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Iron-Based Nanoparticles, an Accurate and Powerful Sniper Targeting SARS- Cov-2

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Abstract

For the past few months, the world has been facing another coronavirus disease, COVID-19, caused by the SARS- CoV-2, giving the rise of a pandemic. In the vast majority of infected individuals, SARS-CoV-2 causes a mild ailment, but in some subjects, it progresses to severe disease or even death, with some groups being at high risk. However, SARS-CoV-2 is not the first coronavirus that caused serious, sometimes fatal, disease. Almost 20 years ago, SARS-CoV and later MERS were coronaviruses that led to severe diseases but did not result in pandemics. Some of the therapeutic lessons learned during the SARS-COV and MERS epidemics are being used now to treat COVID-19 patients, such as the still debated use of Chloroquine. However, there were other important preclinical studies performed around the time of SARS-COV and MERS epidemics that may also be useful applications in the COVID-19 context. This review highlights the benefits that could be gained by revising the non-conventional therapeutic approaches used in the previous coronavirus epidemics in improving the detection, treatment, and prevention tools and developing patient treatment follow-up strategies. Specifically, this review discusses the utilization of iron oxide nanoparticles due to their attractive properties. It also highlights the therapeutic opportunities and future directions of the iron oxide nanoparticles to be eventually employed in the current coronavirus pandemic.

Keywords: SARS-Co V-2; COVID-19; Nanomedicine; Iron Oxide Nanoparticles

Abbreviations: ACE Inhibitors= ACEIs; Acute Lung Injury= ALI; Acute Respiratory Distress Syndrome= ARDS; Angiotensin Converting Enzyme-2= ACE2; Angiogenesis II= AngII; Angiotensin Receptor Blockers= ARB; Antisense Oligonucleotide= ASO; Black, Asian and Minority Ethnic= BAME; Cardiovascular Diseases= CVDs; Computed Tomography= CT; Diabetic Melitus= DM Intensive Care Unit= ICU; Interferon-α= IFN-α; Interferon-β= IFN-β; Iron Oxide NPs= IONPs; Mas Receptors= MasR Middle East Respiratory Syndrome Coronavirus= MERS-CoV; Nanoconjugates= NCs; Nanoparticles= NPs; Nanozymes= IONzymes; Nitric Oxide= NO; Norwegian University of Science and Technology= NTNU; Phosphodiesterases-5= PDE5; Poly (amino ester) with carboxyl groups (PC)-coated magnetic NPs= pcMNPs; Prorenin receptor- Ang II type 1 receptor= PRR-ACE-Ang II-AT1R; Pulmonary Arterial Hypertension= PAH; Reactive Oxygen Species= ROS; Receptor Binding Domain= RBD; Renin Angiotensin System= RAS; Reverse Transcription Polymerase Chain Reaction= RT-PCR; Royal Gwent Hospital= RGH; Severe Acute Respiratory Syndrome Coronavirus= SARS-CoV; Spike protein= S; Transmembrane Protease Serine 2= TMPRSS2; Tumour Necrosis Factor= TNF; World Health Organization= WHO

Introduction

Outbreaks caused by infectious diseases represent a tremendous challenge to humanity, with coronaviruses accounting for a relevant part of them[1]. Coronaviruses are a single-stranded positive-sense RNA family that can affect several vertebrate hosts.

In the past, these viruses were known to cause minor to mild upper respiratory tract diseases with symptoms similar to the common cold in many cases. However, in the last 17 years, three aggressive human coronavirus pathogens appeared as we witnessed the

emergence/re-emergence of zoonotic diseases causing epidemics and pandemics. These include the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)1 with 8098 infected cases and 774 [2] deaths, the Middle East respiratory syndrome coronavirus (MERS-CoV) with 2494 infected cases and 858 [3] deaths, and the most recent outbreak of the novel coronavirus (SARS-CoV-2 (COVID-19) which was first reported in Wuhan-China in December 2019 and was considered a pandemic on March 11th 2020 [4]. As of November 20th, 2020, there are 57,236,335 reported cases, of which 39,722,802 recovered and 1,365,634 died[5]; the current pandemic originated enormous global health, social and economic crises1. SARS-CoV-2 succeeded in crossing species barriers to infect humans and can now be effectively transmitted from one person to another1. So far, 7 coronaviruses affecting humans are known: SARS-CoV, MERS-CoV, and SARS-CoV-2 causing symptoms that start with influenza-like signs that either stays mild and disappears or escalates to severe lung injuries with multiorgan failure, acute respiratory distress syndrome (ARDS), and acute lung injury (ALI); the remaining 4, namely HKU1, NL63, OC43, and 229E, are associated with mild respiratory symptoms [4, 6].

The death rate of SARS-CoV-2 increases by age and the presence of other comorbidities1. SARS-CoV-2 mechanism of action affects three host components: blood, inflammation, and cellular components. In the blood component, the viral proteins "ORF10 and ORF3a" coordinate to attack the heme part of the hemoglobin (1-beta chain), which results in the dissociating of the iron to form porphyrin, decreasing the amount of the functional hemoglobin, which leads to the development of anemia and respiratory distress symptoms [7]. In the inflammation component, it was noticed that the overproduction of proinflammatory cytokines -such as IL-6, IL-1β, and tumor necrosis factor (TNF)- could cause a SARS-CoV-2-induced cytokine storm in addition to the accumulation of the fibrin and thrombin [8]. The sudden cytokine increase elevates the risk of developing vascular hyperpermeability and multiorgan failure, eventually leading to death. The inflammatory component of the SARS-CoV-2 includes a significant upsurge in the reactive oxygen species (ROS), triggering redox imbalance, mitochondrial and lysosomal dysfunction, and rendering the cells even less resistant to infection. Such a sequence of events can result in serious and permanent long-term cellular damage, which accelerates the immune system's aging process and affects tissues/organs (i.e. lung) [8]. In addition, the inflammatory component is responsible for the formation of the ground-glass-like figure of the COVID-19 lung. This indicates that developing immunomodulators or therapeutic strategies to target the inflammatory component, ROS, and the overactive cytokines could be one of the SARS-CoV-2 therapeutic options [7, 9]. The cellular component is the most crucial one in the pathogenesis of SARS-CoV-2, which is why we will be discussing it in depth. So far, angiotensin-converting enzyme-2 (ACE2) receptors have been considered as the primary cellular entry point for three strains of coronavirus: NL63, SARS-CoV, and the novel SARS-CoV-2

[10]. ACE2 receptors are expressed ubiquitously in the blood vessels, heart, lung, kidneys, gut, brain, testis [11], and salivary glands [12]. It is expressed in rodents and humans, and present bound to the cell membrane with low levels in the plasma [11].

The nasal epithelium is now considered the portal entry for the SARS-CoV-2 infection and transmission, where higher viral loads were found in symptomatic and asymptomatic patients. The virus's entry depends on the binding of the spike (S) protein to a specific cellular receptor, which then initiates a series of cellular proteases. A crucial and limiting factor for the viral entry and the initial infection is the ACE2 receptor facilitated by host cell-derived serine protease, the transmembrane protease serine 2 (TMPRSS2). It is worth noting that TMPRSS2 could be used as an alternative entry route for the SARS-CoV-2 using cathepsin B/L [13, 14]. The S protein's high affinity towards the ACE2 is now considered an important determinant factor for the viral replication rate which in turn determines the severity of the disease [15]. Datasets for multiple human tissues, including airways, were retrieved from published/unpublished databases that could be found on European Genome–phenome Archive (https://www.ebi.ac.uk/ega/home), GEO [16], and MedGen. These data were analyzed by both Vieira et al. [17] and Deprez et al. [18]. Results showed a high level of ACE2 expression in nasal secretory cells, multiple types of epithelial cells across the airway, and the alveolar epithelial type II cells13. Looking back at the history and importance of the ACE2 receptors, we will find that the renin-angiotensin system's (RAS) classical view has dramatically changed since the discovery of the ACE2 receptors. Since then, ACE2 was classified as a membrane-bound receptor; it cleaves the angiogenesis II (AngII) to generate the active peptide Ang (1–7). The cellular actions of the Ang (1–7) are then mediated by Mas receptors (MasR) [19] to perform cardio- protective effects.

ACE2 Expression Modulators

ACE2 expression is modulated by the following factors: age, ethnicity, sex, and the existence of other health comorbidities: in SARS-CoV2, these factors have an impact on the susceptibility and severity of the disease11. An in vivo study evaluating the age effect on the expression of several cardiac markers between two groups of 24 month-old and 12 month- old mice showed that 24 month-old ones expressed significant enhancement of the prorenin receptor - Ang II type 1 receptor (PRR-ACE-Ang II-AT1R) axis with a reduction in the ACE2/ Ang (1–7)/MasR axis [20]. Global studies from China, Italy, Spain, UK, and the USA showed that elder people have low expression of ACE2 in the lung11 and therefore are more susceptible and fragile to the disease, which could be attributed to the virus ability to further lower the ACE2 baseline expression in the ACE2 low producing cells [11]. This might be attributed to the fact that aging is a major factor in the development of cardiovascular

diseases (CVDs) due to endothelial cell dysfunction and inflammation [21]. Also, the fetal dataset retrieved and analyzed

from GEO16 revealed the low to no expression of the ACE2 with no co-expression of the TMPRSS2, which might partially explain why SARS-CoV-2 represents a low risk to young generations [13, 14, 22]. In terms of ethnicity and sex, it was shown that the diverse genetic basis in the Black, Asian, and Minority Ethnic (BAME) groups could indeed affect ACE2 functions. Also, it has been shown that other ethnic groups have some structural variations of the ACE2, that confirmed its protective effects due to its low binding affinity to the viral S protein [11]. This could be the reason why people from the BAME origins have high SARS- CoV-2 susceptibility due to the increased affinity of their ACE2 variation to the viral S protein showing more disease severity, which might contribute to the death rate [23-25]. Additionally, Baumer et al. [26] showed that 35% of the SARS-CoV-2 cases that were admitted to the intensive care unit (ICU) and 35% of the deaths in the Royal Gwent Hospital (RGH), Newport, Wales, were of BAME ethnic descent. Another study showed that men had a higher chance of getting SARS-CoV-2 as their cells express a higher percentage of ACE2 compared to women [23, 24].

Risk factors such as elder age and comorbidities (namely, CVDs, Diabetic Mellitus (DM), obesity) are known to worsen SARS-CoV-2 severity, eventually leading to death. Patients with the above-mentioned risk factors share one feature that worsens their SARS-CoV-2 condition, which is the involvement of the endothelial cells in the progression of the SARS- CoV-2 with endothelial cells having different expression profiles of the ACE2 in patients with different comorbidities. The up or downregulation of the expression of this receptor can either benefit or harm the SARS-CoV-2 patients depending on which group they belong to; As it determines the patient's response to the viral invasion. ACE2 is generally expressed by endothelial cells and plays an important role in vasodilation, anti-hypertrophy, and anti-fibrosis [27]. Under normal circumstances, the downregulation of ACE2 leads to an increased function with the ACE/AngII axis inducing anti-apoptotic, thrombotic, proinflammatory, and vasoconstriction effects; while the upregulation of the ACE2/ Ang (1–7)/MasR axis exhibits various cardiovascular protective effects including the vasodilatory, anti-proliferative, anti-atherogenesis, antithrombosis, and antifibrotic effects. Dysregulation between these two axis was reported in SARS-CoV-2 infected patients from high-risk groups. An example of the dysregulation between the two axis was reported in pulmonary arterial hypertension (PAH); with idiopathic or heritable PAH patients expressing an increased level of AngII levels with markedly decreased levels of phosphorylated status (Ser-680) of ACE2 whereas, PAH due to congenital heart disease showed decreased levels of serum ACE2 and Ang (1–7). In contrast, DM and other CVDs such as hypertension are considered high-risk factors for the severity of SARS-CoV-2 due to the significant increase in the expression of the ACE2 receptors increasing the viral entry points [28]. Lately, evidence has emerged, linking obesity to the poor prognosis of patients with SARS-CoV-2. This is attributed to comorbidities associated with obesity; these comorbidities are caused by the endothelial dysfunction leading to hypertension and inflammation [29, 30]. The downregulation of the ACE2 in PAH and old age groups might seem beneficial at first glance, but it also means that once infected, the virus will cause a further deficiency in the low ACE2 bassline, which will worsen the condition. In this category, using the ACE inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARB) could be harmful [24], unlike in DM and other CVDs where they might help as ACE2 is highly expressed in these conditions [31,32]. Surprisingly, respiratory allergies, asthma, and controlled exposure to allergen were not considered high risks for developing severe SARS- CoV-2 despite having a low expression of ACE2 [33]. The fact that PAH, despite having a decreased level of ACE2 expression, is still considered a high SARS-CoV-2 risk group indicates that there might be other factors beyond ACE2 expression, modulating the response of the respiratory allergies, asthma and controlled exposure to allergen groups to SARS-CoV-2 that we are not aware of.

Therapeutic Lessons from Past Coronaviruses

The fact that SARS-CoV-2 shares several similarities with SARS-CoV as it belongs to the β-coronavirus genus, and its receptor-binding domain (RBD) resembles the SARS-CoV one indicates that they may share the same ost-cell receptor6. As such, some medications used to treat SARS-CoV were considered for SARS-CoV-2, like Chloroquine. Chloroquine is an immune modulator used in treating parasitic malaria infections; it inhibits the binding of the parasite to the ACE2 receptors, with some studies showing the antiviral activity of the drug against SARS-CoV-2 [34]. The fact that this medication can act on the ACE2 receptors promoted its use in SARS-CoV and SARS-CoV-2 [35] as it works either by inhibiting the viral fusion through the cell membrane, preventing the glycosylation of the host cell's receptors, or preventing the assembly of the virus in the endoplasmic reticulum [34]. It also inhibits the autophagy process [36, 37]. Ribavirin is another SARS-CoV antiviral drug that was employed for SARS-CoV-2 treatment [38]. The Ritonavir combination with lopinavir, other SARS-CoV antiviral drugs were also evaluated as a therapeutic option. Due to the involvement of inflammation in COVID-19, there have been signs of the benefit of using interferon-α (IFN-α) and interferon-β (IFN-β) treatments. Furthermore, some MERS-CoV in vitro and animal in vivo experiments demonstrated that combining the ribavirin and INFs treatments improved the clinical outcomes [39]. However, translating these findings to be used in the routine clinical treatment of SARS-CoV-2 infected patients needs further investigations [39]. The fact that ACE2 is expressed by various cardiovascular cells also indicates that any imbalance between the ACE axis can harm the heart, with the increase in the ACE/AngII being associated with heart failure while ACE2/ Ang (1–7)/MasR

can prevent such event. Formulating ACEIs and ARB can protect from cardiovascular complications. However, their role in the lung is still unknown and requires further investigation to understand better if they can be used to ameliorate the ALL induced by SARS-CoV-211. SARS-CoV-2-related endothelial cell dysfunction was shown to be accompanied by a reduction in nitric oxide (NO) production. NO was shown to significantly inhibit the viral replication cycle by inhibiting the synthesis of the viral proteins and RNA [40], which gave the scientists another possible therapeutic angle by improving the bioavailability of NO. This is done by either supplementing patients with NO or improving the intrinsic NO bioavailability by inhibiting its degradation through the use of phosphodiesterases-5 inhibitors (PDE5) such as Sildenafil [41]. The NO bioavailability can be improved by packaging it in nanocarriers, which increased the interest in combating the virus by implementing nanomedicine tools. Nanomedicine offers many attractive properties that can overcome the current limitations and surpass the present conventional therapeutic and detection tools.

Current SARS-CoV-2 Nanomedicine Applications

Viruses are often considered nature's devil nanocarriers. They package their genetic materials, protect it from the immune system, prolong its presence in the biological system, deliver it to the host cell, and then transfer it from infected cells to other destinations. They are nature's evolutionary work of art with many unique features, making them smart, attractive, capable, yet dangerous nanoparticles (NPs). Many researchers in the nanomedicine field proposed the use of virus-based NPs as gene therapy tools [42]. Viral nanocarriers are double-edged swords that should be studied thoroughly for their benefits/damages. Indeed, to win the battle of COVID-19, we need to think and implements tools that reassemble the virus's nature. Therefore, the use of nanomedicine to face SARS-CoV-2 is now being evaluated. The nanomedicine community today, more than ever, can significantly contribute to this battle with nanomaterials being developed and thoroughly investigated. Governments/countries, research/academic institutes, health organizations, and charity foundations are providing substantial funds to aid in developing nano-formulations that could be used as diagnostics tools, nanocarriers for therapeutics (drugs and vaccine) as well as developing non-conventional nano-therapies. Ongoing nanomedicine research includes the development of a rapid point-of-care diagnostic tool that will enable us to screen a higher number of persons to capture the silent careers and improve the detection threshold to detect the virus at the early infection stages.

Having such a detection tool will aid in the viral surveillance monitoring to identify regions with increased infection rate using a time effective procedure. In addition, creating a low-cost detection nanocarrier means that low-income communities will have access to such detection tools. Another angle by which we can fight SARS-CoV-2 is reusing existing therapeutic agents while innovating new

ones. By understanding the basic interaction between the SARS-CoV-2 and the host cell, we can develop a nanocarrier that can either block the interaction or act as a new host for the virus. We can also use that interaction to our benefit and design a nano-vaccine. Despite being at the preliminary stages, antiviral nanomedicine therapies are promising, cost-effective, and have high-quality properties that could open new avenues in the prevention, diagnosis, and treatment of COVID-19. The physical size of SARS-CoV-2 makes the relevance of nanotechnology clearer, which is also supported by the antiviral research using nanomaterials [43]. Due to the global pandemic and emerging need for developing prevention and treatment strategies for COVID-19, the World Health Organization (WHO) adopted the strategy of repurposing existing nanomaterials to develop drug/vaccine nano-therapies, detection tools, and antiviral coatings.

Nano-Detection Tools

Current Nano-based diagnostic tools suggested for SARS-CoV-2 include a nano-based-colorimetric bioassay that was developed using gold-NPs; these NPs were capped with a thiol-modified antisense oligonucleotide (ASO) that is specific for N-gene (nucleocapsid phosphoprotein) of the SARS-CoV-2. Capping the gold-NPs is important to ensure the efficient detection of SARS-CoV-2 in COVID-19 patients within 10 minutes [44]. Another study reported the use of polymer-stabilized multivalent gold-NPs functionalized with sialic acid derivative to make it interact with the viral spike glycoprotein [45]. Reverse Transcription Polymerase Chain Reaction (RT-PCR)-based methods are considered SARS-CoV2 gold standard detection tool. However, in their systematic review, Rodriguez et al. [46] showed that this detection tool has false-negative rates of 2-33%46 in repeat sample testing. Also, Cohen and Kessel [47] showed that the SARS-CoV-2 RT-PCR detection tool has false-positive rates 0-16% [47] in repeat sample testing. To overcome the false positive/negative results, a study showed the possibility of increasing the RT-PCR precision using fluorescent-labeled-NPs that are conjugated to viral RNA specific probes [48]. Additionally, another group developed a Nano plasmonic sensor chip that has an extraordinary time efficiency (<15 min) and sensitivity (LOD = 370 vp/mL) as it detects the entire SARS-CoV-2 virus [49]. Finally, the Norwegian University of Science and Technology (NTNU) formed a collaboration with St. Olavs Hospital to develop an iron oxide nanoparticle-based detection Tools [50].

Nano-Based Vaccines

Nano-based vaccines are also drawing attention in facing the current pandemic. The use of nanotechnology in the development of vaccines is called 'Nanovaccinology'; Nanovaccinology is considered an alternative and effective tool that can substitute the conventional vaccines. This is attributed to:

i) their tailorable surface properties and improved stability,

ii) immuno-stimulatory properties,

iii) high payloads,

iv) tunable sizes, which determines the cellular uptake rate, and

v) controllable drug release kinetics [51, 52]. Materials used in the synthesis of the NPs, their surface chemistry, and size are important factors in determining which cells will be activated and the potential immune response that will be triggered [53, 54]. They will also determine the vaccine release rate, pharmacokinetic properties, biodistribution, and the bioavailability of the

immunogenic agents. Vaccines are developed from:

i)   inactivated/killed pathogens (first-generation vaccines),

ii)   synthetic

peptides (second-generation vaccines),

iii) DNA vaccines (third-generation vaccines), and/or iv) live-attenuated microorganisms [53]. The efficacy of these conventional vaccines depends upon using appropriate delivery systems, therefore conjugating them with NPs can improve their efficacy. Nano-based vaccines can benefit from the added NP's properties in guiding the vaccine to the immune cells enhancing the antigen uptake and therefore boosting the host's immunity, and due to the high cellular uptake of some NPs, this can lead to the induction of humoral and cellular responses50. A study showed the possibility of using iron oxide NPs (IONPs), which are currently being employed to treat anemia as nanovaccine due to their in vitro antiviral activity [55]. Additionally, other promising nanomaterials are being studied with 4 COVID-19 nano-based formulations currently in trials, ClinicalTrials.Gov [56]. One nano-vaccine that is currently being investigated employs lipid nanoparticles to carry viral mRNA [57]. Additionally, other studies showed the effectiveness of using Chloroquine NPs [58] as well as the currently ongoing inhaled NO NPs trial [59]. Furthermore, scientists in the nanomedicine field are currently trying to promote nanomaterials in treating and preventing pneumonia caused by SARS-CoV-243. Nanoconjugates (NCs) Based Stem Cell Therapy Patients suffering from SARS-CoV-2 can develop virus-induced lung injuries and, to some extent, present abnormalities in liver function. The fact that some patients suffered from life-time damages in these organs led to considering the use of the Nanoconjugates (NCs) Based Stem Cell Therapy [60]. The main two challenges facing stem cell therapy are i) the low cell retention and survival rate, which in turn affects their repair capacity, and ii) the difficulty monitoring cellular behavior and fate [61]. Due to the NPs superior physical and chemical properties, NCs Based Stem Cell Therapy can overcome

these limitations. In this approach, NPs are loaded/conjugated with functional agents (e.g., dye, gene, targeting ligands….etc) that could be easily taken up by the desired or studied stem cell type to genetically engineer them61. Alternatively, NPs could be used to selectively label stem cells to monitor their behavior and determine their fate; additionally, cells can be labeled with NPs that are surface modified with materials (targeting ligands) that could enhance their retention rate in the desired tissues [61]. NCs were shown effective in autoimmune disorders, CVDs, cancer, …..etc. and are currently being investigated to overcome SARS-CoV-2 induced organ damages [60]. Nano-coating tool NPs from the metals and metal oxides such as iron oxide [62], zinc oxide[63], silica (SiONPs) [64], gold (AuNPs) [64], silver (AgNPs) [65], and cuprous oxide (CuONPs) [66], possesses antibacterial and antiviral properties on their own. For that purpose, surfaces and equipment are coated with them to prevent any bacterial or viral contaminations. Especially ventilators, which are important equipment that are used for treating patients with sever SARS-CoV-2; this will help in better managing ventilator-associated pneumonia [67, 68]. Nowadays, the SARS-CoV-2 nanomedicine research is interested in implementing inorganic NPs of specifically the iron oxide nanoparticle to be used as a detection tool, therapeutic and theragnostic agents in this pandemic for the many attractive properties they have39.

Could iron oxide NPs be the magic bullet for SARS-CoV-2?

From the above ongoing SARS-CoV-2 nanomedicine research, we chose to discuss the super magnetic and iron oxide NPs as they have great potential in helping us fight SARS-CoV2. Previous results evaluating iron oxide NPs showed that they have:

i) anti-inflammatory effects on human endothelial cells and human smooth muscle cells [69],

ii) anti-inflammatory effect on mouse macrophages, and

iii) showed no toxicity to endothelial cells from different origins [70]. With one prototype being loaded with the PDE5 inhibitor, Sildenafil69which can be used as a SARS-CoV-2 therapeutic option. We understand the importance of the vasculature component to the recovery from SARS-CoV-2, particularly the endothelial and inflammatory cells [70]. Therefore, we and others emphasized on the use of this iron-based nano-formulation for the detection and future treatment of COVID-19 disease by benefiting from the current knowledge of SARS-CoV-2 viral invasion, replication and survival cycles as demonstrated in (Figure 1).
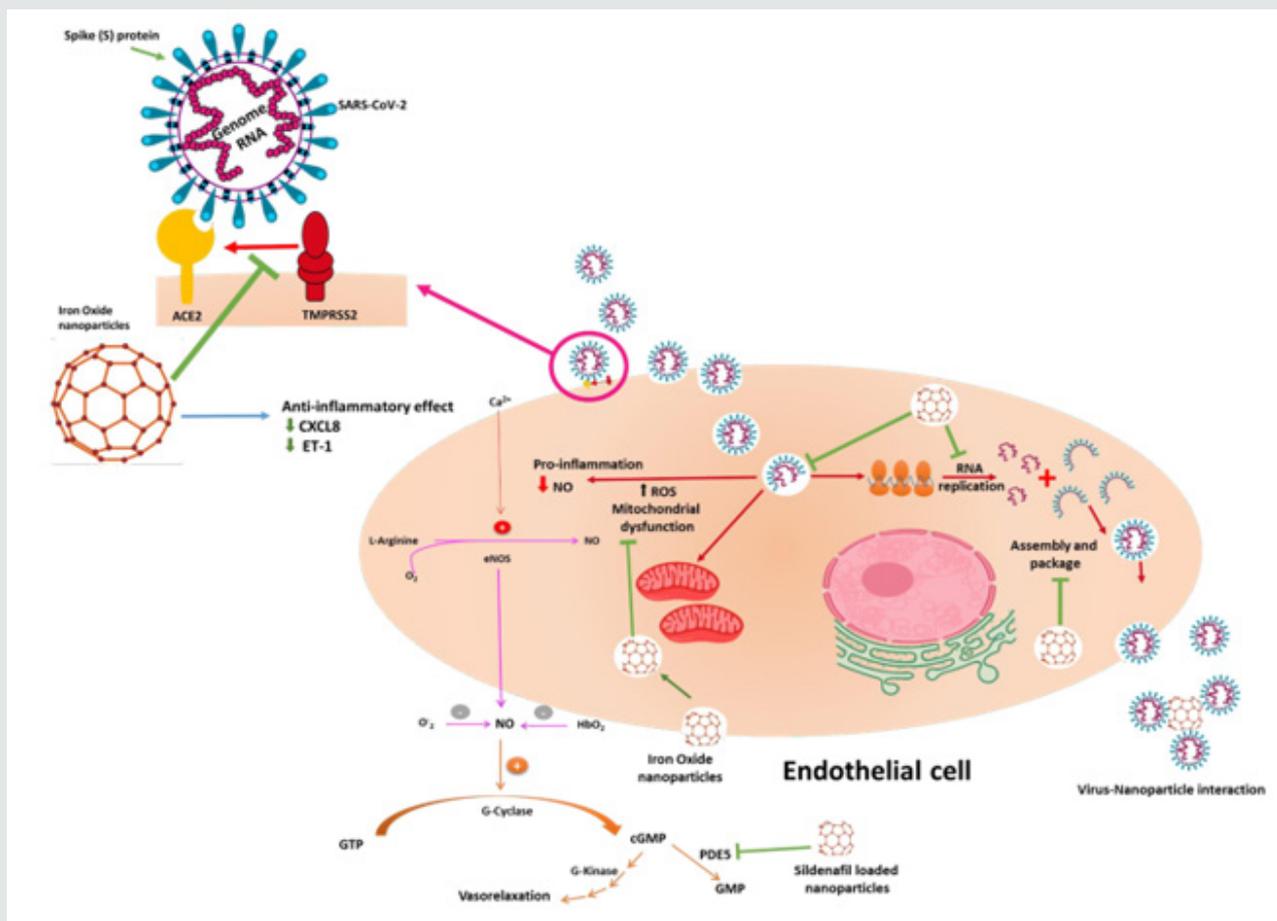
Figure 1: Iron oxide nanoparticle's potential therapeutic and detection properties

In terms of SARS-CoV-2 detection and COVID-19 therapeutic option, there is an interest in iron oxide NPs to be further investigated. SARS-CoV-2 current detection method relies on using RT-PCR; despite being accurate, this method is hampered by the sample processing steps. Zhao et al. developed a rapid, inexpensive, and safe detection procedure by using the poly (amino ester) with carboxyl groups (PC)-coated magnetic NPs (pcMNPs). The pcMNPs, combine the lysis and binding steps into one step, enabling purifying the viral RNA from several samples using manual or automated methods within ≥ 20 min [71]. In support of these findings, another study by Chen et al. showed that iron oxide NPs offer a better viral detection tool [72]. In terms of anti-inflammation/antioxidant effects, iron oxide NPs were shown to have enzyme-like activity, making them classified as nanozymes (IONzymes). Nano-enzymes are favored over natural enzymes as their activity can be modified by tailoring the nanoparticle's size, shape, and surface properties. The IONzymes, being the most typical nano- enzyme, can perform two enzymes like function, the peroxidase, and catalase activities. The nanoparticle's composition, surface modification, and the environment pH determines which enzymatic activity IONzymes will perform73. For example, at acidic

pH conditions, they exhibit peroxidase-like activities. Because of this activity IONzymes are used as biomarker detection tools in several diagnostic immunoassays that are capable of detecting the presence of Ebola, diabetes and certain tumours [74]; in addition, IONzymes have antibacterial effects and improve wound healing process74. Under neutral conditions,

IONzymes exhibit catalase-like activities, reducing the ROS, therefore improving the anti-inflammatory processes [74]. Recent studies showed that SARS-CoV-2 infection is accompanied by a significant increase in the ROS activity, which indicates the therapeutic benefit of using IONzymes in the management of SARS-CoV-2 infection [8, 75]. This catalytic activity was previously shown effective in the peroxidation of the viral lipid envelope, inactivating the enveloped virus [73]. Furthermore, the antioxidant effect of the iron oxide NPs can be further enhanced through the surface-functionalization of the NPs with naturally occurring antioxidant such as gallic acid [76] and dextane conjugated trypsin [77]. In terms of their cardiovascular benefit, a study conducted by Duan et.al showed that iron oxide NPs could be used in treating CVDs associated with oxidative stress as they functioned as an

autophagic-related antioxidant in HUVECs [78]. In addition, iron oxide NPs were shown to have serine protease inhibition activity, indicating that they might inhibit the TMPRSS2 that is required in the binding of the SARS-CoV-2 to the ACE2 without disturbing the ACE/AngII and ACE2/ Ang (1–7)/MasR axis balance. This inhibition can provide an extremely valuable option in the treatment and prevention of the SARS-CoV-277. The exact interaction between the TMPRSS2 and the iron oxide NPs, however, still needs further investigation. In addition, iron oxide NPs were shown to possess antiviral effects against H1N1 influenza A virus, as they inhibit the virus from binding to host cells (i.e. lung epithelial cells) [79]; also, a recent study reported that iron oxide NPs can induce membrane lipid peroxidation in synthesized liposomes, ending the viral replication cycle, which makes it a universal antiviral strategy [73]. Furthermore, it was shown that iron on its own is considered an attractive component to the virus as it is essential for viral survival, cellular invasion, and replications [7]. This explains the fact that anemia is associated with SARS- CoV-2 as the virus attacks the hemoglobin and breaks its down [7].

Therefore, thinking like a virus and creating attractive NPs for the virus might be the way to go. Having an intact nano-formulation that is hard for the virus to breakdown yet can attract the virus and interact with it might help contain the virus and prevent its rapid spread. Iron oxide NPs can attract the virus due to the presence of the iron, they are available in many forms, their stability can be tailored to range from days to months, and they possess antiviral activity with the possibility of loading/tagging them with antiviral drugs. The viral attraction to the iron oxide nanoparticle is currently being used as an antiviral tool and for rapid viral detection [71, 72]. Iron oxide NPs were shown to affect the cellular component of the SARS-CoV-2. As we know, the involvement of the endothelial cell dysfunction was proven to worsen and complicate the SARS-CoV-2 infection. Therefore, using NPs that can be taken up by the endothelial cells, reducing its dysfunctionality would be highly beneficial. So far, iron oxide NPs have been studied to mark and track endothelial cells. Some of them were shown to have no toxicity and reduce the endothelial cell's inflammatory markers (CXCL8 and ET-1) [70]. A particular prototype, nanoMIL-89, was loaded with the PDE5 inhibitor sildenafil (generating Sil@nanoMIL-89) and investigated as an alternative tool in PAH treatment. This prototype was shown to have the above-mentioned anti-inflammatory effects on the endothelial cells, it also reduced the vascular smooth muscle cell proliferation as in PAH these cells undergo an increased proliferation rate70 and finally prolonged the Sildenafil half- life [69]. As we know, PAH is considered one of the high-risk groups in SARS-CoV-2, and developing a tool with several therapeutic properties could reduce the risk of disease worsening. Furthermore, Xiong et al. have shown and discussed the cardioprotective property of the iron oxide NPs [80]. Finally, some iron oxide NPs were shown to accumulate in the lung [70]. The lung is the most vulnerable

organ to the SARS-CoV-2 infection as it has a wide alveolar epithelial cell surface expressing ACE2 receptors that is prone to viral invasion. Once infected, the lung will lose its elasticity due to the reduction in the surfactant quantity; and the consequences of the imbalance in the ACE/AngII axis and ACE2/ Ang (1–7)/MasR axis. Leading to an impairment in the gas exchanges and fibrosis, eventually causing severe bilateral peripheral pneumonia giving the lung its COVID-19 ground glass figure detected by the Computed Tomography (CT) scan 11. The high affinity of the iron oxide NPs to the lung, without causing lung oedema or showing lung toxicity in vivo, makes it interesting and valuable tool to be investigated in this pandemic [81,82].Their accumulation in the lung can be used in treating pneumonia. Caaman o and Morales showed in their study that due to their antibacterial effect, iron oxide NPs improved the antibacterial activity of erythromycin67, which, if tailored, could be used in treating COVID-19 related pneumonia. In addition, it was shown previously that iron oxide NPs inhibited the influenza A virus entry to the epithelial cells, which are the main SARS-CoV-2 entry host [79]. The possibility of aerosolizing these NPs to be inhaled adds more weight to this application, especially for patients under ventilation. Because the inhalation route will provide direct access to the most affected organ (i.e. the lung), increasing the local concentration which will improve the drug's efficacy and avoid the systemic side effects at the same time [39]. In our opinion, NPs are an exciting adjuvant strategy that should be considered particularly when developing vaccines for infectious diseases that so far do not have effective ones, such as SARS-CoV-2. With proper research, nanomedicine could provide enormous potential for SARS-CoV-2 prevention, diagnosis, and treatment. This requires the interdisciplinary collaborations between virologists, biologists, chemists, engineers as well as consulting clinicians to implement nanomedicine in: i) developing affordable and rapid SARS- CoV-2 diagnostic tools to be globally available (e.g. nano-antiviral sensors), (ii) developing nano-formulations (e.g. iron oxide NPs) that can prevent the viral replication and interfere with the RNA synthesis, iii) using nanomaterials that can prevent the interaction between the virus and ACE-2, and finally (iv) to use that knowledge in developing new Nano-based vaccines. Several NPs are currently being studied to be used as a detection tool, with iron oxide NPs attracting the COVID-19 scientific research. The fact that they have antimicrobial effects makes them potential strong candidates in developing contamination-safe equipment and tools.

Conclusion

Life will never be as we knew it before. This pandemic has proven that to win this fight against COVID-19, we need to focus our efforts on improving our scientific community and research capabilities. It showed us that building human capacity in research is the only way to win this battle, and that enriching the knowledge of our communities is our best weapon. Our communities must come together in sticking to the guidelines until we learn to coexist again

naturally. Furthermore, our scientists, including virologists, biologists, chemists, engineers, clinicians, and healthcare workers from all over the world, need to concentrate their efforts on translating and deploying advances in the diagnosis/treatment/prevention strategies, including nanomedicine, to the frontline.

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Conflict of Interest

All authors declare no conflict of interest

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