-kB [295]	Oral [296]	**Monotherapy:** NCT04355676, NCT04349098, NCT04534725	Nausea, fatigue, anorexia, vomiting, weight loss, diarrhea and thrombocytopenia [296]
Tofacitinib	JAK1/3-Inhibitor [297]	Oral [297]	**Monotherapy:** NCT04332042, NCT04415151, NCT04469114	Upper respiratory tract infections, headache, nasopharyngitis, diarrhea, hypertension [297,298]
Ruxolitinib	JAK1/2 inhibitor [299]	Oral [299]	**Monotherapy** NCT04348071, NCT04355793, NCT04354714, NCT04377620, NCT04334044, NCT04338958, NCT04477993, NCT04359290, NCT04581954, NCT04403243, NCT04362137+SOC **In combination** NCT04348695+simvastatin	Thrombocytopenia and anemia. Fatigue, diarrhea, ecchymosis, dizziness and headache [299–301]
Fedratinib	JAK2- inhibitor [302]	Oral [302]	–	Anemia, gastrointestinal disorders, thrombocytopenia, peripheral edema, dyspnea, fatigue and elevation of liver enzymes [302,303]
TD-0903	JAK inhibitor [304]	Inhalation [89]	**Monotherapy** NCT04350736 (completed), NCT04402866	N/A
Duvelisib	Suppression of inflammatory cytokines and chemokines via PI3K δ/γ inhibition [305–307]	Oral [308]	**Monotherapy:** NCT04372602, NCT04487886	diarrhea, rash, neutropenia, fatigue, muscle pain, cough, nausea, upper respiratory infection, pneumonia and anemia elevated liver enzymes, thrombocytopenia [307,308]
Ebastine	Suppression of T-cell pro-inflammatory cytokines IL-1β, IL-8, IL-6, and TNF-α, through PI3Kδ inhibition [309]	Oral [309]	**Combination therapy:** ChiCTR2000030535 + Interferon-Beta + Lopinavir	Dizziness, dry mouth, headache, gastrointestinal disturbances [310]
Sirolimus	Inhibition of mTOR, resulting in the reduction of inflammatory cytokines released due to hyperactivation STAT [311,312]	Oral [311]	**Monotherapy:** NCT04341675, NCT04371640	Hyperlipidemia, thrombocytopenia, anemia and leucopenia [311]
Apremilast	Reduction of pro-inflammatory cytokines via Phosphodiesterase 4 inhibition (PDE-4 inhibitor) [313]	Oral [313,314]	**Monotherapy:** NCT04590586, NCT02735707	Diarrhea, headache, nausea, nasopharyngitis, vomiting, abdominal pain, upper respiratory tract infections [314,315]
Cyclosporin A*	Suppression of inflammatory cytokines through binding of Cyp-A and calcineurin preventing the activation of NF-AT [316]	Oral and I.V. [317]	**Monotherapy** NCT04412785, NCT04392531, NCT04392531	Increased susceptibility to infection, nephrotoxicity, nausea, vomiting, tremor, hirsutism, hypertension, gum hyperplasia, triggering of cancer [317–319]
Colchicine	Disruption of inflammasome activation, suppressing caspase-1 activation and subsequent release of IL-1β and IL-18 [320–322]	Oral [323]	**Monotherapy:** NCT04360980, NCT04350320, NCT04326790, NCT04355143, NCT04510038, NCT04392141, NCT04527562, NCT04322682, NCT04322565, NCT04363437, NCT04403243, NCT04367168, NCT04539873, NCT04375202 +SOC, NCT04355143+SOC, NCT04416334+SOC	Diarrhea, pharyngolaryngeal pain [323]

(*continued on next page*)

Table 4 (*continued*)

Drug	MOA	Route of administration	Clinical Trials	Side effects
			In Combination: NCT04492358+ Prednisolone NCT04328480+/− Lopinavir/Ritonavir	
Acalabrutinib	BTK inhibitor, suppression inflammatory cytokine release [324–326]	Oral [324]	**Monotherapy:** NCT04497948, NCT04380688 + SOC, NCT04346199 + SOC	Headache, diarrhea, upper respiratory tract infections, weight gain, neutropenia, pneumonia anemia, hypertension, atrial fibrillation, bleeding [324] [327]
Fingolimod	Reduction of inflammatory cytokines via sphingosine-1-phosphate agonism [328,329]	Oral [330]	**Monotherapy:** NCT04280588	Headache, diarrhea, back pain, cough, dyspnea, lower respiratory tract infection, elevated liver transaminase, transient bradycardia, hypotension and slowed atrioventricular conduction [331]
Bevacizumab	VEGF mAb [332]	IV [332]	**Monotherapy:** NCT04305106, NCT04344782, NCT04275414	Hypertension, asymptomatic proteinuria, thromboembolism, gastrointestinal perforation [332]
Corticosteroids				
Dexamethasone, Mometasone furoate, Hydrocortisone, prednisolone, Budesonide, Cickesonide	Anti-inflammatory, immunosuppressant, anti-edema, anti- fibrotic [333,334]	IV. [335] Oral [336]	**Monotherapy:** NCT04381936, NCT04325061, NCT04513184, NCT04509973, NCT04499313, NCT04395105, NCT04530409, NCT04344730, NCT04528329, NCT02735707, NCT04348305, NCT04499313, NCT04559113, NCT04438980, NCT04273321, NCT04374071, NCT04329650, NCT04355247, NCT04343729, NCT04263402, NCT03852537, NCT04485429 + SOC NCT04323592 + SOC **In Combination:** NCT04476979 + Tocilizumab NCT04347980 + hydroxychloroquine NCT04456439 + Remestemcel-L + Diphenhydramine NCT04349410+ Solumedrol NCT04452565 + NA-831/ Atazanavir NCT04341038 + Tacrolimus NCT04331470+ Formoterol + Levamisole	Adrenal insufficiency, fluid retention, electrolytes imbalance, myopathy, gastrointestinal disturbances, hormonal imbalance, glaucoma, Neuropsychiatric adverse effects, dermatological side-effects [335–337]
		Intranasal [338], Inhalation [339]	**Monotherapy:** NCT04513184, NCT04484493, NCT04422275, NCT04330586 NCT04416399 NCT04355637 NCT04435795 NCT04377711 NCT04381364 **In Combination:** NCT04331054+ Formoterol + SOC	Headache, epistaxis, nasopharyngitis, ear pain [338,339]

BTK inhibitor: Bruton's tyrosine kinase inhbitor, C5: Complement component 5, CCR5: Chemokine receptor 5, Cyp-A: cyclophilin A, NF-AT: Nuclear factor of activated T-cells, DAMPs: Danger-Associated Molecular Patterns, GM-CSF: Granulocyte-macrophage colony-stimulating factor, IFN-γ: Interferon gamma, IL-6: Interleukin 6, IV: Intravenous injection, JAK1/3-Inhibitor: Janus kinase 1/3-Inhibitor, mAbs: monoclonal antibodies, mTOR: mammalian target of rapamycin, NFkB: Nuclear factor-kappa B, PDE-4 inhibition: Phosphodiesterase 4 inhibitor, PI3Kδ inhibition: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta inhibition, SC: Subcutaneous injection, SOC: Standard of Care,STAT: Signal transducer and activator of transcription, TLRs: Toll-like receptors, TNFα: Tumor necrosis factor alpha VEGF: Vascular endothelial growth factor.

* Inhibition of viral replication and/or cellular entry.

SARS-CoV and MERS-CoV, a number of reports elegantly attempted to delineate the SARS-CoV2 immunopathology [219,222,253–257]. However, in the current situation, where the exact underlying pathways and actions indicted of such detrimental events are not fully understood, here, we choose to tackle SARS-CoV2 induced immunopathology from a treatment perspective and hence will only provide a brief overview of the major pathways and components implicated in SARS-CoV2 immune mediated damage, to further justify the reason for and the means of nano-reformulation of the repurposed immune-modulating drugs.

Severe cases of COVID-19 are characterized by a state of hypercytokinemia or a “cytokine storm” [257]. The cytokine storm commences by the activation of the innate immunity upon SARS-CoV2 infection to epithelial cells. Infected epithelial cells, innate immune and endothelial cells release a multitude of cytokines with aim of halting viral replication and recruiting effector cells to eliminate infected ones. Delayed IFN response (among other factors) results in viral persistence and the consequent sustained release of cytokines along with the immune signaling, trigger a secondary wave of cytokine release ultimately resulting in a cytokine storm [255,256]. Molecules such as interleukin (IL) IL-6, IL-1β, IL-2, IL-7, IL-10, in addition to, IFN-γ, monocyte chemoattractant protein (MCP- 1), macrophage inflammatory protein (MIP-1α) and tumor necrosis factor (TNF-α) are elevated in critical cases and are associated with SARS-CoV2 mediated damage [222,340]. Immunomodulatory drugs that are currently being repurposed for COVID-19 therapy either target the produced cytokines and/or chemokines, or the underlying pathway(s) that result in their uncontrolled release.

SARS-CoV2 infects alveolar epithelial cells resulting in cascade of detrimental events [254] (Fig. 4). Increased degradation of IκB has been reported to occur upon interaction of CoV S-protein with host cell. IκB is an inhibitory protein which under normal conditions resides in the cytoplasm. Through a sequence of events, the degradation of IκB results in the activation and nuclear translocation of nuclear factor (NF-κB) resulting in the transcription of a multiplicity of genes encoding several inflammatory chemokines and cytokines (Fig. 4(i)), including those of the TNF-α/IL-6 axis [29,253,341,342]. IL-6 in particular presents a rather interesting cytokine and a therapeutic target. Elevated IL-6 levels are believed to be predictors for diseases severity and the need for mechanical ventilation [343–345]. In the host cell, IL-6 promotes the downstream activation of Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling (Fig. 4(ii)), which in turn results in further production of IL-6 [219]. Additionally, SARS-CoV2 infection results in the down-regulation of ACE2 receptors on host cells, thus resulting in overproduction of angiotensin II [222]. Indeed, increased angiotensin II plasma levels in SARS-CoV2 infected patients were linearly associated to viral load and lung damage [346]. This increased angiotensin II binds to AT1R, resulting in the activation of JAK/STAT signaling pathway and once more, the overproduction of IL-6 (Fig. 4(iii)). The Angiotensin II/AT1 receptor axis is also implicated in further activation of the NF-κB pathway resulting in a positive feedback loop increasing inflammatory cytokine production (Fig. 4(iv)). It therefore seems rather logical that IL-6 and IL-6 receptor antibodies (such as sarilumab, tocilizumab, sirukumab, siltuximab and olokizumab), drugs reducing the expression or nuclear import of NF-κB (such as CD24Fc and selinoxor) and JAK inhibitors (such as tofacitinib, fedratinib, TD-0903 and ruxolitinib) have all been repurposed for COVID-19 therapy (Table 4).

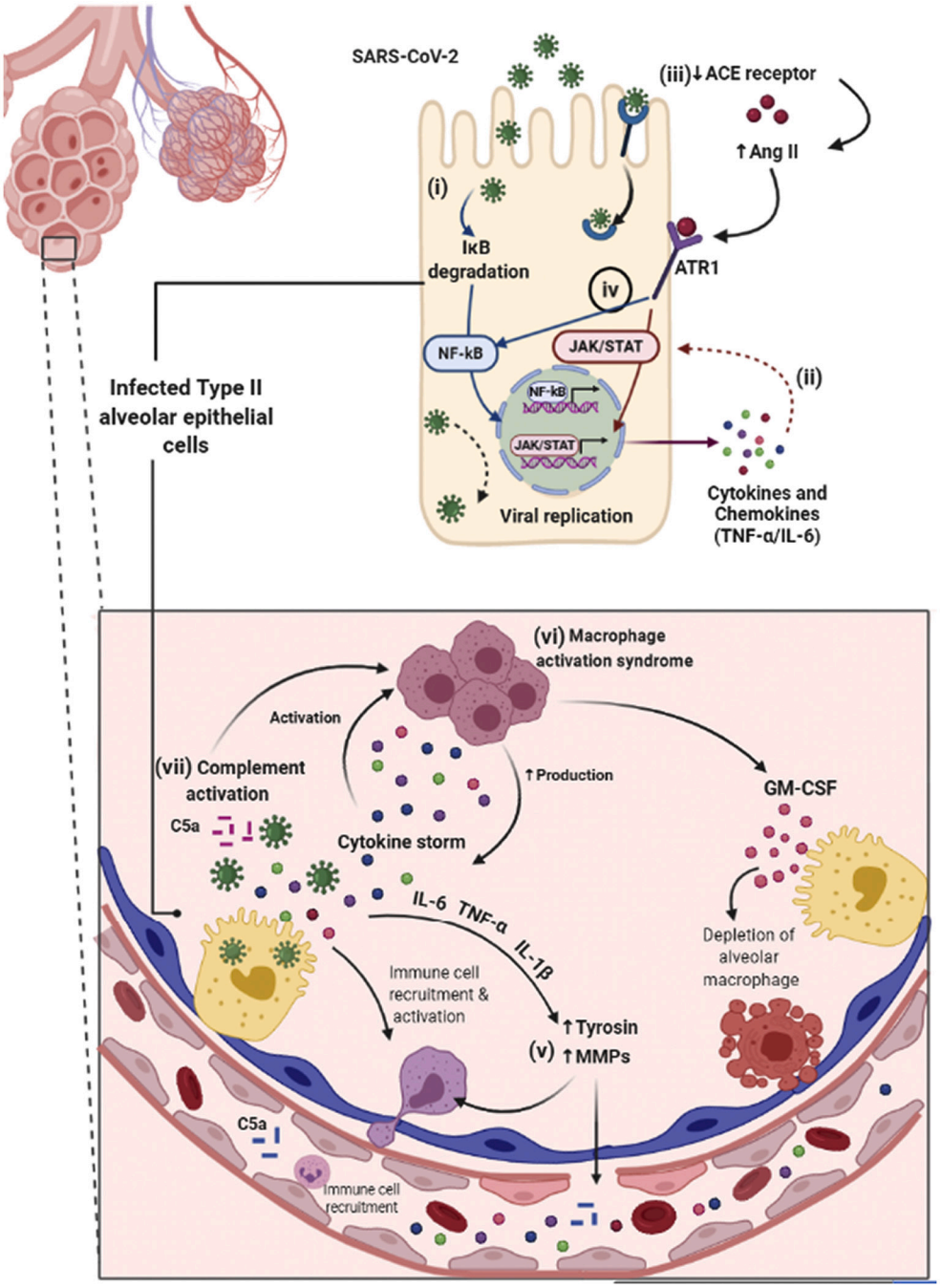

Fig. 4. SARS-CoV2 immunopathology, pathways implicated in hyperinflammation and cytokine storm (i) Interaction of CoV S-protein with host cell results in the degradation of IκB and the activation and nuclear translocation of NF-κB resulting in the transcription of genes encoding several inflammatory chemokines and cytokines inlcuding those of the TNF-α/IL-6 axis (ii) IL-6 promotes activation of JAK/STAT signaling, resulting in further production of IL-6 (iii) SARS-CoV2 infection results in the down-regulation of ACE2 receptors resulting in overproduction of angiotensin II which binds to AT1R, resulting in the further activation of JAK/STAT signaling pathway and the overproduction of IL-6 (iv) The angiotensin II/AT1 receptor axis is implicated in activation of the NF-κB pathway (v) The produced cytokines cause the up-regulation of trypsin expression and activating matrix metalloproteinase resulting in the break down of the basal membrane, increased tissue permeability and immune cell recruitment and (vi) resulting in a MAS-like state. Abbreviations: IL-6: Interleukin 6, NFkB: Nuclear factor-kappa B, JAK/STAT: Janus kinase/signal transducers and activators of transcription, TNFα: Tumor necrosis factor alpha, ACE2: Angiotensin Converting Enzyme 2, AT1R: Type 1 angiotensin II receptor, MMPs: Matrix metalloproteinase, GM-CSF: Granulocyte macrophage-colony stimulating factor, MAS: Macrophage activation syndrome.

In addition to other cytokines, IL-6 produced by the infected host cell, in combination with the released virions and viral components, activate and recruit immune cells [222]. Indeed, IL-6 synergizes with TNF-α and IL-1β, up-regulating trypsin expression and activating matrix metalloproteinase resulting in the breakdown of the basal membrane, increased tissue permeability and immune cell recruitment [347] (Fig. 4 (v)). Macrophage activation syndrome (MAS) is a critical consequence and a contributor to such events (Fig. 4(vi)).The latter is underpinned by data from analysis of bronchoalveolar lavage fluid obtained from COVID-19 patients with severe disease, that show an abundance of proinflammatory monocyte-derived macrophages [348], with a concomitant depletion of tissue-resident alveolar macrophages [348,349]. The latter is potentiated via the action of granulocyte macrophage-colony stimulating factor (GM-CSF). In healthy lungs, GM-CSF is normally released from type II alveolar cells and is necessary for surfactant homeostasis and alveolar macrophage development. In severe inflammatory states, GM-CSF production is up regulated by type II epithelial cells and monocyte-derived macrophages. Monocytes differentiation into the pro-inflammatory phenotype is achieved though activation of the JAK/STAT pathway resulting in a positive feedback loop of GM-CSF production that results in further perpetuation of the inflammatory milieu [254,350,351]. These macrophages in turn result in increased production of IL-6, IL-7, TNF-α and also chemokine ligands CCL, CCL2, CCL3 and CXC-chemokine ligand 10 (CXCL10) [254,352], resulting in an inflammatory cytokine-chemokine cocktail. For such reasons, therapeutic compounds acting through the inhibition of TNF-α (adalimumab), IL-1 (anakinra and canakinumab), GM-CSF (mavrilimumab, gimsilumab, and TJ003234) have also been repurposed and are being clinically evaluated in COVID-19 therapy (Table 4). Bevacizumab a vascular endothelial growth factor (VEGF) antibody, is also being evaluated in COVID-19 (Table 4). The downregulation of ACE2 receptor by SARS-CoV2 is believed to increase VEGF expression which are considered key factors in acute lung injury and ARDS due to their ability to increase vascular leakiness and permeability [353].

Complement activation has been implicated in the immunopathology of MERS and SARS-CoV. Thus, compliment inhibitors (ravulizumab, eculizumab and avdoralimab) are also being repurposed in COVID-19 (Table 4). Activation of C3 and the complement activation fragment anaphylatoxin C5a in particular [354,355], are major contributors, since the pharmacological blockade of their receptors attenuated pulmonary inflammation and led to decreased viral replication in infected lungs [356]. In SARS-CoV2 infection, complement activation, indicated by an increase in C3a in the lung and C5a in serum was reported in patients with severe COVID-19 [357]. More importantly, treatment with anti-C5a antibody resulted in immediate clinical improvement [357]. C3 inhibitors might be more effective, but have yet to be approved. This might be attributed to the upstream positioning of C3 signaling in the innate immune cascade. In fact, C3 inhibition could simultaneously block C3a and C5a generation, as well as intrapulmonary C3 activation and IL-6 release from alveolar macrophages, or other cells that express C3a receptors (C3aRs) and/or C5a receptors (C5aRs), thereby ameliorating lung injury [357].

The use of immunomodulatory drugs might offer a safe haven from the SARS-CoV2 induced hyper inflammation. However, several critical issues have to be considered, the first of which is the treatment timing. Early treatment might adversely affect viral clearance. For such reason, immunomodulatory therapy should not serve as the first line of treatment and the use of antiviral drugs (Table 1) should precede such modalities [358]. In that sense, their effectiveness could be enhanced by nano-reformulation for inhalation therapy. The broad ablation of IL-6 at very early stages of the infection may result in delayed antiviral antibody responses [359]. Within the same framework, treatment modalities employing IFN are used in early diseases stages to halt viral replication (please see Table 1), however, IFN ʎ antibodies (Emapalumab - see Table 4) are also being clinically evaluated in severe disease. The same would apply to other cytokines and chemokines. For instance, GM-CSF is beneficial for maintaining alveolar macrophage function which is necessary during viral assault in early disease and indeed, recombinant inhaled GM-CSF is currently in phase IV studies in patients with COVID-19 infection and acute hypoxic respiratory failure (NCT04326920). At a later stage however, neutralizing excessive GM-CSF may attenuate the cytokine storm and the consequent lung destruction. Notwithstanding, early (but not too early) immunomodulatory intervention, afore the onset of respiratory failure, may prevent poor outcomes. Once inflammation is no longer lung central, the "window of opportunity" for immunomodulatory interventions as referred to by Mehta *et al.* might have already been missed, and patients then spiral down into an abyss of deterioration, during which initiation of treatment would probably not be of substantial clinical benefit [279]. Early identification of patients with potential deregulated immune-responses would therefore allow for better targeting of such "window of opportunity" and hence the identification of robust predictive biomarkers for hyper inflammation represents a holy grail for COVID-19 research [360]. While such biomarkers are yet to be discovered, in the meantime, avoiding the side effects of the generalized systemic inhibition of the implicated immune players seems like a less tortuous route, at least when visioned from the context of nano-reformulation. Most of the cytokines (and/or the implicated players) that are the focus of the investigated drugs are pleiotropic molecules with diverse multifaceted functions including roles in tissue homoeostasis, hematopoiesis, host defenses, epithelial repair among others [361,362] and their generalized inhibition would not result in positive outcomes. For instance, the generalized blockade of IL-6 could result in a rapid suppression of C-reactive protein and fever, complicating the detection of secondary infection or even viral relapse. This could also serve as a false reassurance for the efficacy of the therapeutic agent, since a reduction in C-reactive protein and fever would be regarded as a clinically positive outcome [279]. So far most immunomodulatory drugs assessed in COVID-19 clinical trials are being administered either orally, subcutaneously and intravenously **(**Table 4**)**. This once more spikes the same questions discussed in the previous section of this review; how much of the administered drug actually reaches the lung and as a consequence, where does the remainder of the dose go? Needless to say, elevated IL-6 (among others) plasma levels are observed in critical cases of COVID-19 [363], but it all initially starts in the lungs [279,364]. Would not inhalation therapy allow higher concentrations of the drug at the sight of inflammation, lower concentrations systemically and hence a stronger, more localized action, with reduced adverse effects? We therefore consider the nano-reformulation of the immunomodulatory drugs for inhalation therapy a viable approach to enhance the drug efficacy with the potential of high specific surface area in nanocarriers or nanosized capsules. This is backed up by the urgent appeal from the International Society for Aerosols in Medicine (ISAM), urging governments and decision makers to consider the inhaled route for therapy of COVID-19 [365] and by the adverse effect profile of utilized systemically administered drugs (Table 4). In fact, a nebulized solution of the JAK inhibitor TD-0903 is currently being clinically evaluated in COVID-19 (NCT04402866). In its inhaled form, TD-0903 shows higher lung selectivity and reduced systemic distribution [366]. In this case, its solubility and rather stable nature has enabled its nebulization, but could the same be applied to other drugs? Or would their nano-reformulation offer added advantages? For the latter to materialize it is necessary to point out what would be expected of the carrier system in this case? The critical points that need to be addressed through concerted efforts include, deep lung deposition, preservation of the functionality of the loaded therapeutic molecule and possibly a prolonged residence time and/or sustained drug release. In a similar manner to antiviral drugs, the reformulation of the immunomodulatory drugs into NPs and MPs could facilitate their deposition deep into the lung (Figs. 2 and 3**)**. This would however mandate the optimization of the particle's AD as discussed in the previous section. But other than allocating in the lung, would targeting a specific cell be required?

Should active targeting be employed? While theoretically the modification of the NPs with targeting ligands would be expected to increase their allocation in the target cell [26], in this case the identity of the target cell however remains elusive. Most of the intracellular pathways implicated in the overexpression of the inflammatory cytokines and chemokines are present in epithelium, endothelial and immune cells of the lungs and hence delivering drugs (that act on intracellular targets) to a specific cell would complicate the formulation procedure without much added benefit. At the same time, inflammatory cytokines and chemokines are abundant in the extracellular compartment in the vicinity of the alveolar space and hence intracellular delivery of the drugs would also not be required. One can therefore speculate, that excessive attempts of targeting might not offer substantial benefit and believe that efforts invested in maintaining high drug concentrations in the lung might be of more fruitful outcome. This is in addition to simpler formulation, upscaling and approval procedures. The latter being dependent on the fact that the drugs employed are repurposed drugs that have already been approved for other indications.

Approaches that enhance NP and MP residence deep in the lung and reduce their clearance should enable a sustained therapeutic effect. To that end, modalities that exploit changes associated to lung physiology in COVID-19 as discussed earlier would be rather interesting. Particles that show binding to the ECM components such as collagen for instance [246,247] should serve such target. More importantly however, is the ability of the NPs to preserve the functionality of the loaded molecule. With the exception to a number of low molecular weight compounds, most of the employed therapeutics are protein drugs, more specifically antibodies (Table 5) and hence care has to be taken during formulation to avoid functionality losses [132]. When considering the protein therapeutics in Table 5, to date, to the best of our knowledge, only nano-formulations for bevacizumab [367–373] and tocilizumab [374], an IL-6 antibody [375] and an IL-1 receptor antagonist [376,377] have been reported. In such cases the antibodies were either tagged to the NP surface or encapsulated. Tagging to the surface was achieved either by allowing the antibodies to adsorb to the NP surface [374] or by covalent linking using mild conditions [371,372]. While extremely simple in principle, surface adsorption would result in an uncontrolled density and orientation of antibody on the surface of the NPs [378], possibly hindering binding to the target. Additionally, when exposed to a complex matrix such as lung surfactant or serum, uncontrolled displacement of the adsorbed antibody with other proteins that are of higher affinity or abundance might occur [132]. Covalent linking of the antibodies addresses the aforementioned limitations. The use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) is in fact a very popular approach to do so [101,371,372,375]. EDC is an amine carboxyl linker and is usually used to link the antibody's terminal carboxyl groups to NP surface amines [101]. This would limit the choice of NPs to those with amine groups or would require functionalization of the NP surface with the same. Alternatively, encapsulation of the antibodies would also sever the purpose. In fact, the encapsulation as opposed to surface tagging might bestow additive protection to the loaded macromolecules [379]. Notwithstanding, the correct excipients and formulation approach are necessary to avoid losses of functionality. For instance, bevacizumab has been loaded into PLGA NPs by the double emulsion solvent evaporation technique with an EE% ranging between 67 and 69% [368,370]. While it is true that the protein is initially dissolved in an aqueous solvent, during the primary emulsion step, proteins partitioning at the water–organic solvent interface would be susceptible to denaturation and aggregation [380]. Indeed, Sousa *et al.* [368] clearly demonstrated the aggregation of bevacizumab upon encapsulation into PLGA NPs by the double emulsion solvent evaporation technique. This was demonstrated by the occurrence of intermolecular β-sheets upon investigation of the secondary structure of the protein pre and post loading into NPs. In addition to being therapeutically inactive, the resultant aggregates of denatured proteins could result in immunogenicity or toxicity [381,382]. The addition of bovine serum albumin (BSA) to the inner water phase could avoid such aggregation [383]. Due to their surface active properties the added BSA molecules partition at the interface protecting bevacizumab against entrapment stresses [383]. While it is plausible for the large BSA molecules to reduce loading of therapeutic antibody, BSA surface activity could compensate for the latter since it would result in reduced drug leakage and formation of more stable emulsions. Notwithstanding, while BSA has stabilized bevacizumab [383] and could be expected to stabilize other antibodies (which are the majority of COVID-19 investigated drugs), care has to be taken since albumins have on occasions failed to stabilize other the loaded proteins [384]. Another factor to consider with PLGA NPs is the autocatalytic degradation of the ester backbone, resulting in the acidification within the NP milieu. This acidification could lead to the degradation of the loaded protein [132] and hence the co-encapsulation of magnesium hydroxide could help neutralize this acidic pH [385]. Alternatively, chitosan NPs prepared via inotropic gelation might offer a simpler approach for the encapsulation of sensitive macromolecules. Organic solvents and heat are not employed in ionotropic gelation where the incorporation of therapeutic proteins occurs via mild electrostatic interactions in aqueous, physiological conditions [132]. In fact, for protein delivery, chitosan NPs has shown an ability to stabilize the loaded protein, provide a high EE, reduced burst, and provide a sustained release of active macromolecular drugs [246,386,387]. In addition, the use of chitosan could allow for an increased residence time. The presence of intra-alveolar fibrinous exudates and loose interstitial fibrosis in lungs of severe COVID-19 patients [244], spikes interest as to whether the collagen binding ability of chitosan [246,247] could be exploited for prolonged drug availability at their site of action. Moreover, the presence of surface amines, enables facile functionalization of these NPs by various targeting ligands via the use of commercially available crosslinkers under mild conditions [388]. These targeting ligands would not be intended to target the NPs to a specific cell but to allow for an increased residence time.

These “increased residence” strategies could also be used for the delivery of low molecular weight compounds. In fact, several of the low molecular weight immunomodulatory compounds that are being clinically evaluated in COVID-19 have been nano-scaled (Table 5). Despite being repurposed, some of the clinically evaluated drugs to date have not been formulated in the “nano” form. Selinexor, duvelisib, ruxolitinib, and ciclesonide for instance all show poor water solubility but at the same time show relatively high solubility in ethanol [389,390] and hence could be incorporated into hydrophobic polymeric NPs using the nanoprecipitation technique [132]. Silica NPs could also be used for the loading of hydrophobic drugs [391], these particles offer controlled release advantages given the possibility of the use of gate keepers that control drug diffusion out of the pores [392]. On the other hand, fedratinib and acalabrutinib show pH dependent solubility [393–395] and could hence be encapsulated in liposomal carriers, hydrophilic polymeric NPs or hydrophobic polymeric NPs via double emulsion based approaches [132]. Special considerations in this case have to be taken to avoid low EE%, rapid drug leakage and burst release [132].

More recently, focus has been shifted to a cocktail of immunomodulatory drugs as opposed to the use of a single drug [219,340,396,397]. This is due to the activation of numerous redundant pathways, requiring simultaneous action to exert synergic or additive effects [219]. In that sense, nano-reformulation might also offer added benefits. The ability of a particular carrier system to deposit in the lung, should allow multiple therapeutic agents to co-localize in the same region and hence increasing the chance of synergetic action. However, within the same context, and taking into consideration the existence of a MAS-like state in COVID-19, should not the use of corticosteroids be prioritized [27,364]? Corticosteroids are well known cytokine suppressors, antiedematous and anti-fibrotic agents [27], their use in COVID-19 however remains debatable with evidence to both support [398,399] and advise against [400] their use. Interestingly, the main concern for advising against their use is the delayed (or reduced, depending on time

Table 5
Immunomodulatory drug properties and reported nano-formulations.

Drug	Solubility	Molecular weight	Particle Type	Particle Diameter (nm)	EE%
Macromolecules					
IL-6 Ab	Soluble	≈ 150 KDa	Chitosan-Hyaluronic acid NP [375]	≈120	10 μg/ml#
Tocilizumab			Gold NP [374]	64	20.8 units per NP
Sirukumab			–	–	–
Siltuximab			–	–	–
Olokizumab			–	–	–
Adalimumab			–	–	–
IL1 receptor antagonist			Chitosan NP [376]	≈1000	
			Chitosan-Hyaluronic acid NP^ [405]	≈150	
			Poly (2-hydroxyethyl methacrylate)-pyridine NP [377]	300–700	
Canakinumab	Soluble	≈ 150 KDa	–	–	–
Mavrilimumab			–	–	–
Bevacizumab			SLN [367]	516	30
			Carbon-coated pure iron core magnetic NP [406]	51–90	–
			PLGA [368]	199	82
			PEG coated human serum albumin NP [369]	300	92
			Chitosan coated PLGA [370]	222.28	69.26
			Chitosan NPs [371]	190	38
			Chitosan NPs [373]	78.5	67.6
Leronlimab			–	–	–
Gimsilumab			–	–	–
Sargramostim			–	–	–
Ravulizumab			–	–	–
Eculizumab			–	–	–
Avdoralimab			–	–	–
Emapalumab			–	–	–
TJ003234	–	–	–	–	–
CD24Fc	Soluble [407]	≈30 KDa¥	–	–	–
Low molecular weight compound					
Colchicine	Low [178,408]	399.4 g/mol	MSN coated with folic acid chitosan-glycine complex [409]	330–410	–
			PLA-Eudragit RL NP [410]	450–875	45
			PEGylated gelatin NP [411]	193	72
			Chitosan NP [412]	294	93
			SLN [413]	107	37
Selinexor	Low [178]	443.31 g/mol	–		
Tofacitinib	Low [178]	312.4 g/mol	NLC [414]	–	79
			SLN [415]	–	–
			PLGA [416]	250	60
Ruxolitinib	Low [178]	404.36 g/mol	Gold NP [417]	15	–
Fedratinib	Soluble at low pH [418]	615.62 g/mol	–	–	–
TD-0903	–	–	–	–	–
Dexamethasone	Sparingly soluble [178]	516.41 g/mol	Liposomes [419]	113	1
			PLGA-PEG-PCL NP [420] ECT2-NPs	110–127	53
			PLGA NP [421]	200	95
			PLA-PEG-PLA PCL-PEG-PCL [422]	200–300	50–60
			Chitosan NP [423]	277–289	–
			Chitosan NP [424]	305–400	73
Mometasone furoate	Low [178]	539.45 g/mol	PLGA NP [425]	117	90
			NLC [426]	163	60
			SLN [427]	124	56
			LNC [428]	211	100
Hydrocortisone	Low [178]	362.46 g/mol	Chitosan NP [430]	235	80
Hydrocortisone sodium succinate	Soluble [429]	484.5 g/mol	PCL NP [431]	200	62
Prednisolone sodium phosphate	Soluble [432]	484.39 g/mol	Liposome [434]	340–712	63–91
			Liposome [435]	186	96
Prednisolone acetate		402.49 g/mol	PEGlyated Liposome [436]	82	94
	Low [178]		PEGlyated Liposome [437]	105	2
Methyl prednisolone succinate		496.5 g/mol	Liposome [438]	74	>95
	Soluble [433]		Liposome	500	–
			PEGlyated Liposome [432]	100	
			PEGlyated liposome [439]	100	–
			Eudragit NP	149	51
			PCL NP [440]	234	46
			Chitosan NP [441]	168	79
Budesonide	Low [178]	430.5 g/mol	PLA NP [442]	345	65

(continued on next page)

Table 5 (*continued*)

Drug	Solubility	Molecular weight	Particle Type	Particle Diameter (nm)	EE%
			PLGA NP	220	46
			PEGylated Liposomes [443]	190	4
			Eudragit NP [444]	171	84
			PLGA NP [445]	200	85
			Chitosan NP	363–443	30–65
			Chitosan-PVA NP [446]	416–543	37–75
Ciclesonide	Low [178]	540.7 g/mol	–	–	–
Acalabrutinib	Soluble at low pH [178]	465.51 g/mol	–	–	–
Sirolimus (rapamycin)	Low [447]	914.2 g/mol	SLN [448]	102	43
			PLA NP [449]	250	20 (*w*/w)
			PEG-*b*-poly(γ-benzyl L-glutamate) shelled NP [450]	106	82
			Polymer–lipid hybrid NP [451]	129	64
			Chitosan coated liposome [452]	88–119	84–88
			Liposome [453]	140–211	93–98
			PLGA NP [454]	250	69
			Drug nanocrystal [455]	<400	–
Apremilast	Low [178]	460.5 g/mol	PLGA NP [456]	282–307	40–61
			NLC [457]	758	86
Fingolimod	Soluble [178]	343.93 g/mol	PHBV NP [458]	250	73
			Liposomes [459]	157	85
Duvelisib	Low [178]	416.9 g/mol	–	–	–
Cyclosporin A	Low [178,460]	1202.6 g/mol	LNP [461]	163–270	≈100
			PLGA NP [462]	174	2.67 (wt/vol)
			PLGA NP [463]	163	>85 w/w
			PEG-PLGA NP [464]	8 3	3.3 (w/w)
			Gambogic acid conjugated PEG-PLA NP [465]	200–278	22 (w/w)
			SLN & NLC [466]	200	70–85%
			PLA NP [467]	150	54
			Chitosan nanocapsule [468]	40–60	99.2
			HPMCP NP [469]	50–60	> 95
			PEGylated chitosan-modified LNP [470]	89	69
Thalidomide	Low [178]	258.23 g/mol	Methoxy PEG-PCL NP [471]	50	66
Ebastine	Sparingly soluble	469.7 g/mol	Chitosan NP [472]	169–500	27–44
			Drug nanocrystal [473]	<2000 nm	–

ECT2: pendant cyclic ketals, HPMCP: hydroxypropyl methylcellulose phthalate, LNCs: Lipid nanocapsules, LNP: Lipid nanoparticles, MSN: mesoporous silica nanoparticles NLC: nanostructured lipid carriers, PLGA:Poly(lactic-*co*-glycolic acid), PEG: polyethylene glycol, PLA: Poly-lactic acid, PCL: Polycarpolactone, PVA: Poly (vinyl alcohol), PHBV: poly (hydroxybutyrate-*co*-hydroxyvalerate), SLN: Solid lipid nanoparticles.

[#] Immoblization capacity.

[^] particles loaded with pDNA encoding IL-1 receptor antagonist gene.

[¥] predicted monomer molecular weight.

of treatment) antiviral response, which is also a concern for other immunomodulatory drugs and is actually emphasized when these drugs are used in a cocktail form. These antibody cocktails however, come at a higher cost and since they have not been in use as long as other "tried and tested" drugs such as dexamethasone, budesonide and prednisolone for instance, they come with a unexplored risk and a set of adverse effects [27]. While systemic corticosteroids are being clinically evaluated in COVID-19 (NCT04381936, NCT04445506, NCT04519385, NCT04325061, NCT04513184), inhaled corticosteroids are also being evaluated (NCT04416399, NCT04355637, NCT04193878, NCT04377711 and NCT04330586). The inhaled form should offer less systemic side effects, and since they have been on the market for decades now, offer a shorter route from the perspective of necessary approvals. Notwithstanding, most of these inhaled formulations have been employed in the treatment of asthma and COPD and mainly aim at targeting the bronchi and conducting airways [401] and require multiple treatments per day. It is therefore questionable whether in their current from, these drugs could reach the alveoli. It could be postulated that nebulized free corticosteroids may not achieve sufficient alveolar drug concentrations in COVID-19 infection based on the notion that nebulized antibiotics are not effective in bacterial pneumonia [402]. In that sense, the nano-reformulation of these drugs, might allow enhanced drug delivery deep into the lung and possibly provide a sustained release of drug, hence requiring less frequent dosing. The latter is emphasized by the success of Arikayce, an inhaled liposomal suspension of amikacin which has shown superior ability in depositing deep in the lung and targeting of alveolar macrophages [403]. Several nanocarriers have been successfully loaded with corticosteroids (Table 5), among which several have been employed in inhalation therapy (Table 3). Should not these systems be expedited for use in COVID-19? One last note, corticosteroids, specifically ciclesonide and mometasone were able to suppress SARS-CoV-2 replication *in -vitro* to a similar degree as lopinavir. The target for ciclesonide seems to be the nonstructural protein 15 (NSP15) [404], which might provide added reason for the nano-reformulation of such drugs.

4. Perspectives and conclusions

While this account strongly advocates the nano-reformulation of both antiviral and immunomodulating drugs for inhalation therapy, it is also noteworthy that in some cases the systemic administration of these nano-drugs might be warranted. In case the proposed window of opportunity has been missed and that inflammation is no longer lung centralized, the ability to increase immunosuppressive drug concentrations in the target immune cell would be highly needed. In that sense, relying on the consensus that intravenously administered NPs with specific physicochemical properties accumulate in macrophages [26], drug targeting to phagocyte rich myeloid and lymphoid tissues becomes possible [27]. Systemic administration might also be useful for drugs with targets located in endothelial cells. These cells have been central

orchestrators of cytokine amplification during other respiratory virus infections [474]. Fingolimod is a sphingosine-1-phosphate receptor regulator (FTY720) and has proven rather useful in multiple sclerosis [328]. Fingolimod is currently being investigated in COVID-19 (NCT04280588), with high potential to ameliorate the cytokine storm [329]. It is speculated that sphingosine-1-phosphate agonism results in cytokine suppression via the action of fingolimod in lung endothelial cells [329]. Fingolimod could also stabilize the pulmonary endothelial barrier hence decreasing inflammatory infiltrate and subsequent ARDS [475]. In such case, the delivery of fingolimod loaded NPs to lung endothelial cells following intravenous administration might be warranted.

Another rather critical point to consider is the effect of the excipients. While there is a general notion that organic NPs composed of lipids and biodegradable and/or biocompatible polymers are inert, it has recently become clear that such excipients are not that inert, especially when nanoscopic [476,477]. For instance, despite being well-established excipients in the pharmaceutical industry and components of several oral formulations, ammonio methacrylate copolymers (types A and B; Eudragit® RL and RS) acquired immunostimulatory properties when formulated into NPs [476]. Within the same context, cationic polyamidoamine dendrimer NPs could induce lung injury via deregulation of the renin-angiotensin system which is mainly due to their ability to bind to ACE2 receptors [221]. On the other hand, chitosan NPs showed anti-inflammatory effects on LPS-inflamed Caco-2 cells and significantly inhibited LPS-induced production of TNF-α, IL-8 and MCP-1, among others, in a dose-dependent manner [478]. In such cases care has to be taken so that the excipients used actually provide synergistic rather than opposing actions.

From a formulation perspective, it would be rather interesting to have a nano-system that is capable of loading sufficient drug, preserving its functionality, allocating to the target tissue passively, accumulating in the target cell actively, and even show intracellular trafficking abilities to deliver the drug to a specific compartment and or organelle. This system could even provide a tailored drug release profile, or only release the drug in response to a specific stimulus. In that sense, one would refer to this ridiculously smart system as a nanorobot! But is that all that allure really necessary and possible? While the formulation of such nanorobots would be impressive, would these systems function as expected *in-vivo*? What would be the cost of these systems and the path required to achieve the necessary approvals? In the current situation, where time is critical and health care systems are struggling to find the means to cover COVID-19 related expenses, should not all nano-scientists focus on the simplest, cheapest, most effective solutions? One that would provide the most benefit, in the shortest time possible with lowest costs? We therefore call out for all the nano scientists, to step in and help the potential of nanomedicine in curbing this pandemic materialize. Nanoformulation of drugs represent a promising resource to unify the progress in nanotechnology and understanding of surface chemistry with known drug-delivery mechanisms to enhance the site-specific delivery. With the recurrent spillovers of CoVs in humans, the detection of numerous coronaviruses in bats, including many SARS-related ones, future zoonotic transmission events may continue to occur [8].The presence of an inhaled carrier system capable of delivering antiviral or immunomodulatory drugs should be available as part of the repertoire in the fight against future outbreaks.

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