




No small matter: a perspective on nanotechnology-enabled solutions to fight COVID-19

Georgia Wilson Jones¹, Marco P Monopoli², Luisa Campagnolo³, Antonio Pietroiusti³, Lang Tran^{**},⁴ & Bengt Fadeel^{*,5} 

¹International Medical School, University of Rome Tor Vergata, 00133 Rome, Italy

²Department of Chemistry, Royal College of Surgeons in Ireland, Dublin, D02 YN77, Ireland

³Department of Biomedicine & Prevention, University of Rome Tor Vergata, 00133 Rome, Italy

⁴Institute of Occupational Medicine, Edinburgh, EH14 4AP, UK

⁵Institute of Environmental Medicine, Karolinska Institutet, 171 77 Stockholm, Sweden

*Author for correspondence: bengt.fadeel@ki.se

**Author for correspondence: lang.tran@iom-world.org

There is an urgent need for safe and effective approaches to combat COVID-19. Here, we asked whether lessons learned from nanotoxicology and nanomedicine could shed light on the current pandemic. SARS-CoV-2, the causative agent, may trigger a mild, self-limiting disease with respiratory symptoms, but patients may also succumb to a life-threatening systemic disease. The host response to the virus is equally complex and studies are now beginning to unravel the immunological correlates of COVID-19. Nanotechnology can be applied for the delivery of antiviral drugs or other repurposed drugs. Moreover, recent work has shown that synthetic nanoparticles wrapped with host-derived cellular membranes may prevent virus infection. We posit that nanoparticles decorated with ACE2, the receptor for SARS-CoV-2, could be exploited as decoys to intercept the virus before it infects cells in the respiratory tract. However, close attention should be paid to biocompatibility before such nano-decoys are deployed in the clinic.

First draft submitted: 8 July 2020; Accepted for publication: 4 August 2020; Published online: 2 September 2020

Keywords: bio-mimicking particles • coronavirus • cytokine storm • nanomedicine • nanosafety

In December 2019, local health facilities in Wuhan, China reported the emergence of several cases of pneumonia of unknown origin, and studies of epithelial cells isolated from the lungs of infected individuals revealed the presence of a novel coronavirus [1]. Most cases with onset before 1 January 2020 were linked to the Huanan Seafood Wholesale Market (Hubei, China) [2]. The zoonotic origin of this novel coronavirus is debated [3,4]. At any rate, it is clearly not a purposefully manipulated virus [5]. On 11 March 2020, WHO characterized COVID-19 as a pandemic. At the heart of the pandemic lies a nano-sized coronavirus [6]. It has been argued that viruses are neither dead nor alive, as they reproduce in host cells by hijacking their replication machinery while they appear as inanimate objects outside the host. Therefore, it is conceivable that one may learn lessons from the study of artificial nanoparticles and how these interact with cells. Furthermore, nanoparticles may be harnessed for the treatment of virus infections. Here, we provide an overview of the virus and of critical virus–host interactions including the multifaceted immune response and highlight attempts to develop antiviral therapies against COVID-19. We also address whether synthetic nanoparticles, especially bio-mimicking particles, may be used to combat this devastating disease.

SARS-CoV-2: a killer with a crown

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the pathogen behind the ongoing coronavirus pandemic known as COVID-19, where CO stands for ‘corona’, VI for ‘virus’ and D for ‘disease’, according to an official statement issued by WHO on 11 February 2020. SARS-CoV-2 is a member of the coronavirus family, which also encompasses severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory

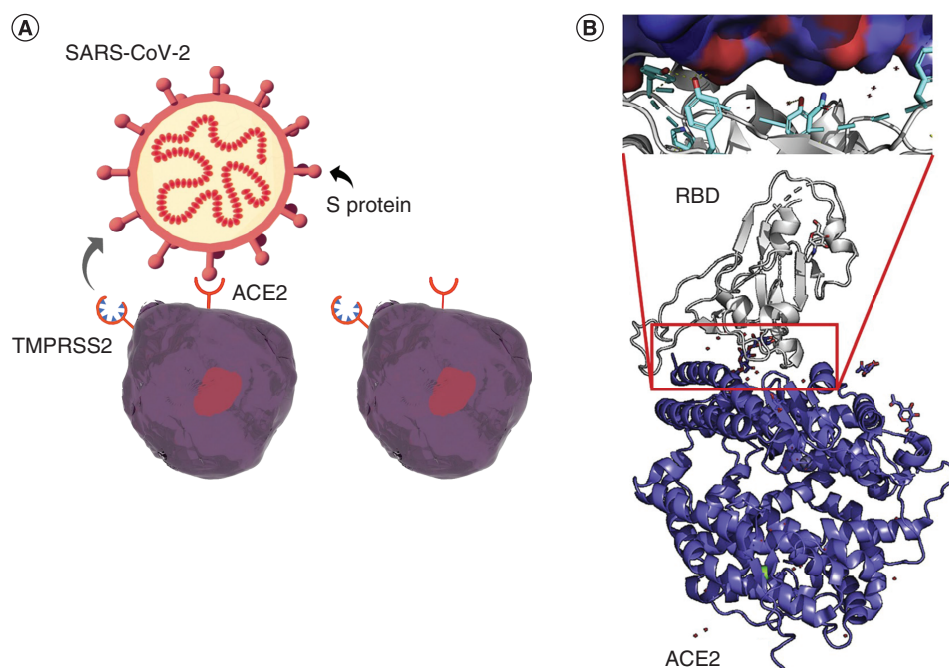


Figure 1. SARS-CoV-2 binds the host receptor, ACE2. (A) Schematic illustration of the coronavirus, SARS-CoV-2 and its single-stranded RNA genome. The S protein in the envelope of the virus is also shown. The spikes on the surface of coronaviruses give this virus family its name – corona, which is Latin for ‘crown’. Shown below the virus in schematic form are host cells (for instance, nasal or lung epithelial cells) expressing ACE2, the main cellular receptor for SARS-CoV-2, and TMPRSS2, a protease that processes the S protein, readying the virus for fusion with the membrane of the host cell [16]. It is likely that other host receptors and proteases may also be involved in virus entry into host cells (not shown). **(B)** Structure of the receptor binding domain of the S protein of SARS-CoV-2 complexed with ACE2. ACE2 is shown in blue, the receptor binding domain of SARS-CoV-2 is shown in gray. The closeup shows specific hydrogen bindings of a Tyr cluster.

S: Spike; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Figure 1B reproduced with permission from [8] © Elsevier Inc. (2020).

syndrome coronavirus (MERS-CoV), two highly transmissible and pathogenic viruses that have likely originated in bats, a natural reservoir for coronaviruses [7]. SARS-CoV-2 has four structural proteins, the S (spike), E (envelope), M (membrane) and N (nucleocapsid) proteins [8]; additionally, nonstructural proteins encoded by the virus in infected cells, but not incorporated into the virion, also play a key role. The surface of the virion is decorated with the transmembrane S glycoproteins which are assembled in homotrimers and give the structure its crown-like shape (hence, the name ‘corona’). The S protein, the major immunogenic determinant of SARS-CoV-2 [9], mediates host receptor binding with the entry receptor, ACE2 [10]. Similar to other coronaviruses, the S protein harbors a region known as the receptor binding domain (RBD) that mediates the interaction with the host receptor whereupon host proteases cleave the spike, facilitating virus entry and the activation of membrane fusion (Figure 1) [11]. Biophysical and structural evidence provided by computational modeling has shown that the RBD of SARS-CoV-2 binds to ACE2 with greater affinity than that of SARS-CoV [12]. A salient characteristic of SARS-CoV-2 which is not observed in SARS-CoV is the presence of a furin cleavage site between the S1 and S2 subunits of the S protein, allowing proteolytic cleavage by furin [13]. This may influence cellular tropism, transmissibility and pathogenicity, especially as furin is copiously expressed in human airway epithelium [14]. In fact, using biochemical and pseudovirus entry assays, furin pre-activation was shown to increase SARS-CoV-2 entry into human cell lines [15]. Thus, unlike SARS-CoV, cell entry of SARS-CoV-2 is facilitated by furin, and this may reduce its dependence on target cell proteases for entry into host cells. Notwithstanding, the serine protease TMPRSS2, which primes the S protein of other pathogenic human coronaviruses, such as SARS-CoV and MERS-CoV, was shown in recent studies to be essential for SARS-CoV-2 entry into host cells [16]. Moreover, the serine protease inhibitor camostat mesylate,

which blocks TMPRSS2 activity and has been approved for clinical use for an unrelated condition, reduced viral entry into the Calu-3 cell line and in primary human airway epithelial cells [16].

The virus must be internalized into a host cell in order to reproduce itself. Ou *et al.* [9] have shown that SARS-CoV-2 enters cells mainly through endocytosis, and that cathepsin L but not cathepsin B is critical for entry. The authors also confirmed that human ACE2 is the receptor for SARS-CoV-2. The importance of lysosomal cathepsins for endocytosis has been demonstrated previously for SARS-CoV and MERS-CoV [17]. Once inside the cell, the infecting RNA acts as an mRNA which is translated by host ribosomes to produce the viral replicative enzymes, which, in turn, generate new viral genomes and the mRNAs for the synthesis of the components necessary to assemble new viral particles [18]. RdRp is a central component of the viral replication and transcription machinery and serves as a target for antiviral drugs such as remdesivir [19]. The virus then exploits the host cellular machinery to perform protein translation. These proteins are cleaved by the viral main protease (M^{Pro}) – another key drug target – and papain-like protease (PL^{Pro}) [20]. Finally, the mature virus is assembled into virions which are released by exocytosis to infect other host cells.

ACE2 & other cellular receptors

ACE2 is ubiquitously expressed and is present on many different cell types such as alveolar epithelial cells, vascular endothelial cells, smooth muscle cells, small intestine enterocytes, renal tubular epithelium and many more [21]. Furthermore, TMPRSS2 was found to display an even broader tissue distribution, leading to the suggestion that ACE2, rather than TMPRSS2, may act as a factor limiting viral entry. Sungnak *et al.* [22] surveyed the expression of viral entry-associated genes in single-cell RNA-sequencing data from multiple tissues. They found that *ACE2* and *TMPRSS2* were co-expressed in specific respiratory, corneal and intestinal epithelial cells. Indeed, nasal epithelial cells, especially nasal goblet and ciliated cells, showed the highest level of expression within the respiratory system, which may implicate the nasal epithelium as the major site for acquiring the infection and propagating transmission [22]. In another recent study leveraging single-cell RNA-sequencing data, Ziegler *et al.* [23] identified *ACE2* and *TMPRSS2* co-expression in lung type II pneumocytes, ileal absorptive enterocytes and nasal goblet secretory cells. The authors could also show that *ACE2* is an interferon-stimulated gene (ISG) in human, but not mouse, airway epithelial cells [23]. It is well known that interferon (IFN) induction of ISGs is essential for host anti-viral responses. However, the fact that SARS-CoV-2 utilizes ACE2 to gain entry into host cells suggests that SARS-CoV-2 (and SARS-CoV) might exploit the tissue protective responses of the host. It is certainly intriguing in this context that bats, a natural reservoir for coronaviruses, evidently seem to cope with these viruses. In a recent study using bat cell lines with inducible or constitutive IFN responses infected with vesicular stomatitis viruses, evidence was presented that IFN responses enable bats to host the viruses [24]. The authors suggested that viruses that have evolved in bats with enhanced IFN capabilities could achieve more rapid within-host transmission without causing pathology to their hosts. Unfortunately, as pointed out by the authors, this would likely lead to extreme virulence upon spillover to hosts lacking similar vigorous immune responses [24].

Hou *et al.* [25] provided further evidence that nasal surfaces are the dominant initial sites of SARS-CoV-2 respiratory tract infection. Using sensitive RNA *in situ* mapping, the highest *ACE2* expression was found in the nose with decreasing expression throughout the lower respiratory tract (in normal human airways). In concordance with these results, the authors found that virus infectivity/replication efficiency varied markedly from proximal airway to alveolar respiratory regions; type II cells appeared to be one of the primary targets [25].

While the current evidence points to ACE2 as the principal receptor for SARS-CoV-2, a recent preprint has put forward the idea that CD147 may also serve as a receptor [26]. Hence, using *in vitro* systems, the authors showed that meplazumab, an anti-CD147 antibody, inhibited the viruses from invading host cells, and the interaction between CD147 and the S protein was demonstrated, along with the co-localization of CD147 and S protein in SARS-CoV-2 infected Vero E6 cells. CD147, also known as Basigin, is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily. Interestingly, Basigin has been shown to be an essential receptor on red blood cells for the malaria parasite, *Plasmodium falciparum* [27]. In another very recent preprint, two additional receptors, CD209L (or, L-SIGN) and CD209 (or, DC-SIGN) were proposed [28]. Previous work has shown that CD209L/L-SIGN is expressed in human lung in type II alveolar cells and endothelial cells, and the S protein of SARS-CoV was shown to use CD209L/L-SIGN as a receptor [29]. CD209L/L-SIGN now emerges as an alternative receptor for SARS-CoV-2 insofar as the S protein RBD binds to CD209L/L-SIGN (and CD209/DC-SIGN) and endothelial cells endogenously expressing CD209L/L-SIGN are permissive for SARS-CoV-2 infection while soluble CD209L-Fc reduced virus entry by nearly 50% [28].

Cardiovascular complications are emerging in COVID-19 [30]. It is notable that ACE2, the principal receptor for SARS-CoV-2, is expressed not only in the respiratory tract but also by endothelial cells. Interestingly, Monteil *et al.* [31] showed that SARS-CoV-2 can infect human blood vessel organoids derived from induced pluripotent stem cells. In a recent case report, Varga *et al.* [32] provided evidence suggestive of viral infection of endothelial cells and diffuse endothelial inflammation in patients with COVID-19, and suggested that strategies to protect the vasculature may be particularly relevant in patients with pre-existing endothelial dysfunction which is associated with male sex, smoking, hypertension, diabetes, obesity and cardiovascular disease. Nevertheless, while the aim is to avert the virus at the portal of entry to the respiratory tract, COVID-19 may be better understood as a form of systemic hyperinflammation.

Double-edged immune response

COVID-19 is undoubtedly one of the most serious healthcare issues of our time. Indeed, although most patients show a very mild, self-limiting respiratory disease, patients may also succumb to a severe disease with pneumonia, a cytokine 'storm' leading to acute respiratory distress syndrome (ARDS), multiorgan failure and death [33,34]. In an early report published in March 2020 in which the clinical course and risk factors for mortality of adult patients with COVID-19 in Wuhan were evaluated, multivariable regression analysis showed that in-hospital death from the infection was associated with older age and sequential organ failure [35]. Other early reports support the view that mortality is high among those individuals who succumb to severe disease [36].

Understanding the physiological and immunological processes that drive the clinical manifestations of COVID-19 is critical for the development of effective therapies [37]. Most cases are mild, with flu-like symptoms and dry cough, but in severe cases, COVID-19 can progress to ARDS, similar to SARS and MERS [37]. In addition, unbridled inflammation with massive release of cytokines (so-called cytokine storm) inflicts organ damage leading to organ failure and death [38,39]. Therefore, the disease is due not only to the virus but is also the result of an excessive and detrimental host response. This is why, in severe cases, drugs such as dexamethasone that suppress the immune system might prove useful [40]. However, while hyperinflammation in the lungs and other organs may inflict serious damage, the decision to treat critically ill patients with immunosuppressive drugs is very much debated at the present time [41,42]. Nevertheless, clinical trials are underway to assess whether drugs that antagonize pro-inflammatory cytokines (e.g., tocilizumab, a humanized monoclonal antibody targeting IL-6) could ameliorate COVID-19, which in its severe form is a sepsis-like condition [39]. Furthermore, it has been pointed out that the risk factors for severe COVID-19 are shared with idiopathic pulmonary fibrosis, namely increasing age, male sex and comorbidities such as hypertension and diabetes [43]. It has therefore been argued that antifibrotic therapy also should be considered. However, this would not address the issue of immune dysregulation; it is also unclear whether such therapies, currently used in chronic fibrotic disorders like idiopathic pulmonary, are effective in the setting of acute coronavirus infections [43].

Clearly, the immune response is a double-edged sword, but what do we currently know regarding the involvement of different immune cell types? Liu *et al.* [44] examined lymphocyte subsets and cytokine responses in 40 patients with COVID-19 and could show that patients with severe COVID-19 had lymphopenia and increased neutrophil counts along with higher levels of circulating pro-inflammatory cytokines when compared with patients with mild COVID-19. In particular, the neutrophil-to-lymphocyte ratio and neutrophil-to-CD8⁺ T-cell ratio emerged as prognostic factors affecting the prognosis for severe COVID-19. These data suggest that depletion of lymphocytes, particularly cytotoxic T lymphocytes, coupled with elevated neutrophils capable of mediating a pro-inflammatory cytokine 'storm' may be key events in the pathogenesis of COVID-19 [45]. Neutrophils may also emit so-called neutrophil extracellular traps or NETs which could lead to pulmonary damage and/or thrombotic complications [46,47]. Treatment with recombinant DNase I to dissolve NETs is approved for patients with cystic fibrosis and could potentially reduce pulmonary symptoms in COVID-19 [46]. Zhang *et al.* [48] analyzed the clinical, and immunological data from 326 patients with COVID-19 and found that lymphocytopenia, especially the reduced CD4⁺ and CD8⁺ T-cell counts upon admission, was predictive of disease progression. High levels of IL-6 and IL-8 were observed in patients with severe or critical disease and correlated with decreased lymphocyte count. Guan *et al.* [49] analyzed 1099 cases of COVID-19 and found lymphocytopenia to be one of the most common features, present in 83.2% of the patients on admission. In another recent study, the immune responses of 54 COVID-19 patients, 28 of whom had severe respiratory failure, were examined. The authors found a profound depletion of CD4⁺ lymphocytes, CD19⁺ lymphocytes and natural killer (NK) cells in patients with severe disease [50]. Zheng *et al.* [51] also noted, in a cohort of 68 COVID-19 patients, that the total number of NK cells and CD8⁺ T cells was decreased in patients with

SARS-CoV-2 infection. The authors suggested that therapeutic approaches to prevent the functional exhaustion of cytotoxic lymphocytes and consequently contribute to virus elimination in the early stage of SARS-CoV-2 infection are warranted [51]. Others have documented decreased numbers of NK cells in COVID-19 patients and found that the impaired immune cell cytotoxicity is IL-6 dependent [52]. If this is confirmed, then therapies that control inflammation might also promote antiviral immune responses. Mathew *et al.* [53] performed high-dimensional flow cytometry-based immune profiling of 125 patients with COVID-19 and the results suggested that distinct ‘immunotypes’ may be linked to disease severity.

Much has been said about the cytokine ‘storm’ in COVID-19, but it is important to note that recent studies have shown that patients afflicted with COVID-19 as well as relevant disease models of COVID-19 display a chemokine-dominant hypercytokinemia [54,55]. In a recent preprint, Laing *et al.* [56] reported the results of flow cytometry-based immuno-phenotyping along with cytokine and chemokine profiling in 63 hospitalized COVID-19 patients and identified a sepsis-like ‘signature’ characterized by sustained CXCL10/IP10 overexpression. Furthermore, Ellinghaus *et al.* [57] conducted a genomewide association study involving 1980 patients with severe COVID-19 disease at seven hospitals in Italy and Spain. The study revealed a novel susceptibility locus in patients with COVID-19 with respiratory failure at locus 3p21.31 and suggested a potential involvement of the ABO blood-group system at locus 9q34.2 as previously reported by other investigators [57]. Interestingly, at locus 3p21.31, the association signal spanned six genes including several chemokine receptor-encoding genes [57]. The region on chromosome 3 was confirmed to be associated with severe COVID-19 in a dataset recently released by the COVID-19 Host Genetics Initiative (<https://www.covid19hg.org/>) [58]. Taken together, these results imply a key role for chemokine signaling in severe COVID-19.

Single-cell RNA sequencing has been applied in several recent studies to characterize the immune responses in COVID-19. Wilk *et al.* [59] utilized single-cell RNA sequencing to profile peripheral blood mononuclear cells (PBMCs) in seven patients hospitalized for COVID-19 and could detect a ‘reconfiguration’ of the peripheral immune cell phenotype, with a developing neutrophil population seen only in patients with ARDS. Wen *et al.* [60] sought to characterize the transcriptional changes in PBMCs during the recovery stage of ten patients with COVID-19 by single-cell RNA sequencing. They found that T cells decreased whereas monocytes increased in patients in the early recovery stage. Liao *et al.* [61] characterized immune cells in bronchoalveolar lavage (BAL) fluid from three patients with moderate COVID-19 and six patients with severe/critical COVID-19 by using single-cell RNA sequencing, and found that monocyte-derived macrophages were abundant in the BAL fluid from patients with severe disease while moderate cases were characterized by the presence of clonally expanded CD8⁺ T cells. Chua *et al.* [62] performed single-cell RNA sequencing in 19 patients with moderate or severe COVID-19 disease and five healthy controls and found evidence that critical cases exhibited stronger interactions between epithelial cells and immune cells, as evidenced by activated immune cells including macrophages expressing an array of chemokines and other pro-inflammatory factors. The authors suggested that targeting chemokine receptors might constitute a viable therapeutic option [62]. Together, these single-cell atlases begin to shed light on the immune responses in COVID-19 patients with varying severity of disease. However, deconvoluting these data is not trivial and discerning purposeful from detrimental immune responses remains a formidable task.

COVID-19 therapies: drug repurposing

The current pandemic has prompted an exceptional cooperation between the pharmaceutical industry, scientific community and governments to expedite the discovery of therapeutic options. On 20 March 2020, WHO announced the launch of SOLIDARITY, a large clinical trial to test repurposed drugs and other drug candidates [63]. The trial considers drugs that have shown promise in animal studies against other coronaviruses which cause SARS and MERS [64]. The trial also encompasses drugs that target the RNA polymerase RdRp, a central component of the viral replication and transcription machinery, such as remdesivir, a drug that was originally developed to fight Ebola and related viruses. It is fascinating that clinical trials for drugs that target the viral replication machinery are taking place in parallel with basic research on the molecular basis for this process [65]. Given the prominence of IL-6 and other cytokines in the cytokine ‘storm’ in severe COVID-19, it is unsurprising that tocilizumab is also being evaluated in patients with COVID-19 [66]. Preliminary data showed that tocilizumab improved the clinical outcome in patients with severe and critical COVID-19 and may represent an effective treatment to reduce mortality [67]. Toniati *et al.* [68] reported promising results in a prospective series of 100 consecutive patients in Italy with confirmed COVID-19 pneumonia and ARDS. However, the efficacy of tocilizumab needs to be validated in randomized clinical trials.

The antimalaria drug, chloroquine, has also been in focus in the past few months [69]. This is not the first time that chloroquine or hydroxychloroquine have been repurposed; in fact, thanks to their anti-inflammatory properties, they are already used in the treatment of autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus. However, some experts believe that ‘hydroxychloroquine and its close chemical cousin chloroquine have attracted disproportionate attention in the coronavirus pandemic’ [70]. Chloroquine has been described to have broad spectrum antiviral effects [71]. The drug prevents acidification of lysosomes, thereby hindering fusion with endocytic vesicles. This, in turn, is likely to interfere with endocytic trafficking, causing a cellular logjam that blocks effective transport of cargo to and from the cell membrane [72]. In addition to the well-known functions of chloroquine with regard to endosomal pH, the drug was shown to prevent terminal glycosylation of immunoglobulins [73], and it has been suggested that chloroquine interferes with glycosylation of the virus receptor ACE2, which may serve to explain its anti-SARS effect at least in *in vitro* assays [71]. Additionally, it has been suggested that chloroquine is a zinc ionophore, which could have implications for coronaviruses, in light of the fact that Zn^{2+} ions inhibit RdRp [74]. In an early study conducted at the dawn of the pandemic, Wang *et al.* [75] demonstrated the effectiveness of remdesivir and chloroquine in controlling SARS-CoV-2 infection in Vero E6 cells. However, we are not aware of any studies showing antiviral effects of chloroquine in relevant animal models. In fact, many scientists are now rethinking chloroquine and are asking whether the drug might even suppress immune responses to the virus [76]. The recent controversies surrounding chloroquine and hydroxychloroquine have prompted WHO to suspend this therapeutic regimen for COVID-19. Two very recent papers have provided evidence that chloroquine seems to target a pathway that is not operational in human lung cells [77], and that hydroxychloroquine does not prevent SARS-CoV-2 infection in macaques [78].

Drug repurposing or repositioning is the process whereby existing (‘old’) drugs with an established mechanism of action and well-known toxicity profile are utilized to treat diseases for which they were not initially intended [79]. Given the current global pandemic, and in lieu of an effective vaccine, it is logical to try to tackle COVID-19 with existing pharmaceuticals. However, this is hampered by an incomplete understanding of the interactions between SARS-CoV-2 and its host. Gordon *et al.* [80] addressed this by cloning, tagging and expressing 26 of the 29 SARS-CoV-2 proteins in human HEK293T cells with subsequent identification of the human proteins associated with each using affinity purification mass spectrometry. They identified 332 interactions between viral and host proteins. Furthermore, against these targets, they identified 69 existing drugs (29 US FDA-approved drugs, 12 drugs in clinical trials and 28 preclinical compounds). This impressive effort, involving some 125 co-authors, yielded an interaction ‘landscape’ of SARS-CoV-2 proteins and host proteins, and may serve to guide drug repurposing as well as support new drug development against COVID-19 [80]. Other investigators have applied integrative network-based systems pharmacology-based approaches to identify potentially repurposeable drugs [81]. Jin *et al.* [82] deployed a combination of structure-assisted drug design, virtual drug screening and high-throughput screening to identify drug candidates that target the SARS-CoV-2 main protease (M^{pro}). They assayed over 10,000 compounds including approved drugs, drug candidates in clinical trials and other pharmacologically active compounds as inhibitors of M^{pro} . Ebselen displayed the strongest inhibition of M^{pro} activity with an IC_{50} of 0.67 μ M. Ebselen also showed antiviral activity in SARS-CoV-2 infected Vero E6 cells [82]. Moreover, ebselen, a synthetic organoselenium drug, is known to have very low cytotoxicity. In conclusion, this comprehensive study has shown that rapid drug discovery for new infectious diseases is feasible [82]. In another, very recent large-scale study, Riva *et al.* [83] profiled a library of known drugs encompassing approximately 12,000 clinical-stage or FDA-approved small molecules. The authors identified 100 drugs that inhibited SARS-CoV-2 replication in mammalian cells, including 21 for which a dose-response relationship with antiviral activity could be established. The authors concluded that the availability of human safety and pharmacological data should facilitate the rapid assessment of these compounds for COVID-19 [83].

Air pollution: a risk factor in COVID-19?

Pollution is a major environmental cause of disease, and ‘disproportionately kills the poor and the vulnerable’ [84]. Could air pollution also represent a risk factor for COVID-19? Air pollution is a heterogeneous combination of various gases, such as nitrous oxide (NO_2) and ozone, semi-volatile liquids, and particulate matter (PM) of different diameters, which poses a serious hazard to public health globally. PM is a complex mixture of natural, artificial, organic and inorganic components, and there is consensus that ultrafine particles (i.e., the nano-sized fraction of PM) represent the most dangerous component with respect to adverse health effects [85]. It has been estimated that air pollution causes greater morbidity and mortality than any other environmental factor, accounting

for millions of deaths worldwide each year [86]. It is important to note that air pollution travels across national boundaries, continents and oceans [84]. There appears to be a large overlap between risk factors for COVID-19 and the conditions caused and/or exacerbated by exposure to fine PM (PM_{2.5}). The observation that regions with high levels of air pollution, such as Lombardy in Northern Italy, also have the highest number of COVID-19 infections and casualties suggests a possible correlation between air pollution levels and disease severity. This, together with the notion that air pollution can cause inflammatory damage to the airways, as well as the cardiovascular system [86], is suggestive of a relationship between air pollution and severe cases of COVID-19. Recent results seem to indicate that long-term exposure to NO₂ may be an important contributor to fatality in individuals infected with SARS-CoV-2 in Italy, Spain, France and Germany [87]. However, the methodological approach has been called into question [88,89]. Studies performed in China have also suggested a correlation between short-term exposure to PM_{2.5} (and NO₂ and O₃) and COVID-19 infection [90]. In a recent preprint, researchers studied the association between fine PM exposure and the risk of death from COVID-19 in the USA [91]. The authors adjusted for socioeconomic and behavioral variables such as obesity and smoking and found that a small increase in long-term exposure to PM_{2.5} leads to a large increase in the COVID-19 death rate. Specifically, they reported that an increase in 1 µg/m³ in PM_{2.5} was associated to an 8% increase in mortality [90]. In another nationwide study, Liang *et al.* [92] did not observe significant associations between long-term exposures to PM_{2.5} or O₃ and COVID-19 death outcomes, while NO₂ concentrations were positively associated with both COVID-19 fatality and mortality rate. The authors concluded that long-term exposure to NO₂ may enhance susceptibility to severe COVID-19 outcomes, independent of long-term PM_{2.5} and O₃ exposure. However, as pointed out by Riccò *et al.* [93], it is important to ask whether this is evidence of causation or merely a correlation; indeed, the link between SARS-CoV-2 infection and air pollution may be confounded by a number of factors.

Experimental studies have shown that SARS-CoV-2 remains infectious in aerosols for hours [94] and on various surfaces up to days, even though the virus is susceptible to standard disinfection procedures [94,95]. Furthermore, Zhang *et al.* [96] provided evidence that airborne transmission is the dominant route to spread the disease, and the authors also concluded that the wearing of face masks corresponds to the most effective means of preventing transmission between individuals. A related question is whether the virus can ‘hitchhike’ on air pollution particles – can PM act as a vector? In a recent study, Italian researchers have addressed this hypothesis by collecting 34 PM₁₀ samples in the Bergamo region (i.e., the epicenter of the Italian COVID-19 epidemic) from 21 February to 13 March 2020 [97]. The authors found that SARS-CoV-2 RNA can be detected on PM. Even though these are preliminary results, they may indicate that high PM concentrations might enhance viral persistence in the atmosphere. However, not all experts agree with this, and a multiplicity of interrelated factors may come into play [98]. At any rate, the impact of air pollution (as a potential risk factor and/or as a novel vector for the virus) is something that needs to be carefully considered. The mechanisms underlying the pulmonary and cardiovascular effects caused by ultrafine particles [85] are also relevant for COVID-19, and important lessons may be learned from previous studies of PM.

Lessons from nanosafety: the bio-corona

Studies conducted in the past decade have revealed that engineered nanomaterials are rapidly coated with a ‘corona’ of proteins and other biomolecules as they enter into a biological system [99]. The structural and functional properties of the so-called bio-corona are intimately linked with the behavior of the nanomaterials in biological systems including their ability to cross biological barriers. Reciprocally, the composition of biomolecules constituting the bio-corona is determined by the portal of entry and by the transfer of the nanomaterials between different biological compartments [100]. In other words, the bio-corona that is formed in the lungs upon inhalation is different from the bio-corona that is formed in the blood stream. The bio-corona, in effect, is what cells ‘see’ when they encounter nanomaterials [101]. One of the biggest challenges is perhaps the development of nanoparticles capable of targeting in complex biological media where the bio-corona derived from circulating blood proteins may irreversibly cover the nanoparticle binding moieties affecting the interaction with cellular receptors [102,103]. Additionally, pulmonary biofluids such as mucus or lung lining fluid form a formidable barrier that can immobilize pathogens but could also hinder nanoparticles before they come into contact with the lung epithelium. Therefore, nanoparticle exposure after inhalation must be closely studied to understand the particle behavior in relevant fluids such as lung surfactant or mucus. In an intriguing twist, respiratory syncytial virus and herpes simplex virus type 1 (HSV-1) were recently found to accumulate distinct protein coronas in different biological fluids [104]. Moreover, the protein corona formed on the virus was shown to affect infectivity and immune cell activation [104]. Earlier studies have shown

that the formation of the bio-corona on tobacco mosaic virus-like particles can significantly affect viral tropism and biodistribution even though corona formation is attenuated when compared with solid particles of similar size [105]. Berardi *et al.* [106] reported that no detectable corona was formed on cowpea mosaic virus and bluetongue virus recombinant core-like particles of 30 and 70 nm, respectively. Moreover, the ‘nonsticky’ nature of the viral particles allowed them to penetrate mucin layers. These data suggest similarities and differences between synthetic and natural nanoparticles and highlight the importance of understanding and decoding the nano-bio interface. This is certainly relevant for the use of synthetic nanoparticles for drug delivery.

Protein corona formation is not necessarily an impediment in nanomedicine. Pollok *et al.* [107] reported the spontaneous formation of a corona of IFN- α protein on magnetic nanoparticles with a shell of biodegradable chitosan which was exploited to generate IFN- α -loaded nano-carriers. The authors could show that in comparison with free IFN- α , IFN- α -loaded nanoparticles resulted in a more sustained STAT1 activation, with persistent induction of the expression of effector genes conferring cellular immunity against vesicular stomatitis virus infection [107]. These *in vitro* studies provide an example of a beneficial corona effect. On the other hand, inadvertent corona formation may promote adverse effects. For instance, Wang *et al.* [108] reported that certain types of silica nanoparticles could selectively recruit TGF- β 1 into their corona. Once embedded into the corona, TGF- β 1 was significantly more stable than in its free form, and its fibrosis-triggering activity in a mouse model was prolonged [108]. Therefore, close attention to the bio-corona is needed to exploit nanoparticles for clinical use.

Nanomedicine: bio-mimicking particles

Engineered nanomaterials are ideally positioned to interface with biological systems including with cells of the immune system [109]. Furthermore, numerous studies have shown that nanoparticles can be harnessed for drug delivery, and several authors have suggested that such strategies could be used to fight COVID-19 [110–112]. Furthermore, nanoparticles of various compositions are frequently deployed to deliver ‘old’ drugs (i.e., drug repurposing) including poorly soluble drugs [113]. For instance, ebsefen, a poorly soluble compound with promising anti-SARS-CoV-2 activity [82] (see above) may benefit from nano-enabled drug delivery. Another exciting prospect is the fact that nanoparticles may act as drugs *per se*. Certain varieties of carbon quantum dots, also known as carbon dots, were shown to prevent entry of the common cold-coronavirus HCoV-229E, possibly through interference with the S protein and its corresponding cellular receptor(s) [114], and similar findings were reported for carbon dots and HSV-1 [115]. Furthermore, nanoparticles could function as decoys for viruses in the absence of a pharmacological drug. To this end, a promising approach is the design of synthetic multivalent binders that interfere with pathogen adhesion [116]. Lauster *et al.* [117] engineered a multivalent binder based on a spatially defined arrangement of ligands for the hemagglutinin (HA) protein of the influenza A virus (IAV). The authors used bacteriophage capsids as rigid scaffolds for the display of sialic acid ligands to match the binding sites of the trimeric HA. Using this ingenious construct, they could show that structurally defined multivalent binders can function as highly efficient and specific IAV inhibitors and have potential to be developed into novel antivirals for the treatment of influenza [117]. The construction of similar particles that hold promise for efficient and specific viral inhibition may also yield novel antivirals for the treatment of COVID-19. Nie *et al.* [118] developed heteromultivalent inhibitors of IAV engaging both HA and neuraminidase (NA). In another very recent study, the authors developed ‘spiky’ nanostructures with a topology that matched that of IAV [119]. They could show that spiky nanoparticles bind better to the IAV virion than smooth nanoparticles. Furthermore, the particles were coated with erythrocyte membranes as a form of ‘camouflage’. Using a different approach, Cagno *et al.* [120] developed broad-spectrum antiviral nanoparticles that prevented the first step of virus–cell interaction by mimicking heparan sulfate proteoglycans (HSPGs), a highly conserved target of viral attachment ligands of different viruses. While SARS-CoV and SARS-CoV-2 both bind to ACE2, it has been speculated that these viruses may use HSPGs to attach to the cell surface of a variety of cell types [121]. Further studies are warranted to study the role of HSPGs and whether modulation of heparan sulfate or addition of exogenous heparin could prevent infection.

The development of nanoparticles ‘gift-wrapped’ in cell membranes has become fashionable in recent years. Hence, nanoparticles were cloaked in macrophage membranes to bind and neutralize endotoxins and sequester cytokines in sepsis [122], and in platelet-derived membranes to deliver drugs while avoiding macrophage clearance [123], or cloaked with bacteria-secreted outer membrane vesicles in order to endow the particles with pathogen-associated molecular patterns of native bacteria, leading to uptake by neutrophils, a clever Trojan horse-like approach to deliver drugs to tumors [124], to give only a few examples. Can similar strategies be employed to fight virus infections? Rao *et al.* [125] created a nano-decoy to trap Zika virus which is primarily spread by the *Aedes aegypti*

mosquito. The nano-decoys were fabricated by fusing mosquito medium host cell membrane-derived vesicles onto FDA-approved gelatin nanoparticles. After the adsorption by nano-decoys, which were twice as big as the virus, the *in vitro* infectivity of the Zika virus was reduced, though the nano-decoy-adsorbed Zika virus could still infect cells. Then, type I IFN- α/β receptor-deficient (A129) mice challenged with Zika virus were used as a model to evaluate the *in vivo* effect of the nano-decoy approach. Notably, iv. injection with nano-decoys after Zika virus infection resulted in a significant reduction in mortality [125]. This proof-of-concept study shows that nano-decoys cloaked in cell membranes to capture the virus might be useful in terms of reducing viral infectivity. However, in order to bring this to the clinic, the approach needs to be developed with autologous cell membranes to avoid unwanted immune reactions to the nano-constructs. Other investigators have recently developed a biomimetic ‘nanosponge’ consisting of a polymeric nanoparticle core wrapped with cell membranes from human lung epithelial (NL-20) or macrophage-like (THP-1) cell lines [126]. Using an *in vitro* model of SARS-CoV-2 infection of Vero E6 cells, the authors could show that the nano-decoys reduced infectivity with IC₅₀ values for both epithelial- and macrophage-derived nano-decoys of around 800 $\mu\text{g}/\text{ml}$ based on the membrane protein concentration [126]. However, the utility of this approach needs to be demonstrated in appropriate animal models. The use of cell membranes derived from transformed cell lines also needs to be carefully considered (or avoided altogether). Nanosponges with red blood cell membranes that adsorb bacterial toxins were previously reported, but here the cell membranes were derived from mice and applied to mice [127]. Chen *et al.* [128] prepared poly(lactic-co-glycolic acid) (PLGA) nanoparticles cloaked with red blood cell membranes and further endowed these polymeric particles with magnetic functionality by encapsulating superparamagnetic iron oxide nanoparticles. They could show that the cell-mimicking nanoparticles enabled enhanced detection of influenza viruses. Wei *et al.* [129] produced polymeric nanoparticles mimicking T cells using similar PLGA particles by utilizing membranes from the SUP-T1 lymphoblastic lymphoma cell line and found that these particles were endowed with cell surface antigens critical for binding of HIV. Furthermore, the T-cell mimicking particles inhibited HIV infection of PBMCs *in vitro* [129]. The authors presumed that the nanoparticles would be eliminated by the reticuloendothelial system if administered *in vivo*. Considering the accumulation of macrophages and overproduction of reactive oxygen species (ROS) in atherosclerosis, Gao *et al.* [130] developed a biomimetic nano-carrier whereby ROS-responsive nanoparticles prepared via self-assembly of amphiphilic, oxidation-sensitive chitosan oligosaccharides were enveloped with macrophage membranes derived from the murine RAW264.7 macrophage cell line for atherosclerosis treatment (using a mouse model). The authors speculated that while live macrophages may be activated by cytokines or chemokines to release more cytokines, macrophage membranes on the surface of nanoparticles may sequester pro-inflammatory cytokines and chemokines thereby decreasing the local inflammation [130]. This might be relevant for the cytokine ‘storm’ in severe COVID-19 disease.

These nano-decoy approaches are based on the use of nanoparticles coated with cell membranes that are thought to express known and unknown receptor(s) for the virus in question; alternatively, these cell membranes may act as nonspecific sponges for cytokines. However, a different approach is to decorate nanoparticles with the actual receptor, or with the minimal binding domain of a known receptor, such as ACE2 in the case of SARS-CoV-2 (Figure 2). It has been suggested that infections with SARS-CoV result in ACE2 downregulation through binding of the viral S protein to ACE2 [131]. Given that ACE2 is ‘a key negative regulatory factor for severity of lung edema and acute lung failure’, the observed ACE2 downregulation may contribute to the severity of lung disease in SARS patients. Preclinical studies reported 15 years ago showed that recombinant human ACE2 attenuates acute lung failure in *Ace2*-deficient as well as in wild-type mice [132]. Interestingly, administration of recombinant human ACE2 also ameliorates avian influenza (also known as ‘bird flu’) H5N1 virus-induced lung injury in mice [133]. Monteil *et al.* [31] recently showed that clinical grade soluble recombinant human ACE2, a drug that has undergone Phase II clinical testing in patients with ARDS, can inhibit SARS-CoV-2 infection *in vitro* in a dose-dependent manner. However, the RAS system is a complex network [134] and studies in relevant *in vivo* models are warranted to verify this. Furthermore, a recent study has shown that human ACE2 fused to the Fc portion of human immunoglobulin IgG1 (ACE2-Ig) has a high binding affinity for the RBD of SARS-CoV and SARS-CoV-2 and neutralizes virus pseudotyped with S proteins of SARS-CoV or SARS-CoV-2 *in vitro* [135]. The IC₅₀ values of ACE2-Ig for SARS-CoV and SARS-CoV-2 neutralization were 0.8 and 0.1 $\mu\text{g}/\text{ml}$, respectively. Circulating levels of ACE2 are normally very low. Therefore, as pointed out by the authors, one safety concern for the systemic administration of recombinant ACE2 proteins is that they could have adverse cardiovascular effects. We suggest, instead, that nanoparticles decorated with ACE2 are formulated for local delivery into the nasal cavity, as studies have shown that the nose is likely to be the major initial site of infection with SARS-CoV-2 [25]. The nanoparticle

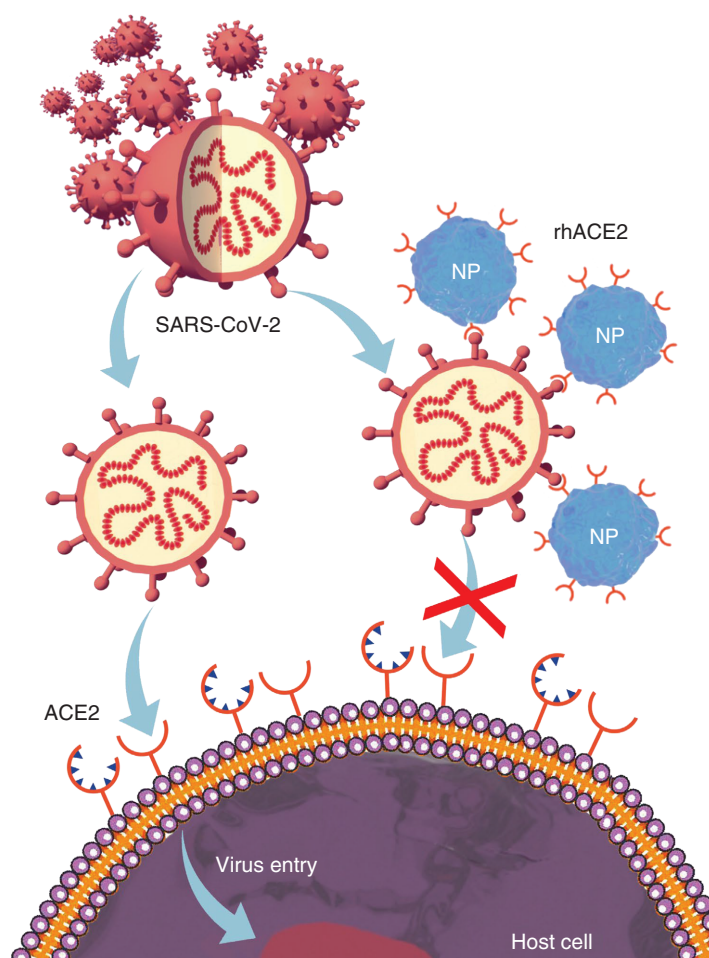


Figure 2. Potential nano-enabled solution: synthetic decoys. This schematic figure shows SARS-CoV-2, the deadly coronavirus that causes COVID-19 in humans, and its host receptor, ACE2. We and others have postulated that synthetic nanoparticles decorated with recombinant human ACE2 (or with the minimal binding domain of ACE2) could act as decoys, intercepting the virus and thereby preventing the entry of the virus into susceptible host cells. NP: Nanoparticle; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

surfaces could be functionalized to promote phagocytic clearance upon binding to the virus, for instance by incorporating known ‘eat-me’ signals [136], thereby limiting systemic effects. However, nanoparticles should be carefully selected and screened with respect to safety to avoid any unwanted effects. Sun *et al.* [137] reported that cationic polyamidoamine dendrimer (PAMAM) nanoparticles, but not their anionic counterparts triggered acute lung injury and the authors provided evidence that these nanoparticles could bind directly to ACE2 thereby leading to a downregulation of its expression in lung tissue. Others have proposed that extracellular vesicles (i.e., natural, membrane-bound nanoparticles) could be deployed as ACE2-expressing decoys [138]. Further *in vitro* and *in vivo* studies to explore natural or synthetic nanoparticles as decoys for SARS-CoV-2 are warranted. The advantage of using ACE2-decorated nanoparticles over soluble ACE2 or ACE2-Ig [139] is that the multivalent display of the receptor might be a more effective means of luring the virus away from host cells in the respiratory tract. Taken together, synthetic or semi-synthetic nanoparticles with acceptable safety profiles and a well controlled bio-corona may be decorated with receptors that bind the S protein and as such could potentially provide a barrier against infection.

Conclusion & future perspective

In the present perspective, we have discussed the novel coronavirus, SARS-CoV-2 and the devastating COVID-19 pandemic. We have presented suggestions for nanotechnology-enabled solutions to combat the disease, including nonspecific ‘nano-sponges’ or virus-specific ‘nano-decoys’. To borrow a phrase from the classic spaghetti western, we have attempted to cover ‘the good, the bad and the ugly’. According to this analogy, the coronavirus, a natural nanoparticle, is ‘bad’, while engineered nanoparticles are ‘good’ insofar as they can be harnessed to treat the disease, and PM, a potential risk factor for contracting severe COVID-19, is simply ‘ugly’. Notably, all three entities (i.e., viruses, engineered nanoparticles and ultrafine particles) are nano-sized objects and our thesis therefore is that ‘nano’ *per se* is neither good nor bad; ‘nano’ is simply a size range at which many biological interactions occur. Importantly, the biological responses to different nano-sized agents are often conserved (i.e., exuberant cytokine responses, fibrosis, etc.) [85]. Understanding and manipulating nano-bio interactions [140] may afford new ways to prevent or treat disease. Moreover, understanding how to mitigate adverse immune responses to coronaviruses without compromising the protective responses is of great importance [141,142]. However, the development of effective nanotechnology-enabled solutions that could be used in patients will require a long journey from the bench to the clinic. Hopefully, we may benefit from the considerable experience that now exists with respect to nanomedicine (and nanosafety). Another urgent priority is to promote immunization against the virus. Nanotechnology may be relevant for antigen and/or adjuvant delivery in vaccination [143,144]. Furthermore, nanomaterials may be used as sensors for diagnostics, as discussed recently by other authors [145].

Despite the rapid advances in our understanding of the pathogenesis of COVID-19 [146], we have learned that we need to learn more. One cannot assume that SARS-CoV-2 will behave like other viruses; it appears to combine the transmissibility of common cold coronaviruses with the lethality of MERS-CoV and SARS-CoV [147]. Fortunately, as highlighted in a recent commentary, ‘one lesson of the current outbreak is that expeditious research is feasible’ [148]. Indeed, we have learned that this novel virus ‘continues to challenge us in unconventional ways’ and ‘pushes us to be ever more creative and flexible in how we address those challenges’ [149]. However, this does not mean that we should abandon the usual rigorous standards of science in basic and clinical research [148]. In this context, nanotechnology may provide solutions to address the ongoing pandemic with respect to new therapies and vaccines [143,145]. However, like all new therapies, nanomedicines must be proven safe and need to undergo clinical trials [150]; ultimately, ‘nano’ is merely a toolbox and not a universal remedy.

Executive summary

The structure of the SARS-CoV-2 coronavirus

- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the pathogen behind the ongoing coronavirus pandemic known as COVID-19.
- SARS-CoV-2 has four structural proteins, the S (spike), E (envelope), M (membrane) and N (nucleocapsid) proteins, and the S protein binds to the cellular receptor, ACE2.

COVID-19 & its immunological manifestations

- A majority of patients with COVID-19 show a mild, self-limiting respiratory disease, but patients – especially elderly individuals – may also succumb to a severe disease with pneumonia, acute respiratory distress syndrome, multiorgan failure and death.
- Understanding the immunological processes (including the so-called cytokine storm) that drive the clinical manifestations of COVID-19 is critical for the development of new therapies.

Potential risk factors for severe COVID-19 disease

- Pollution is a major environmental cause of morbidity and mortality and it has been speculated that air pollution could represent a risk factor for susceptibility to severe COVID-19.

Nanotechnology-enabled approaches for COVID-19

- So-called nano-decoy approaches based on synthetic nanoparticles coated with immune cell membranes may act as nonspecific sponges for cytokines and/or pathogenic viruses.
- However, a different approach is to decorate nanoparticles with a specific receptor, or with the minimal binding domain of a known cellular receptor, such as ACE2.
- Nanotechnology may provide novel therapeutics and vaccines to address the ongoing pandemic; however, like all new therapies, nanomedicines first need to be proven safe.

Acknowledgments

This paper serves as partial fulfillment of the requirements for a thesis of GWJ at the International Medical School of the University of Rome Tor Vergata, Rome, Italy.

Financial & competing interests disclosure

The authors are supported by the European Commission through H2020-BIORIMA (grant agreement no. 760928). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

- Zhu N, Zhang D, Wang W *et al.* A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* 382(8), 727–733 (2020).
- Li Q, Guan X, Wu P *et al.* Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *N. Engl. J. Med.* 382(13), 1199–1207 (2020).
- Zhou P, Yang X, Wang X *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579(7798), 270–273 (2020).
- Xiao K, Zhai J, Feng Y *et al.* Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins. *Nature* 583(7815), 286–289 (2020).
- Andersen K, Rambaut A, Lipkin W, Holmes E, Garry R. The proximal origin of SARS-CoV-2. *Nat. Med.* 26(4), 450–452 (2020).
- Matsuyama S, Nao N, Shirato K *et al.* Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. *Proc. Natl Acad. Sci. USA* 117(13), 7001–7003 (2020).
- Cui J, Li F, Shi Z. Origin and evolution of pathogenic coronaviruses. *Nat. Rev. Microbiol.* 17(3), 181–192 (2019).
- Dömling A, Gao L. Chemistry and biology of SARS-CoV-2. *Chem* 6(6), 1283–1295 (2020).
- Ou X, Liu Y, Lei X *et al.* Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat. Commun.* 11(1), 1620 (2020).
- Lan J, Ge J, Yu J *et al.* Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* 581(7807), 215–220 (2020).
- Shang J, Ye G, Shi K *et al.* Structural basis of receptor recognition by SARS-CoV-2. *Nature* 581(7807), 221–224 (2020).
- Wrapp D, Wang N, Corbett K *et al.* Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367(6483), 1260–1263 (2020).
- Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. *Mol. Cell* 78(4), 779–84.e5 (2020).
- Coutard B, Valle C, de Lamballerie X, Canard B, Seidah N, Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res.* 176, 104742 (2020).
- Shang J, Wan Y, Luo C, *et al.* Cell entry mechanisms of SARS-CoV-2. *Proc. Natl Acad. Sci. USA* 117(21), 11727–11734 (2020).
- Hoffmann M, Kleine-Weber H, Schroeder S *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181(2), 271–80.e8 (2020).
- **This paper (and reference 15) serves to elucidate the mechanism of host cell entry by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).**
- Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV – a target for vaccine and therapeutic development. *Nat. Rev. Microbiol.* 7(3), 226–236 (2009).
- Romano M, Ruggiero A, Squeglia F, Maga G, Berisio R. A structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. *Cells* 9(5), 1267 (2020).
- Gao Y, Yan L, Huang Y *et al.* Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science* 368(6492), 779–782 (2020).
- Zhang L, Lin D, Sun X *et al.* Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors. *Science* 368(6489), 409–412 (2020).

21. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* 203(2), 631–637 (2004).
22. Sungnak W, Huang N, Bécavin C *et al.* SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat. Med.* 26(5), 681–687 (2020).
23. Ziegler CGK, Allon SJ, Nyquist SK *et al.* SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* 181(5), 1016–35.e19 (2020).
24. Brook CE, Boots M, Chandran K *et al.* Accelerated viral dynamics in bat cell lines, with implications for zoonotic emergence. *Elife* 9, e48401 (2020).
25. Hou Y, Okuda K, Edwards C *et al.* SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. *Cell* 182(2), 429–46.e14 (2020).
- **This paper (along with reference 22) reveals that the highest ACE2 expression is found in the nose.**
26. Wang K, Chen W, Zhou YS *et al.* SARS-CoV-2 invades host cells *via* a novel route: CD147-spike protein. *BioRxiv*. doi:10.1101/2020.03.14.988345 (2020) (Online).
27. Crosnier C, Bustamante LY, Bartholdson SJ *et al.* Basigin is a receptor essential for erythrocyte invasion by *Plasmodium falciparum*. *Nature* 480(7378), 534–537 (2011).
28. Amraie R, Napoleon MA, Yin W *et al.* CD209L/L-SIGN and CD209/DC-SIGN act as receptors for SARS-CoV-2 and are differentially expressed in lung and kidney epithelial and endothelial cells. *BioRxiv*. doi:10.1101/2020.06.22.165803 (2020) (Online).
29. Jeffers SA, Tusell SM, Gillim-Ross L *et al.* CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus. *Proc. Natl Acad. Sci. USA* 101(44), 15748–15753 (2004).
30. Gupta A, Madhavan MV, Sehgal K *et al.* Extrapulmonary manifestations of COVID-19. *Nat. Med.* 26(7), 1017–1032 (2020).
31. Monteil V, Kwon H, Prado P *et al.* Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 181(4), 905.e7–913.e7 (2020).
- **Using *in vitro* models, the authors show that soluble ACE2 can block SARS-CoV-2 infection.**
32. Varga Z, Flammer A, Steiger P *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395(10234), 1417–1418 (2020).
33. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate COVID-19. *N. Engl. J. Med.* doi:10.1056/NEJMcp2009249 (2020) (Epub ahead of print).
34. Berlin DA, Gulick RM, Martinez FJ. Severe COVID-19. *N. Engl. J. Med.* doi:10.1056/NEJMcp2009575 (2020) (Epub ahead of print).
35. Zhou F, Yu T, Du R *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 395(10229), 1054–1062 (2020).
36. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. *Lancet* 395(10229), 1014–1015 (2020).
37. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat. Rev. Immunol.* 20(6), 363–374 (2020).
38. Hirano T, Murakami M. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. *Immunity* 52(5), 731–733 (2020).
39. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science* 368(6490), 473–474 (2020).
40. Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. *Nature* 582(7813), 469 (2020).
41. Mehta P, McAuley D, Brown M, Sanchez E, Tattersall R, Manson J. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395(10229), 1033–1034 (2020).
42. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *Lancet* 395(10230), 1111 (2020).
43. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir. Med.* doi:10.1016/S2213-2600(20)30225-3 (2020) (Epub ahead of print).
44. Liu J, Li S, Liu J *et al.* Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine* 55, 102763 (2020).
45. Kuppalli K, Rasmussen A. A glimpse into the eye of the COVID-19 cytokine storm. *EBioMedicine* 55, 102789 (2020).
46. Barnes BJ, Adrover JM, Baxter-Stoltzfus A *et al.* Targeting potential drivers of COVID-19: neutrophil extracellular traps. *J. Exp. Med.* 217(6), e20200652 (2020).
47. Zuo Y, Yalavarthi S, Shi H *et al.* Neutrophil extracellular traps in COVID-19. *JCI Insight* 5(11), 138999 (2020).
48. Zhang X, Tan Y, Ling Y *et al.* Viral and host factors related to the clinical outcome of COVID-19. *Nature* 583(7816), 437–440 (2020).
49. Guan WJ, Ni ZY, Hu Y *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 382(18), 1708–1720 (2020).
50. Giamarellos-Bourboulis EJ, Netea MG, Rovina N *et al.* Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 27(6), 992–1000.e3 (2020).

51. Zheng M, Gao Y, Wang G *et al.* Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell. Mol. Immunol.* 17(5), 533–535 (2020).
52. Mazzoni A, Salvati L, Maggi L *et al.* Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J. Clin. Invest.* doi:10.1172/JCI138554 (2020) (Epub ahead of print).
53. Mathew D, Giles JR, Baxter AE *et al.* Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* (2020) (Epub ahead of print).
54. Blanco-Melo D, Nilsson-Payant BE, Liu WC *et al.* Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 181(5), 1036–45.e9 (2020).
55. Zhou Z, Ren L, Zhang L *et al.* Heightened innate immune responses in the respiratory tract of COVID-19 patients. *Cell Host Microbe* 27(6), 883–90.e2 (2020).
56. Laing AG, Lorenc A, del Molino del Barrio I *et al.* A consensus COVID-19 immune signature combines immuno-protection with discrete sepsis-like traits associated with poor prognosis. *MedRxiv.* doi:10.1101/2020.06.08.20125112 (2020) (Online).
57. Ellinghaus D, Degenhardt F, Bujanda L *et al.* Genomewide association study of severe COVID-19 with respiratory failure. *N. Engl. J. Med.* doi:10.1056/NEJMoa2020283 (2020) (Epub ahead of print).
- **The first genomewide association study of severe COVID-19 involving 1980 patients in Europe.**
58. COVID-19 Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. *Eur. J. Hum. Genet.* 28(6), 715–718 (2020).
59. Wilk AJ, Rustagi A, Zhao NQ *et al.* A single-cell atlas of the peripheral immune response in patients with severe COVID-19. *Nat. Med.* 26(7), 1070–1076 (2020).
60. Wen W, Su W, Tang H *et al.* Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov.* 6, 31 (2020).
61. Liao M, Liu Y, Yuan J *et al.* Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat. Med.* 26(6), 842–844 (2020).
62. Chua RL, Lukassen S, Trump S *et al.* COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat. Biotechnol.* 38, 970–979 (2020) (Epub ahead of print).
63. Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. *Science* 367(6485), 1412–1413 (2020).
64. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat. Rev. Drug Discov.* 19(3), 149–150 (2020).
65. Wang Q, Wu J, Wang H *et al.* Structural basis for RNA replication by the SARS-CoV-2 polymerase. *Cell* 182(2), 417–28.e13 (2020).
66. Cao X. COVID-19: immunopathology and its implications for therapy. *Nat. Rev. Immunol.* 20(5), 269–270 (2020).
67. Xu X, Han M, Li T *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. *Proc. Natl Acad. Sci. USA* 117(20), 10970–10975 (2020).
68. Toniati P, Piva S, Cattalini M *et al.* Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun. Rev.* 19(7), 102568 (2020).
69. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat. Biotechnol.* 38(4), 379–381 (2020).
70. Ledford H. Chloroquine hype is derailing the search for coronavirus treatments. *Nature* 580(7805), 573 (2020).
71. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. *Lancet Infect. Dis.* 6(2), 67–69 (2006).
72. Hu T, Frieman M, Wolfram J. Insights from nanomedicine into chloroquine efficacy against COVID-19. *Nat. Nanotechnol.* 15(4), 247–249 (2020).
73. Thorens B, Vassalli P. Chloroquine and ammonium chloride prevent terminal glycosylation of immunoglobulins in plasma cells without affecting secretion. *Nature* 321(6070), 618–620 (1986).
74. te Velthuis AJW, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn²⁺ inhibits coronavirus and arterivirus RNA polymerase activity *in vitro* and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog.* 6(11), e1001176 (2010).
75. Wang M, Cao R, Zhang L *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res.* 30(3), 269–271 (2020).
76. Meyerowitz E, Vannier A, Friesen M *et al.* Rethinking the role of hydroxychloroquine in the treatment of COVID-19. *FASEB J.* 34(5), 6027–6037 (2020).
77. Hoffmann M, Mösbauer K, Hofmann-Winkler H *et al.* Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. *Nature* doi:10.1038/s41586-020-2575-3 (2020) (Epub ahead of print).
78. Maisonnasse P, Guedj J, Contreras V *et al.* Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature* doi:10.1038/s41586-020-2558-4 (2020) (Epub ahead of print).

79. Pushpakom S, Iorio F, Eyers P *et al.* Drug repurposing: progress, challenges and recommendations. *Nat. Rev. Drug Discov.* 18(1), 41–58 (2018).
80. Gordon DE, Jang GM, Bouhaddou M *et al.* A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 583(7816), 459–468 (2020).
81. Zhou Y, Hou Y, Shen J *et al.* Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov.* 6, 14 (2020).
82. Jin Z, Du X, Xu Y *et al.* Structure of M^{PfO} from SARS-CoV-2 and discovery of its inhibitors. *Nature* 582(7811), 289–293 (2020).
- **The authors screened 10,000 compounds, identifying six that inhibit the M^{PfO} of SARS-CoV-2.**
83. Riva L, Yuan S, Yin X *et al.* Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing. *Nature* 10.1038/s41586-020-2577-1 (2020) (Epub ahead of print).
- **The authors profiled 12,000 compounds, identifying several inhibitors of SARS-CoV-2 replication.**
84. Landrigan PJ, Fuller R, Acosta NJR *et al.* The Lancet Commission on pollution and health. *Lancet* 391(10119), 462–512 (2018).
85. Stone V, Miller MR, Clift MJD *et al.* Nanomaterials *versus* ambient ultrafine particles: an opportunity to exchange toxicology knowledge. *Environ. Health Perspect.* 125(10), 106002 (2017).
86. Al-Kindi S, Brook R, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. *Nat. Rev. Cardiol.* doi:10.1038/s41569-020-0371-2 (2020) (Epub ahead of print).
87. Ogen Y. Assessing nitrogen dioxide (NO₂) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci. Total Environ.* 726, 138605 (2020).
88. Chudnovsky AA. Letter to editor regarding Ogen, Y. 2020 paper: “Assessing nitrogen dioxide (NO₂) levels as a contributing factor to coronavirus (COVID-19) fatality”. *Sci. Total Environ.* 740, 139236 (2020).
89. Pisoni E, van Dingenen R. Comment to the paper “Assessing nitrogen dioxide (NO₂) levels as a contributing factor to coronavirus (COVID-19) fatality”, by Ogen, 2020. *Sci. Total Environ.* 726, doi:10.1016/j.scitotenv.2020.138605 (2020) (Epub ahead of print).
90. Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: evidence from China. *Sci. Total Environ.* 727, 138704 (2020).
91. Wu X, Nethery R, Sabath B, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States: a nationwide cross-sectional study. *MedRxiv.* doi:10.1101/2020.04.05.20054502 (2020) (Epub ahead of print).
92. Liang D, Shi L, Zhao J *et al.* Urban air pollution may enhance COVID-19 case-fatality and mortality rates in the United States. *MedRxiv.* doi:10.1101/2020.05.04.20090746 (2020) (Online).
93. Riccò M, Ranzieri S, Balzarini F, Bragazzi NL, Corradi M. SARS-CoV-2 infection and air pollutants: correlation or causation? *Sci. Total Environ.* 734, 139489 (2020).
94. van Doremalen N, Bushmaker T, Morris D *et al.* Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N. Engl. J. Med.* 382(16), 1564–1567 (2020).
95. Chin AWH, Chu JTS, Perera MRA *et al.* Stability of SARS-CoV-2 in different environmental conditions. *Lancet* doi:10.1016/S2666-5247(20)30003-3 (2020) (Epub ahead of print).
96. Zhang R, Li Y, Zhang AL, Wang Y, Molina MJ. Identifying airborne transmission as the dominant route for the spread of COVID-19. *Proc. Natl Acad. Sci. USA* 117(26), 14857–14863 (2020).
97. Setti L, Passarini F, De Gennaro G *et al.* SARS-Cov-2RNA found on particulate matter of Bergamo in Northern Italy: first evidence. *Environ. Res.* 188, 109754 (2020).
98. Domingo JL, Marquès M, Rovira J. Influence of airborne transmission of SARS-CoV-2 on COVID-19 pandemic. *Environ. Res.* doi:10.1016/j.envres.2020.109861 (2020) (Epub ahead of print).
99. Monopoli MP, Åberg C, Salvati A, Dawson KA. Biomolecular coronas provide the biological identity of nanosized materials. *Nat. Nanotechnol.* 7(12), 779–786 (2012).
100. Pietroiusti A, Campagnolo L, Fadeel B. Interactions of engineered nanoparticles with organs protected by internal biological barriers. *Small* 9(9–10), 1557–1572 (2013).
101. Walczyk D, Bombelli FB, Monopoli MP, Lynch I, Dawson KA. What the cell “sees” in bionanoscience. *J. Am. Chem. Soc.* 132(16), 5761–5768 (2010).
102. Salvati A, Pitek AS, Monopoli MP *et al.* Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface. *Nat. Nanotechnol.* 8(2), 137–143 (2013).
103. Tonigold M, Simon J, Estupinan D *et al.* Pre-adsorption of antibodies enables targeting of nanocarriers despite a biomolecular corona. *Nat. Nanotechnol.* 13(9), 862–869 (2018).
104. Ezzat K, Pernemalm M, Pålsson S *et al.* The viral protein corona directs viral pathogenesis and amyloid aggregation. *Nat. Commun.* 10(1), 2331 (2019).

105. Pitek AS, Wen AM, Shukla S, Steinmetz NF. The protein corona of plant virus nanoparticles influences their dispersion properties, cellular interactions, and *in vivo* fates. *Small* 12(13), 1758–1769 (2016).
106. Berardi A, Baldelli Bombelli F, Thuenemann EC, Lomonosoff GP. Viral nanoparticles can elude protein barriers: exploiting rather than imitating nature. *Nanoscale* 11(5), 2306–2316 (2019).
107. Pollok S, Ginter T, Günzel K *et al.* Interferon alpha-armed nanoparticles trigger rapid and sustained STAT1-dependent anti-viral cellular responses. *Cell Signal.* 25(4), 989–998 (2013).
108. Wang Z, Wang C, Liu S *et al.* Specifically formed corona on silica nanoparticles enhances transforming growth factor β 1 activity in triggering lung fibrosis. *ACS Nano* 11(2), 1659–1672 (2017).
109. Shvedova AA, Kagan VE, Fadeel B. Close encounters of the small kind: adverse effects of man-made materials interfacing with the nano-cosmos of biological systems. *Annu. Rev. Pharmacol. Toxicol.* 50, 63–88 (2010).
110. Sportelli MC, Izzi M, Kukushkina EA *et al.* Can nanotechnology and materials science help the fight against SARS-CoV-2? *Nanomaterials* 10(4), 802 (2020).
111. Sivasankarapillai VS, Pillai AM, Rahdar A *et al.* On facing the SARS-CoV-2 (COVID-19) with combination of nanomaterials and medicine: possible strategies and first challenges. *Nanomaterials* 10(5), E852 (2020).
112. Nasrollahzadeh M, Sajjadi M, Soufi GJ, Irvani S, Varma RS. Nanomaterials and nanotechnology-associated innovations against viral infections with a focus on coronaviruses. *Nanomaterials* 10(6), E1072 (2020).
113. Yang B, Shi J. Developing new cancer nanomedicines by repurposing old drugs. *Angew. Chem. Int. Ed. Engl.* doi:10.1002/anie.202004317 (2020) (Epub ahead of print).
114. Loczechin A, Séron K, Barras A *et al.* Functional carbon quantum dots as medical countermeasures to human coronavirus. *ACS Appl. Mater. Interfaces* 11(46), 42964–42974 (2019).
115. Barras A, Pagneux Q, Sane F *et al.* High efficiency of functional carbon nanodots as entry inhibitors of herpes simplex virus type 1. *ACS Appl. Mater. Interfaces* 8(14), 9004–9013 (2018).
116. Fasting C, Schalley CA, Weber M *et al.* Multivalency as a chemical organization and action principle. *Angew. Chem. Int. Ed. Engl.* 51(42), 10472–10498 (2012).
117. Lauster D, Klenk S, Ludwig K *et al.* Phage capsid nanoparticles with defined ligand arrangement block influenza virus entry. *Nat. Nanotechnol.* 15(5), 373–379 (2020).
- **The authors developed topology-matching, multivalent nano-scale inhibitors of influenza virus.**
118. Nie C, Parshad B, Bhatia S *et al.* Topology-matching design of an influenza-neutralizing spiky nanoparticle-based inhibitor with a dual mode of action. *Angew. Chem. Int. Ed. Engl.* doi:10.1002/ange.202004832 (2020) (Epub ahead of print).
119. Nie C, Stadtmüller M, Yang H *et al.* Spiky nanostructures with geometry-matching topography for virus inhibition. *Nano Lett.* 20(7), 5367–5375 (2020).
120. Cagno V, Andreozzi P, D'Alicarnasso M *et al.* Broad-spectrum non-toxic antiviral nanoparticles with a virucidal inhibition mechanism. *Nat. Mater.* 17(2), 195–203 (2018).
121. Tiwari V, Beer JC, Sankaranarayanan NV, Swanson-Mungerson M, Desai UR. Discovering small-molecule therapeutics against SARS-CoV-2. *Drug Discov. Today* 25(8), 1535–1544 (2020).
122. Thamphiwatana S, Angsantikul P, Escajadillo T *et al.* Macrophage-like nanoparticles concurrently absorbing endotoxins and proinflammatory cytokines for sepsis management. *Proc. Natl Acad. Sci. USA* 114(43), 11488–11493 (2017).
123. Hu CM, Fang RH, Wang KC *et al.* Nanoparticle biointerfacing by platelet membrane cloaking. *Nature* 526(7571), 118–121 (2015).
124. Li M, Li S, Zhou H *et al.* Chemotaxis-driven delivery of nano-pathogenoids for complete eradication of tumors post-phototherapy. *Nat. Commun.* 11(1), 1126 (2020).
125. Rao L, Wang W, Meng Q *et al.* A biomimetic nanodecoy traps Zika virus to prevent viral infection and fetal microcephaly development. *Nano Lett.* 19(4), 2215–2222 (2018).
126. Zhang Q, Honko A, Zhou J *et al.* Cellular nanosponges inhibit SARS-CoV-2 infectivity. *Nano Lett.* 20(7), 5570–5574 (2020).
- **Nanoparticles cloaked with cell membranes inhibit SARS-CoV-2 infection in an *in vitro* model.**
127. Hu CM, Fang RH, Copp J, Luk BT, Zhang L. A biomimetic nanosponge that absorbs pore-forming toxins. *Nat. Nanotechnol.* 8(5), 336–340 (2013).
128. Chen H, Fang Z, Chen Y *et al.* Targeting and enrichment of viral pathogen by cell membrane cloaked magnetic nanoparticles for enhanced detection. *ACS Appl. Mater. Interfaces* 9(46), 39953–39961 (2017).
129. Wei X, Zhang G, Ran D *et al.* T-cell-mimicking nanoparticles can neutralize HIV infectivity. *Adv. Mater.* 30(45), e1802233 (2018).
130. Gao C, Huang Q, Liu C *et al.* Treatment of atherosclerosis by macrophage-biomimetic nanoparticles *via* targeted pharmacotherapy and sequestration of proinflammatory cytokines. *Nat. Commun.* 11(1), 2622 (2020).
131. Kuba K, Imai Y, Rao S *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* 11(8), 875–879 (2005).

132. Imai Y, Kuba K, Rao S *et al.* Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 436(7047), 112–116 (2005).
133. Zou Z, Yan Y, Shu Y *et al.* Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. *Nat. Commun.* 5, 3594 (2014).
134. Vaduganathan M, Vardeny O, Michel T, McMurray J, Pfeffer M, Solomon S. Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. *N. Engl. J. Med.* 382(17), 1653–1659 (2020).
135. Lei C, Qian K, Li T *et al.* Neutralization of SARS-CoV-2 spike pseudotyped virus by recombinant ACE2-Ig. *Nat. Commun.* 11(1), 2070 (2020).
136. Bagalkot V, Deiluiis JA, Rajagopalan S, Maiseyeu A. “Eat me” imaging and therapy. *Adv. Drug Deliv. Rev.* 99(Pt A), 2–11 (2016).
137. Sun Y, Guo F, Zou Z *et al.* Cationic nanoparticles directly bind angiotensin-converting enzyme 2 and induce acute lung injury in mice. *Part. Fibre Toxicol.* 12, 4 (2015).
138. Inal JM. Decoy ACE2-expressing extracellular vesicles that competitively bind SARS-CoV-2 as a possible COVID-19 therapy. *Clin. Sci.* 134(12), 1301–1304 (2020).
139. Batlle D, Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? *Clin. Sci.* 134(5), 543–545 (2020).
140. Wang Y, Cai R, Chen C. The nano-bio interactions of nanomedicines: understanding the biochemical driving forces and redox reactions. *Acc. Chem. Res.* 52(6), 1507–1518 (2019).
141. Manjili RH, Zarei M, Habibi M, Manjili MH. COVID-19 as an acute inflammatory disease. *J. Immunol.* 205(1), 12–19 (2020).
142. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. *J. Exp. Med.* 217(6), e20200678 (2020).
143. Chauhan G, Madou MJ, Kalra S, Chopra V, Ghosh D, Martinez-Chapa SO. Nanotechnology for COVID-19: therapeutics and vaccine research. *ACS Nano*. 14(7), 7760–7782 (2020).
144. Shin MD, Shukla S, Chung YH *et al.* COVID-19 vaccine development and a potential nanomaterial path forward. *Nat. Nanotechnol.* 15, 646–655 (2020).
145. Weiss C, Carriere M, Fusco L *et al.* Toward nanotechnology-enabled approaches against the COVID-19 pandemic. *ACS Nano* 14(6), 6383–6406 (2020).
146. Vabret N, Britton GJ, Gruber C *et al.* The Sinai Immunology Review Project. Immunology of COVID-19: current state of the science. *Immunity* 52(6), 910–941 (2020).
147. Cyranoski D. Profile of a killer: the complex biology powering the coronavirus pandemic. *Nature* 581(7806), 22–26 (2020).
148. London AJ, Kimmelman J. Against pandemic research exceptionalism. *Science* 368(6490), 476–477 (2020).
149. Singer DS. NCI’s work to advance cancer research while responding to the COVID-19 pandemic. *Cancer Cell* 37(6), 746–748 (2020).
150. Fadeel B, Farcal L, Hardy B *et al.* Advanced tools for the safety assessment of nanomaterials. *Nat. Nanotechnol.* 13(7), 537–543 (2018).