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Drug delivery systems as immunomodulators for therapy of infectious disease: Relevance to COVID-19 ☆

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ABSTRACT

The emergence of SARS-CoV-2, and the ensuing global pandemic, has resulted in an unprecedented response to identify therapies that can limit uncontrolled inflammation observed in patients with moderate to severe COVID-19. The immune pathology behind COVID-19 is complex and involves the activation and interaction of multiple systems including, but not limited to, complement, inflammasomes, endothelial as well as innate and adaptive immune cells to bring about a convoluted profile of inflammation, coagulation and tissue damage. To date, therapeutic approaches have focussed on inhibition of coagulation, untargeted immune suppression and/or cytokine-directed blocking agents. Regardless of recently achieved improvements in individual patient outcomes and survival rates, improved and focussed approaches targeting individual systems involved is needed to further improve prognosis and wellbeing. This review summarizes the current understanding of molecular and cellular systems involved in the pathophysiology of COVID-19, and their contribution to pathogen clearance and damage to then discuss possible therapeutic options involving immunomodulatory drug delivery systems as well as summarising the complex interplay between them.

Contents

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1. SARS-CoV-2; the infectious agent of the COVID-19 pandemic

The emergence of coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic that keeps threatening millions of lives globally. To date, there are no specific treatments available, resulting in significant morbidity and mortality. Due to being highly transmissible, SARS-CoV-2 has spread all over the world [1,2] and, to date (April 2021), there have been over 129 million recorded infections resulting in 2.8 million associated deaths. To enter host cells, SARS-CoV-2 uses the same receptor as SARS-CoV, namely trans-membrane angiotensin converting enzyme 2 (ACE2) [3,4]. To allow infection, SARS-CoV-2 furthermore requires a proteolytic process of the S protein to activate the endocytic route, involving transmembrane protease serine protease 2 (TMPRSS2), cathepsin L and furin [1,5].

While a significant proportion of infections occur unnoticed or mildly symptomatic (estimates range up to 80%), symptomatic COVID-19 patients can present with sever acute respiratory illness with fever and respiratory symptoms, such as cough and shortness of breath and are therefore selected for viral testing [6]. Additionally, possibly due to the ubiquity of the angiotensin system, non-respiratory symptoms may also present such as gastro-intestinal and neurological symptoms [6]. Interestingly, children and young people less frequently develop severe symptoms in the acute phase of infection. While the reasons for this are incompletely understood, hypotheses are manifold and, among others, include (i) co-clearance with other viruses in children, (ii) sufficient early clearance in the upper respiratory tract through increased type 1 interferon induction, (iii) reduced ACE2 expression in the lower respiratory tract preventing virus migration and entry into bronchial epithelia, and iv) an altered balance between ACE2 and ACE1-(3-)7 contributing to reduced tissue damage [7,8]. However, a subset of children and young people develop a hyper-inflammatory syndrome, usually weeks after acute infection, that can include gastrointestinal symptoms, cardiac involvement, respiratory symptoms and failure, inflammation of skin and mucous membranes (including conjunctiva), and many more [9,10]. The symptom complex has been termed MIS-C (USA), PIMS-TS (UK) and MIS (WHO). Case definitions differ slightly, but it is now accepted that they all describe the same disease process [11]. While pathophysiological mechanisms likely differ from acute COVID-19 in adult patients, immunological features suggestive of cytokine storm syndrome (cytopenias, hyperferritinaemia, hypertriglycerdiaemia, elevated transaminases, CrP and cytokines, etc.) [10,12]. Thus, understanding shared and unique infection and immunological mechanisms in children and adults will help to prevent and treat infection, and control inflammation and damage.

Whilst there is a concerted effort to identify therapeutics with antiviral properties [13], also a number of immune modulators have shown to improve patient outcome including dexamethasone [14,15], the recombinant IL-1 receptor antagonist anakinra [16,17] and the IL-6 receptor blocking antibodies tocilizumab and sarilumab [18]. To help reduce the hyperactive nature of the immune system in patients with COVID-19 [19,20], various immune-modulating therapeutics that regulate different aspects of inflammation are undergoing clinical trials for the treatment of COVID-19 i.e. modulation of the hyperinflammatory phase of infection (dexamethasone, Janus kinase/JAK inhibitors), counteracting the cytokine storm (cytokine blocking agents, including anakinra and tocilizumab), and stimulation of host immunomodulatory and antiviral activity [21]. Along these lines, the FDA has issued an emergency use authorisation for the antiviral drug remdesivir, given in combination with the JAK1/2 inhibitor baricitinib and monoclonal antibody therapy bamlanivimab as well as casirivimab and imdevimab (Regeneron) for COVID-19 [22,23].

Corticosteroids, known to have untargeted but significant immunosuppressive effects, specifically dexamethasone and hydrocortisone have been shown to improve recovery in critically ill patients [24]. The NHS in the United Kingdom, and the FDA in the USA [25], also recommends the interleukin-6 inhibitors tocilizumab or sarilumab, as an alternative [26]. In adult patients with acute COVID-19, IL-6-producing CD14+ CD16+ inflammatory monocytes are significantly increased [27]. Hence tocilizumab and sarilumab can bind specifically to both membrane-bound and soluble IL-6 receptors, thereby inhibiting signal transduction and the production of downstream inflammatory molecules. Baricitinib, through its mechanism of action, has been predicted to reduce both viral entry via binding to AP2-associated protein kinase (AAK1) and cyclin G-associated kinase (GAK) and preventing viral dependant clathrin-mediated endocytosis [28,29], and inflammation [30,31]. Additionally, its low plasma protein binding properties and minimal interaction with CYP enzymes and drug transporters allow for well-tolerated concomitant use. However, the use of Baricitinib is related to hyperlipidaemia, a symptom of cytokine storm in some patients) and increased thromboembolic events, which is concerning given that COVID-19 patients are at risk of developing thromboembolism [32].

However, despite several ongoing studies and in light of available data, there are no drugs or other therapeutics presently approved to specifically prevent COVID-19. The vast majority of immunomodulatory agents being studied have toxicity concerns, as well as solubility, stability and bioavailability limitations that ultimately lead to a high degree of pharmacokinetic and individual variability. This subsequently leads to a lack of efficacy, due to the presence of subtherapeutic concentrations. Furthermore, the question of when to use immunomodulating agents requires to be answered. Usually, cytokine blocking strategies are trialled in patients on intensive care units with respiratory or multi-organ failure, and it remains unanswered whether ventilator treatment and organ damage may be prevented if treated earlier [33,34]. Finally, due to their expense and route of administration, it can be difficult to roll out therapeutics, such as anakinra or tocilizumab, to a potentially large number of patients. Thus, application

of non-biological drugs, that may be given orally, may have a number of logistical and financial advantages supporting efforts to assess drug repurposing, immune modulating drugs; supported by the success of dexamethasone in the RECOVERY trial [35]. However, pharmacological therapy for long-term mitigation of COVID-19 remains a scientific and health-care challenge, and may be assisted by the application of novel state-of-the-art drug delivery systems.

This manuscript reviews available medications used for the treatment of hyper-inflammation in acute COVID-19 in adults. It touches on the special immunological situation in children and young adults to underscore key discussion points, and provides an overview of potential future treatment targets and drug delivery systems. Treatment of long-COVID-19 is not within the focus of this review.

2. Immunological responses in COVID-19

SARS-CoV-2 infections range from asymptomatic courses to systemic inflammatory disease (COVID-19) and death. Unknown age, gender and ethnicity related factors are involved in determining outcomes, as children and young people (particularly young women) usually develop less severe symptoms and/or disease courses when compared to adults. Ethnic minorities are overrepresented across age groups in relation to both number of patients and deaths in the UK and beyond [9,33,36].

In adult COVID-19, significant inflammation is observed in the lungs of patients that is characterized by the presence and involvement of activated macrophages [37], neutrophils [38], CD4+ and CD8+ T cells [39]. Preliminary evidence suggests that, in addition to the lungs, infection of peripheral monocytes and activation of immune signalling mechanisms in the peripheral blood of COVID-19 patients may be present and support systemic inflammation and multi-organ damage [40]. Type 1 interferons are part of the innate anti-viral responses, as their expression is induced by the cytoplasmic nucleic acid detection and mobilization machinery. Therefore, induction of type I interferons is, usually, associated with clearance of viral infections. Interestingly, in the case of SARS-CoV-2 infections/COVID-19, there is evidence of suppression of these cytokines by the virus [41], alongside increased levels of IL-1, IL-6 and TNFα that are associated with increased disease severity [42]. Furthermore, later in disease, as a result of tissue damage and cell death, type 1 interferon expression may "derail" and perpetuate inflammation and damage [9]. This is likely of significant relevance, as pathological spontaneous and/or increased activation of the type 1 interferon pathway is associated with autoimmune/inflammatory conditions, such as SLE, that share some clinical aspects of COVID-19, including cytokine storm, tissue damage, thromboembolic events, end others [9,43]. Below, we discuss the involvement of particular immune mechanisms, in COVID-19, and how drug delivery systems, such as nanoformulation, may improve therapeutic options.

2.1. Inflammasomes

Inflammasomes are multi-protein complexes that assemble during the innate immune response to "danger signals" that include (but are not limited to) microbes or cellular stress [44]. Activation of inflammasomes requires the interaction of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) with pattern recognition receptors (PRRs) [45,46]. Activation of the most commonly studied inflammasome, the Nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 (NLRP3) inflammasome requires two signals. The first, also known as the priming step, for example the interaction of Lipopolysaccharide (LPS) with Toll-like receptor 4 (TLR4) which results in upregulation of the NF-κB pathway leading to increased production of NLRP3, pro-IL-1β and pro-IL-18 [45]. The second signal required can be one of the following: relocalisation of the NLRP3 to the mitochondria; the release of mitochondrial factors such as reactive oxygen species (ROS), mitochondrial DNA or cardiolipin; potassium efflux through ion channels or lysosome release of cathepsin [45]. The most commonly studied NLRP3 inflammasome consists of the NLRP3 receptor, ASC and caspase-1. Following the formation of the inflammasome complex, pro-caspase-1 is proteolytically cleaved to produce active caspase-1, which subsequently is able to cleave pro-IL-1β and pro-IL-18 into their active forms [47]. Caspase-1 also cleaves gasdermin D, which proceeds to form pores in the cell membrane causing cytosol contents to leak out of the cell, resulting in pyroptotic cell death [46,48]. Dysregulated inflammasome activation and the use of NLRP3 inhibitors for treatment has been linked to a number of diseases including, but not limited to: Cryopyrin-associated periodic syndrome (CAPS), gout and Type-II diabetes [49].

Notably, products of inflammasome activation, namely mature IL-1β and IL-18, are also involved in the induction of adaptive immune responses that are also involved in inflammation and damage of COVID-19. IL-1β is involved in effector T cell differentiation and activation, including Th17 responses [50], and IL-18 plays an important role in IFN-γ secretion, stimulation of NK cells and proliferation of Th1 cells [47]. Thus, inhibition of inflammasome assembly or its products may be promising in the search for therapeutic options in COVID-19.

2.1.1. Role of the inflammasome in COVID-19

A number of viral components are known activators of inflammasome complexes, examples of which are listed in Table 1. Early reports on clinical and laboratory features of SARS-CoV2 infections in Wuhan suggested pathological inflammasome activation with increases in IL-1β, IL-1_{RA} and IFN-γ serum levels observed in infected patients when compared to healthy individuals [51]. Increased IL-18 serum levels have also been identified in a number of other studies in COVID-19 patients, and correlations have been identified between IL-18 secretion and disease severity [52,53]. Severe COVID-19 disease states compared to moderate disease states also associate with elevated serum lactate dehydrogenase (LDH), a product of inflammasome activation & IL-1β/IL-18 release mediated cell death [51,54]. More recently, primary human monocytes infected *in vitro* with SARS-CoV-2 demonstrate NLRP3-dependent activation of caspase-1 and IL-1β release, although increased LDH release and ASC speck formation was NLRP3 independent and likely through another inflammasome complex [55]. On the day of hospitalisation, COVID-19 patients exhibit higher serum concentrations of active caspase-1 and IL-18 when compared to healthy individuals [55]. As discussed previously, disease severity (and fatal outcomes) associated with serum levels of IL-18 [55]. Therefore, as also in patients with autoimmune/inflammatory disease at risk for or experiencing cytokine storm syndrome and/or macrophage activation, serum IL-18 may serve as a predictive biomarker for severe disease, and therapies targeting the inflammasome and associated cytokines may help treating patients who are more likely to develop severe or fatal COVID-19. Indeed, *post-mortem* analysis of fatal COVID-19 patients' lung tissues found increased levels of NLRP3 and ASC specks compared to controls [55,56]. Furthermore, obese patients (BMI > 30) have significantly greater IL-18 levels, which correlates with obese individuals having increased systemic inflammation, causing them to be in a 'primed state' which may be resulting in increased activation of the inflammasome and the increased mortality in the context of SARS-CoV-2 infection [55,57,58]. Thus, therapies targeting the

Table 1
Examples of viral components, known to activate inflammasomes.

Viral component	Mechanism of activation	References
Viroporins e.g. M2 (influenza), 2B (Rhinovirus/EMCV), SH (RSV), E/3a (coronavirus) and p7 (CSFV)	Viroporins can oligomerize, modifying membrane permeability and causing increased ion transport through host cell membranes. Alongside increasing mitochondrial ROS, both of which can act as signals for NLRP3 inflammasome activation.	[59,60]
Virus-derived ssRNA	Detectionof ssRNA by TLR-7/8 in the endosomal compartment leads to subsequent activation of NF-κB.	[61–63]
Virus derived dsRNA	Detection of dsRNA by TLR-3 on the plasma membrane or endosomal compartment. Retinoic acid inducible gene-I can also sense dsRNA directly leading to NF-κB activation via mitochondrial antiviral signalling protein, alongside directly activating caspase-1 through interactions with ASC.	[60,61,63,64]
Virus derived dsDNA	AIM2 can directly sense cytoplasmic dsDNA. TLR9 can also senses dsDNA in the endosomal compartment, leading to NF-κB activation.	[61–63,65]

inflammasome and associated cytokines may be particularly useful for obese individuals.

2.1.2. Possible inflammasome targeted therapeutic treatment options for COVID-19

Several therapies have been developed to moderate pathological NLRP3 inflammasome activation, subsequent conversion of pro-IL-1β and pro-IL-18 into its active forms, and excess pro-inflammatory cytokine signalling. Therapies include, but are not limited to, Tranilast, Belnacasan and Rapamycin [66–68].

Tranilast originally was discovered as an anti-allergic drug for the treatment of inflammatory diseases, such as asthma [69]. It directly targets and binds to the NACHT domain of NLRP3, leading to inhibition of oligomerization, preventing caspase-1 activation and secretion of mature IL-1β and IL-18 [66]. Tranilast is currently being explored in a phase 1 clinical trial for its promise in helping treat COVID-19 patients with severe immunological responses that may lead to cytokine storm and/or ARDS [70]. Belnacasan (VX-765) and Pralnacasan are pro-drugs of selective caspase-1 inhibitors [67,71]. Targeting caspase-1 with Belnacasan and Pralnacasan precludes increased production of IL-1β, IL-18 and IFN-γ *in vitro* (human immune cells) and *in vivo* (mouse models of arthritis) [67]. Targeting the inflammasome at this point, no alterations in upstream inflammasome component formation has to be considered, which may reduce undesirable side effects. Rapamycin, a specific mTOR inhibitor, has been demonstrated useful in the treatment of a number of (inflammatory) diseases, including Cancer [72]. Rapamycin reduces LPS-induced acute lung injury in mice via inhibition of the NLRP3 inflammasome through enhanced autophagy and diminished NF-κB activation [68]. Other therapies that target the activation of the NLRP3 inflammasome and have been suggested for use in COVID-19 treatment include: Colchicine, Curcumin and Quercetin [73–75].

An alternative method of modulating inflammasome activation is to regulate inflammasome-associated cytokines following their secretion, previously demonstrated for controlling responses to IL-1 using anakinra (rec. IL-1 receptor antagonist) [76]. Anakinra is an IL-1 receptor antagonist, which has been demonstrated to improve conditions such as CAPS and Still's disease [76,77]. Anakinra promises in moderate to severe COVID-19 patients in combination with twice a day orally and 400 mg Lopinavir with 100 mg ritonavir twice a day orally [78]. Furthermore, in a small cohort of patients with severe COVID-19 with secondary hemophagocytic lymphohistiocytosis, anakinra reduced mortality at day 21 by 10% [79]. Other studies have also shown improvements in severe COVID-19 patients treated with Anakinra [80,81]. Although a study on its use in mild to moderate COVID-19 patients has shown no improvement in patient outcomes [82].

2.1.3. Drug delivery systems for targeting the inflammasome in COVID-19

Drug delivery systems have been used for many years to improve the efficacy and safety of therapies, in order to better treat a number of diseases including, cancer [83].

Spray dried nanoformulation of Tranilast, a drug that has poor oral bioavailability, has been used improve solubility and increase drug levels *in vivo* [84]. Belnacasan has previously been formulated in gated mesoporous silica nanoparticles to increase its delivery to macrophages. When administered intravenously, it showed significantly reduced inflammation *in vivo* when compared to free drug [85].

Other drugs which have been suggested for inflammasome modulation and explored in nanoformulations include: Colchicine (inhibition of NLRP3 assembly by downregulation of the pyrin gene [86]), Curcumin (suppression of P2x7R expression [87]) and Quercetin (prevention of ASC oligomerisation[88]) [89–91]. A number of different nanoformulations have been developed for their potential use to improve the bioavailability of rapamycin.

Rapamycin is poorly soluble, undergoes extensive first pass metabolism and its bioavailability can be altered by diet [92]. Nanoformulations of rapamycin have been designed for a number of treatments, including but not limited to: immune suppression in transplant patients, lymphangioleiomyomatosis and age-related diseases including cancer and may have applications in COVID-19 [93–96].

2.2. The complement system

The complement system is an important component of the innate immune response. Soluble complement components located throughout the body, carried within vasculature, possess the ability to recognise pathogens themselves or support the activity of other opsonins [97]. The complement system may be initiated by an assortment of stimuli, each ensuing a distinct route of instigation that results in the activation of the main body of the cascade. The classical pathway recognises immune complexes, comprising of either IgG or IgM coupled with a pathogen or non-self-antigen, triggering a conformational change in complement component (C)1q, which sequentially leads to activation of C1r along with C1s and cleaving of C2 and C4 [98]. The same outcome is shared by the lectin pathway, which relies upon a multi-protein complex containing mannan-binding lectin and two protease zymogens (MASP-1 and MASP-2) to be activated, and recognises carbohydrate ligands upon cell surfaces [99,100]. The third and final route of activation, known as the alternative pathway, does not lead to the creation of the C4bC2a configuration C3 convertase. While the classical and lectin pathways are activated through specific interactions of foreign material with host molecules, the alternative pathway is constantly in a state autoactivation that is controlled via self-regulation. This process, coined as "tick over", involves the continual low-level production of altered C3(H_2O)

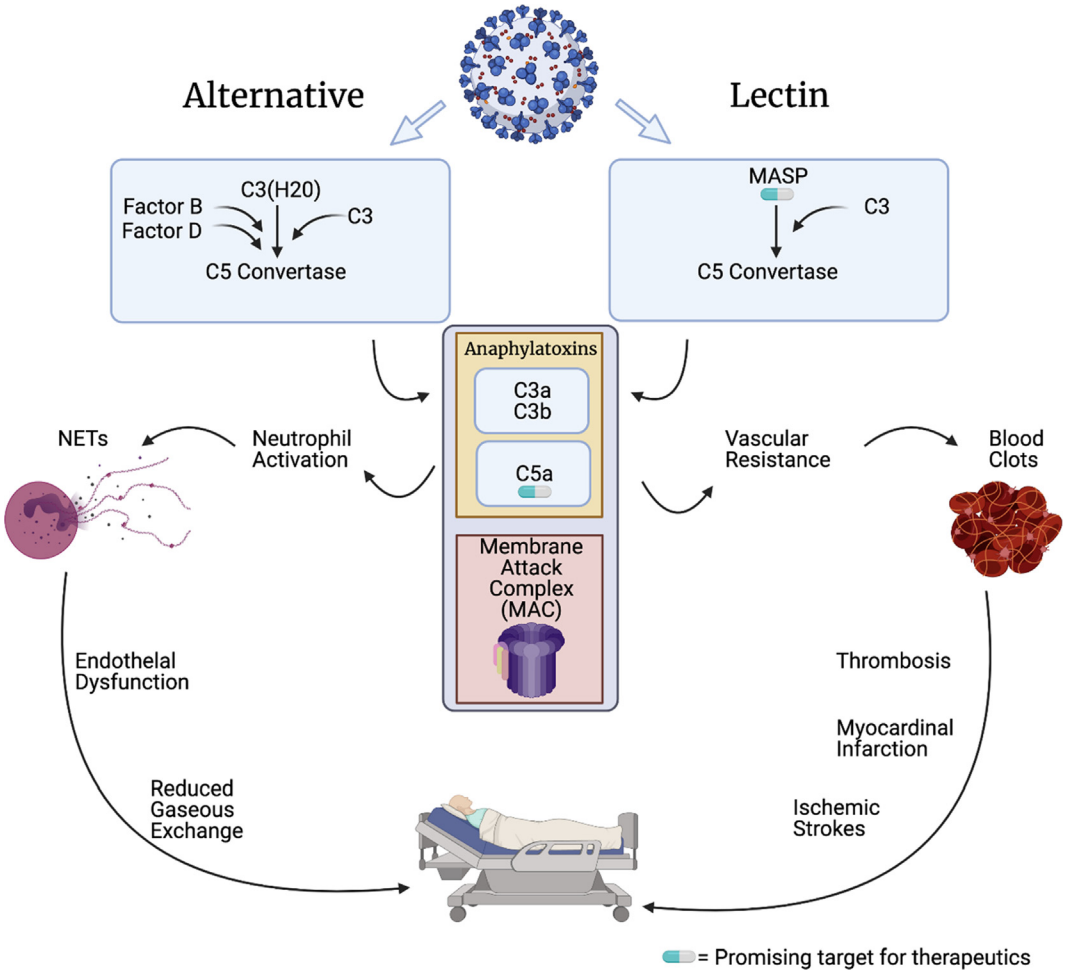

Fig. 1. A visual representation of the mechanisms of complement activation by SARS-CoV-2, and the routes by which this may directly lead to symptoms and ultimately hospitalisation. Also highlighted are areas of the pathway which are currently showing promise in the development of treatments for those suffering with infection.

molecules capable of binding factor B [101]. The binding of this complex to hydroxyl groups on cell-surface carbohydrates leads to the amplification of the active C3 molecules and in turn the production of C3 convertase [102]. Although it appears that the alternative pathway is, primarily, activated during SARS-COV2 infection there are suggestions that secreted nucleoprotein dimers also cause activation via the lectin pathway [103,104].

2.2.1. Complement in COVID-19

Complement activation has been demonstrated in SARS-CoV-2 infection (Fig. 1). Once activated, the complement system works to dispose of any foreign material or infected cells through a combination of chemotaxis and opsonisation alongside the production of proinflammatory anaphylatoxins (C3a/C5a) [105–107]. All of these are present during infection with SARS-COV2, and have been linked to the pathogenesis and severity of disease [108]. This is of particular interest due to the damage inflicted upon the lungs, and the high significance of respiratory failure as contributors for hospital admission and mortality of those diagnosed with COVID19 [109]. This in emphasised further by the finding that those patients who require invasive respiratory therapy exhibit greater levels of C5a, implying a greater degree of complement activation, along with the deposition of active complement proteins within lung tissue [110,111].

A range of complement-mediated mechanisms have been identified as contributors to serve organ damage in COVID-19 [103]. The production of C5a and activation of membrane attack complex (MAC) result in the activation of neutrophils [112]. Within immune responses, this cell population aids in phagocytosis and degranulation alongside the production of neutrophil extracellular traps (NETs) [113]. Consisting of DNA, histones, and other intracellular proteins, NETs are externalised during neutrophil's response to immune activation [114]. Once ejected, they aid in the trapping of microbes for phagocytosis, the further release of proinflammatory molecules and amplification of the cascade through both the classical and alternative pathways [115,116]. However, NETs frequently also induce dysfunction in nearby endothelial cells, resulting in increased occurrence of atherosclerosis and atherothrombosis [117]. Negative effects of this can be seen in COVID-19 patients, as SARS-CoV-2 infection causes neutrophil activation within the lungs [118,119]. The level of neutrophil migration and activation correlates with disease severity to such a degree that it can be used as a predictor of disease outcomes [120]. Significant inflammation, alongside tissue damage and cell death reduce gas exchange to the point where patients' needs cannot be met by the reduced lung capacity [121,122]. Lastly, the role of NETosis in COVID-19 is further underscored by the ability of SARS-CoV-2 to stimulate the release of NETs from healthy neutrophils [123].

In addition to the production of NETs, the activation of the complement cascade promotes coagulation [124]. Complement factor 5a has prothrombic effects through upregulating release of tissue factor from endothelial cells [125]. A precursor to the

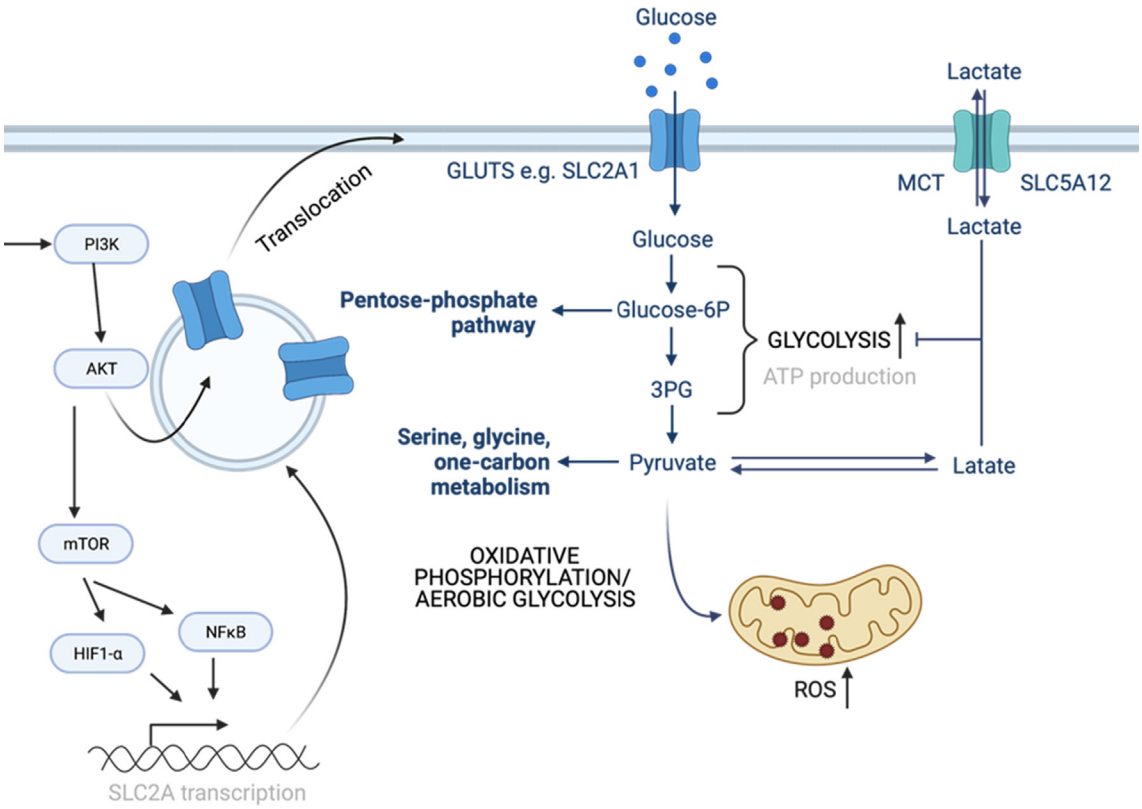

Fig. 2. Expression and trafficking of GLUTs for glucose metabolism and immune cell activation.

complement cascade, MASP, can cleave prothrombin to thrombin, in addition to the MAC aiding in prothrombinase assembly [126,127]. Complement activation may furthermore increase vascular resistance within major organs, resulting in an amplifying effect upon the prothrombotic conditions [103]. As such, the intense complement activation in COVID-19 have been linked to embolisms and blood vessel occlusion resulting in ischemic strokes, myocardial infarction and deep-vein thrombosis thrombosis [128].

2.2.2. Targeting complement activation in COVID-19

Considering the points above, the complement system may be a promising treatment target to reduce morbidity and mortality in COVID-19. Urwyler *et al* utilized a C1 inhibitor in non-critical COVID-19 patients, of which all were discharged from hospital within 22 days, compared to a matched control population of 15 patients [129]. Similarly, a MASP2 inhibitor was used to greater success, allowing patients suffering with severe COVID to be discharged within 90 days, compared to retrospective control groups [130]. Targeting the complement cascade is also desirable considering vaccinations. Numerous approved vaccines, specifically those involving the use of PEGylated liposomes within formulation, may result in hypersensitivity reactions (CDC COVID-19 Response Team and Food and Drug Administration, 2021). It is likely that these are the result of complement activation-related pseudoallergy (CARPA) [131]. CARPA is thought to occur through the activation of immune reaction conductors, such as basophils or mast cells, through IgE independent reactions, but is defined by complement activation which can also be observed in COVID-19 patients [132,133].

C5 inhibitors (e.g. eculizumab) have also shown promise in critically ill COVID-19 patients. While they did not reduce mortality, inhibitors sufficiently limited inflammation, namely complement activation and IL-6 levels [134].

In addition to being targeted in the treatment of COVID-19, there is scope for the complement system to aid in the efficacy of vaccines [135,136]. Interaction between C1q molecules and antibodies produced following vaccination may allow for greater effectiveness of vaccines [136].

Although not the focus of the current review, complement mediated recognition of nanoparticles is a well described phenomena for this type of drug delivery system and has been reviewed, extensively, elsewhere [137,138]. Although it may hamper the development of such delivery systems, and should always be considered during preclinical evaluation, a number of efforts have been made to define how complement mediated recognition may be avoided [139–141].

2.3. Immune cell metabolism

Cell metabolism plays a vital role in the rapid activation and function of the human immune response, summarised in Fig. 2. Following stimulation – either by infection or cell damage – immune cells become activated and respond [142,143]. This, in turn, results in greater bioenergetic requirements that are facilitated by glucose uptake, amino acids and fatty acid availability [144–147]. In the initial stages of immune activation, there is a greater dependence on the uptake of glucose via membrane-associated carrier proteins [148], such as glucose uptake transporters (GLUTs) [149,150]. GLUTs are solute carrier (SLC) [151] transporters, which aid with glucose uptake into immune cells switching from oxidative phosphorylation (OXPHOS) to glycolysis, to fulfil the high demand for rapid synthesis of ATP [146,152–154]. Each immune cell requires large quantities of glucose for activation, and when physiological and pathological conditions change, the need for glucose increases. This results in GLUTs, such as SLC2A1 (GLUT1), being translocated from reservoirs in cytoplasmic vesicles to the surface of the plasma membrane [155–161]. Once

taken up by immune cells, glucose is metabolised to produce ATP and a number of other metabolites, such as lactate [162,163]. A number of regulatory proteins, known for their association with immune cell activation, such as the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/ mammalian target of rapamycin (mTOR) pathway [164,165], hypoxia inducible factor 1-alpha (HIF1-α) [166] and nuclear factor-κB (NFκB) [167], are involved in the regulation of SLC2A1 and other GLUT expression and activity [160].

Due their role in supporting immunological responses, the activity of GLUTs in immune cells has drawn considerable attention. Glucose uptake by GLUTs has already been recognised to be involved in the pathophysiology of infectious diseases as the metabolism of cells increases and, as a consequence, glucose is taken up at a higher rate for aerobic glycolysis [168–170]. This allows for the metabolism of the cells to favour aerobic glycolysis, known as the Warburg effect, due to their increased levels of glucose uptake, supressing further the microenvironment of cells due to lactate production [168,171,172]. Activation of immune cells, such as naïve CD4+ T cells, rely on an increase in surface expression of SLC2A1 to enable differentiation into effector T cells [173]. Indeed, glucose uptake is crucial for T cell proliferation and activation [174], with SLC2A1 regulation and translocation being a key step in this mechanism of glucose uptake. It has also been suggested that activated T cells rely largely on aerobic glycolysis [175], therefore, large amounts of glucose are required to meet this demand.

GLUTS, such as SLC2A1, transport glucose into cells to be broken down via glycolysis. The products of glycolysis are then metabolised in the mitochondrion by the tricarboxylic acid cycle where pyruvate is converted to acetyl-CoA to fuel oxidative phosphorylation (OXPHOS). ATP, needed for cellular activation, can be generated from glucose via both glycolysis and OXPHOS. Cells can switch from OXPHOS to aerobic glycolysis for fast synthesis of ATP, causing an increase in reactive oxygen species (ROS) production. The expression and translocation of GLUTS are regulated by a number of pathways, via proteins shown above. Created with BioRender.com

2.3.1. The role of immunometabolism in COVID-19

A growing body of literature links glucose metabolism to COVID-19. In response to SARS-CoV-2 infection, immune cells, particularly pulmonary macrophages, exhibit significant production of interleukin 6 (IL-6) amongst other proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α) [176]. Excessive production of IL-6 (alongside IL-1, IL-18 and others) contributes to the excessive inflammation in COVID-19 [177] through the induction of a cytokine storm [178]. The increased immune response to SARS-CoV-2 leading to a cytokine storm and subsequent immune exhaustion may be the product of aerobic glycolysis, which further leads to increased oxidative stress of the immune cells [179,180].

One of the most prevalent concerns is around COVID-19 patients with pre-existing conditions such as diabetes. Diabetes is associated with defective glucose metabolism and control of glucose levels within the blood. Hyperglycaemia increases replication SARS-CoV-2 in monocytes through increased ACE2 expression on the cell surface [176]. Moreover, elevated glucose levels weaken antiviral immune responses [181,182], with a report showing that from March to May 2020, one-third of all COVID-19-related deaths in England occurred in people with type 1 (TD1) or type 2 (T2D) diabetes [183]. Notably, patients with insulin resistant T2D were at a higher risk of SARS-CoV-2 infection [176,184]. With the switch from oxidative phosphorylation (OXPHOS) to aerobic glycolysis, the concentration of lactate – a by-product of the metabolic process – is increased to a level which may cause severe complications in patients who are at risk of hyperglycaemia; particularly those with COVID-19 infections [182].

The immune system defends against pathogens throughout the life time. As metabolic pathways are bioenergetically demanding, with age, immunometabolism and thus the immune response will decline [185]. While COVID-19 is a disease affecting all ages, older individuals seem to be more prone to infection, and at increased risk of severe COVID-19 and related complications [186]. Impaired immune functions do not occur instantly; symptoms and physiological effects developing gradually over a period of time, known as immunosenescence [187–189]. As age progresses, we lose the ability produce cells that are able to recognise and deal with new infections such as SARS-CoV-2 or to respond adequately to vaccines [190–192].

During SARS-CoV-2 infection, glycolysis-associated genes are upregulated in monocytes of patients [176], such as 6-phospho fructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) [193,194]. In addition to this, the replication of SARS-CoV-2 is supported and maintained when the switch from OXPHOS to aerobic glycolysis occurs [176]. The SARS-CoV-2 genome encodes proteins that target the NF-κB pathway [195], which in turn also causes the switch to aerobic glycolysis, whilst regulating the translocation of GLUTs, promoting glucose uptake into the cells. In addition, SARS-CoV-2 infected patients, when compared to healthy donors, exhibit elevated levels of hypoxia-inducible factor-1α (HIF-1α) in monocytes [176]. HIF-1α induces transcription of genes and upregulate several enzymes involved with glycolysis [196–198], alongside increasing the regulation and translocation of glucose uptake transporters, such as GLUT1 [166]. HIF-1α levels are elevated due to mitochondrial reactive oxygen species (ROS) production, which is increased during SARS-CoV-2 infection [176]. Therefore, there is a cycle of higher levels of glucose uptake via increased GLUT expression, leading to aerobic glycolysis and consequentially increased ROS production and HIF-1α levels.

2.3.2. Immunometabolism as a potential target in COVID-19

Therapeutics have been developed to help combat the COVID-19 pandemic, with the hopes of providing aid as researchers formulate the vaccines to target mutating strains of the virus. As glucose metabolism has been identified as a possible therapeutic target, several treatments may be beneficial. While currently few studies focus on SLC targeted treatments, in particular the facilitative GLUT transporters, some research into the potential therapeutics targeting the sodium glucose cotransporter family is performed. The potential of the SGLT2 inhibitor dapagliflozin is currently being tested in two phase 3 trials, DARE-19 (NCT04350593) and TACTIC-E (NCT04393246), to assess if there can be an improvement on clinical recovery and respiratory complications for non-critically ill patients, who are hospitalised due to COVID-19 [199,200]. Dapagliflozin has been nanoformulated with the intention to control diabetes [201], which could also be utilised for use for the treatment of COVID-19, with an increased permeability [202], optimal drug release profile in simulated gastric fluid and improved oral hypoglycaemic activity [201].

Blocking HIF-1α may limit viral replication and control cytokine storm as a result of COVID-19. Codo and colleagues [176] suggested that the glycolysis inhibitor 2-deoxyglucose (2-DG) may be used to block viral replication by lowering glucose transport, reducing the induction of ACE2 and IL-1β, TNF-α and IL-6 expression. The therapeutic utility of 2-DG is low due to the compound having poor accumulation in targeted organs and a short half-life as it is rapidly metabolised. However, nanoformulations of 2-DG exist [203–205] and may be considered as therapeutic in COVID-19 due to the improved biodistribution of 2-DG. In addition, authors [176] showed that inhibiting HIF-1α via BAY87-2243 also reduced replication of SARS-CoV-2. The same inhibitor reduces the accumulation of HIF-1α proteins in non-small cell lung cancer cells [206]. However, a previous phase 1 clinical trial (NCT01297530)

investigating the candidate agent BAY87-2243 for the treatment of neoplasms was withdrawn [207], because of significant toxicity to patients.

In patients with diabetes, medication to lower lactate/LDH levels may be beneficial and effective during COVID-19 due to the immune suppressive activity of lactate [182]. LDH controls the production and release of lactate. Studies looking into the role of LDH in pancreatic cancer has shown that hyperglycaemia-induced HIF-1α accumulation increases LDH activity [208]. A recent study also concluded that in patients of severe COVID-19 cases, the LDH levels in blood are frequently higher [209]. In addition to this, a study by Zhu et al. [184] showed that lactate inhibits the retinoic acid-inducible gene I (RIG-I)-like receptor (RLR), reducing SARS-CoV-2 clearance. From this, lactate as a target for a therapeutic may aid in controlling the inflammatory immune response in patients with COVID-19 and pre-existing diabetes. Reducing LDH expression by either knockdown methods [210] or by the inhibitor FX11 has been shown to inhibit tumour progression [211,212].

2.3.3. Drug delivery strategies targeting immunometabolism in COVID-19

The potential of these drugs to be repurposed and nanoformulated would benefit as potential therapeutics for COVID-19. Furthermore, metformin, currently used to treat T2D, could be a beneficial therapeutic in COVID-19 treatment. Metformin is known to modulate metabolism [213] and has been suggested to demonstrate benefits such as anti-inflammatory properties as well as reduced mortality [214,215] during COVID-19 infection. Metformin is already given as an extended release formulation, however, there are developments for metformin nanoparticles which aid in extended release, lower dose frequencies and improvements of compliance [216].

COVID-19 relies on glucose metabolism in the form of increasing aerobic glycolysis levels to maintain high levels of ATP production, so the GLUTs, glycolysis products and regulators of the SLCs may be beneficial drug targets for new lead compounds. A vaccine is most useful for long term effects, however with the ever-mutating SARS-CoV-2, therapeutics targeting different parts of immune metabolism pathways may be a potential target for therapeutics, especially as therapeutics will more readily available in poorer countries and places where the vaccine is too expensive or cannot be stored and easily accessed. It has previously been addressed that most available inhibitors of glycolysis have limited uses due have low potency and high levels of toxicity [217], however nanoformulations of pre-existing compounds could prove useful during the COVID-19 pandemic.

3. Coagulation and the endothelium in COVID-19

The proinflammatory state, observed in COVID-19, is associated with a unique coagulopathy and procoagulant endothelial phenotype. The most common profile of coagulopathy observe in patients with COVID-19 is elevated fibrinogen and D-dimer levels [218] as well as mild prolongation of PT/aPTT [219] however, this differs from the patterns observed in classic disseminated intravascular coagulopathy (DIC) and bacterial sepsis or trauma as this prolongation in minimal. In addition to soluble factors, in a meta-analysis of 7613 COVID-19 patients lower platelet counts were associated with severe disease with non-survivors having much lower counts than survivors [218,220,221]. Endothelial cell dysfunction has also been reported in COVID-19 as ACE2 is expressed in arterial and venous endothelial cells as well as arterial smooth muscle cells [222] and endothelial cells have been shown to be capable of being infected by SARS-CoV-2 [223,224]. Activated endothelial cells initiate coagulation by expressing P-selectin, von Willebrand factor and fibrinogen which leads to platelet binding, fibrin formation and clotting of red blood cells [225]. The majority of patients that do not survive COVID-19 die from acute respiratory distress syndrome (ARDS), pulmonary oedema, cytokine storm, multiple organ failure and diffuse coagulopathy [226]. The involvement of endothelial cells, in ARDS, has been linked to their production of inflammatory cytokines and chemokines, permissibility of leukocyte infiltration and vascular leakage [227–229].Taken together, it is clear that endothelial cell represent a possible target for the treatment of COVID-19.

3.1. Therapeutic options, related to coagulation and endothelial function, in COVID-19

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are widely used in the management of COVID-19 patients. Parenteral UFH at therapeutic dosage has also been used for the anticoagulant managements of COVID-19 patients however, frequent monitoring is required to maintain therapeutic doses. In addition to heparins, antiplatelet drugs, ACE2 enhancers, bradykinin inhibitors, HMGB1 antagonists and RAGE inhibitors have all been proposed as possible therapeutic options to affect endothelial cell dysfunction [230]. Glycyrrhizin, is a known inhibitor of HMGB1 [231] and micelles made of glycyrrhizin have been formulated [232] however, no direct studies of the use of these molecules in COVID-19 have been carried out. Whilst there is clearly a potential benefit of targeting endothelial cell functions, in COVID-19, as yet there have been no studies in this area.

3.2. Drug delivery strategies for targeting coagulation and the endothelium

LMWH has very low oral bioavailability due to its size and negative charge and subsequent poor penetration through the intestinal wall which is overcome by parenteral administration. Repeated parenteral administration that is intravenous, subcutaneous and therapeutically monitored intravenous infusions are invasive and further, repeated administrations increase the invasiveness. A number of efforts have been made to develop parenteral sustained release dosage forms [233] that would improve the use of LMWH therapy, particularly in COVID-19. Additionally, a number of the antagonist molecules that have been proposed, previously [230], to affect endothelial cell function would benefit from drug delivery strategies targeting endothelial cells or improving their uptake into endothelial cells. Even though the endothelium accessible to drugs circulating in the blood, most drugs, including biotherapeutics, have no endothelial affinity and only a minor fraction is taken up by these cells [234]. Strategies to target the endothelium have, traditionally, used nanoparticles coated with monoclonal antibodies against endothelial cell surface proteins such as ICAM-1, VCAM-1 and VE-cadherin [235].

4. Intersection of inflammasome activation, complement and endothelial cell functions that relate to COVID-19 disease pathology

Unfavourable outcomes, in COVID-19, associate with complement activation and coagulopathy [236] and, intriguingly, children and young people may less frequently develop severe COVID-19 manifestations due to the absence of comorbidities (including obesity, metabolic syndrome, etc.), age related differences in immune function/profile and ‘‘healthier” endothelia. Endothelial activation/damage may be a key factor for disease severity and complications in older patients or those with medical conditions influencing endothelial function, such as systemic autoimmune/inflammatory

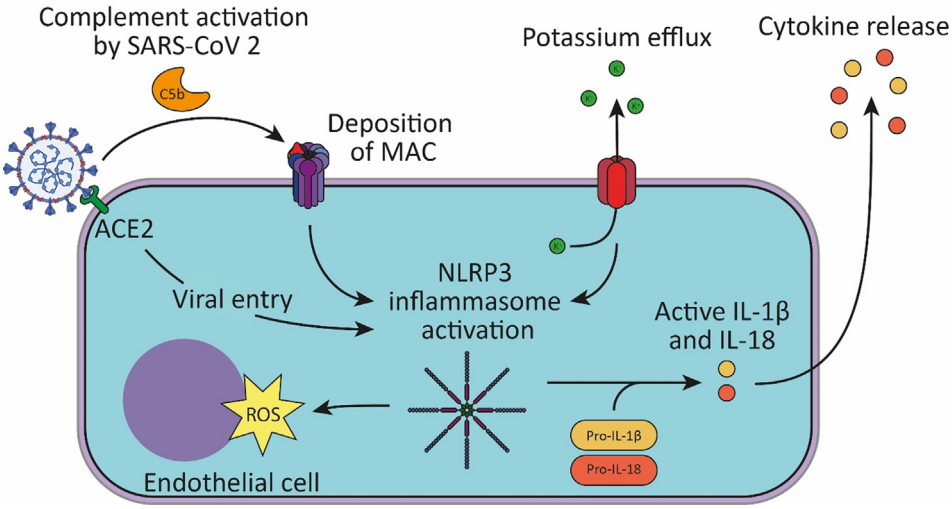

Fig. 3. Schematic of possible, cellular, interactions in endothelial cells which relate to SARS-CoV-2 pathogenesis. Infection of endothelial cells, via ACE2, results in sensing of SARS-CoV-2 antigens by intracellular pattern recognition receptors, such as the NLR proteins and leads to inflammasome activation. Activation of extracellular complement cascade, by SARS-CoV-2 may result in deposition of the membrane attack complex (MAC) on the surface of endothelial cells which may either be taken up, via endocytosis, or result in efflux of potassium ions from the cells leading to inflammasome activation. Endothelial cell activation, via inflammasome signalling, may then lead to increase in the expression of von Willebrand Factor (vWF) and tissue factor on the cell surface, in turn affecting the thrombogenic systems and leading to inflammatory cytokine release.

disease. Of patients who die from COVID-19, 71% meet the criteria for DIC, whereas only 0.6% of patients who recover do[237]. As discussed in Section 2.2, the complement system is a key component of the innate immune system and specific complement proteins, related to both the classic and alternative activation pathways, have been demonstrated to be much higher in plasma samples from older patients [238]. As with the complement system, inflammasome activity, outlined in Section 3, has been linked to age-related inflammation (Inflammaging) which in turn is associated with increased risk of various diseases, particularly cardiovascular related disease [239,240]. This has, primarily been associated with nucleotide metabolism such as N4-acetylcytidine (N4A) and adenine downstream of oxidative stress, which have been shown to increase blood pressure in a number of models [241]. Additionally, endothelial cell ageing, and senescence, is triggered by vascular inflammation and oxidative stress [242]. Complement activation has been demonstrated in both children and adults with COVID-19 [243–246], inflammasome activation [247–251] (increased plasma IL-1b/IL-18, clinical response to IL-1 blockade) occurs and haematological profiles suggest a procoagulant profile [243,252–257]; all of which are linked, mechanistically [258–262]. Complement (membrane attack complex) deposition on endothelial cells activates the NLRP3 inflammasome [263,264] which, in turn, may drive the inflammation observed in severe COVID-19 cases in children and adults as well as affecting endothelial cell integrity/function, which impacts on the coagulation cascade. The end result of these, overlapping, systems, as summarised in Fig. 3, likely results in the procoagulant states observed in severely affected COVID-19 patients and individuals with other systemic inflammatory conditions characterised by endothelial activation (such as SLE). Application of drug-delivery strategies, for therapeutics mentioned above, may serve to improve the outcome in patients with COVID-19 however, so far it is not clear how intervening in one "system", such as inflammasome activation, affects outcomes in related systems.

5. Drug delivery strategies for immune modulation in infectious disease

Researchers are making numerous efforts to develop therapeutic strategies to prevent COVID-19. These include prophylactic interventions to minimise hospitalisations, pharmacological agents to treat or reduce transmission during early infection, as well as improving recovery in more severe disease stages. Drug candidates for SARS-CoV-2 consist of antivirals, host targeted immune modulators, anti-inflammatory drugs and neutralising monoclonal antibodies [265].

Due to the lack of specific treatments currently available for COVID-19 prevention, employing differing strategies for the delivery and formulation of repurposed drugs should be considered. Reformulation and changes in the dosing schedule or route of administration may therefore be required. By any route of administration, the key requirements are the delivery and maintenance of effective concentrations at vulnerable cellular and tissue sites, as well as within the systemic circulation [13]. Similarly, the emergence of several advanced drug delivery technologies in recent years provides a strong starting point for approaches against COVID-19. Nano-based therapeutics offer several opportunities to address the limitations of current therapies. Such systems could potentially modify pharmacokinetics/pharmacodynamics properties resulting in dose reduction, reduced toxicity, and improved drug bioavailability, thereby maintaining their immunomodulatory effects and subsequent suppression of viral spread. Previous knowledge of respiratory viruses has shown the crucial nature of localising therapies efficiently to particular targets [266]. SARS-CoV-2 primarily spreads through the respiratory tract and affects alveolar cells. It thereafter systemically impacts the heart, liver, and kidneys [267,268]. The receptor responsible for SARS-CoV-2 entry, ACE2, is highly expressed in the respiratory tract and other organs and tissues, encompassing the CVS, CNS and GIT [222,269]. Particularly high expression of ACE2 in lung and bronchial branches makes the alveolar epithelial cells more accessible for SARS-CoV-2. A strategy to neutralise SARS-CoV-2 at the cellular level is to inhibit host cell protein function (ACE2, TMPRSS2, furin and cathepsin), as adopted in other viral therapies [270,271]. Moreover to specifically combat the surge in inflammatory cytokines, targeting alveolar macrophages expressing ACE2 [272] as well as components of the inflammatory system (interleukin-1, interleukin-6, interferon-γ, and granulocyte-monocyte stimulating factor) may lead to clinical improvement. Hence, applying appropriate delivery devices or formulations could enable more targeted and accessible administration, by delivering drugs directly to the primary sites of infection.

The majority of the repurposed drugs being investigated are traditionally administered systemically, through oral or parenteral administration. Consideration is also being given to delivery via the inhalation and intranasal routes, focusing on effective concentrations at the sites of infection, particularly at the upper respiratory tract/lungs and the mucous membranes present in the nasal cavity and throat. In 2004, a study by Chen et al. reported that a low dose of inhaled nitric oxide could shorten the time of ventilator support for SARS-CoV infected patients [273]. Due to the genetic similarity of SARS-CoV-2 with its parent SARS-CoV, inhaled immunomodulatory drugs could have potential. Delivery of medications via inhalation generally allows for a lower dose than is necessary with systemic delivery (oral or injection), and thus fewer and less severe adverse effects [274]. In a recent study, nebulized ivermectin, capable of delivering particles with alveolar deposition, was administered *in vivo* to rats [275]. Results displayed pharmacodynamic concentrations of ivermectin in the lungs at seven days post-intervention. Similarly, niclosamide has shown promising *in vitro* antiviral efficacy against SARS-CoV-2 [276]. A potential immunomodulatory response has also been observed, involving an up-regulation in IL-1β activity and decreased expression of IL-6, TNF-α [277]. However, in its oral dosage form, systemic drug levels are too low to inhibit SARS-CoV-2. As an alternative, direct delivery of niclosamide to the respiratory tract as an aerosol could target the primary site of SARS-CoV-2 acquisition and spread. Several clinical trials investigating the use of inhaled NIC are currently underway (NCT04644705 and NCT04558021). Similarly, Pulmoquine Therapeutics is developing an aerosolised formulation of hydroxychloroquine to achieve higher drug concentrations in epithelial airway cells than that observed with oral therapy, while also minimising off-target effects [278,279]. This could be important in helping to mitigate the impacts of the cytokine storms in patients. An interferon-β1a (SNG001) formulation, is being investigated for the treatment of patients admitted to hospital with COVID-19 [280]. This was done to maximise exposure of interferon-β in the lungs, resulting in a robust local antiviral and immunomodulatory response, whilst limiting systemic exposure. A phase 2 trial displayed that patients who received SNG001 (daily inhaled dose of 6 MIU via nebuliser for 14 days) recovered more rapidly from SARS-CoV-2 infection, providing a strong rationale for further trials [280]. The anti-inflammatory activity of another drug of interest, dexamethasone, could be further potentiated through its reformulation [281]. Pulmonary delivery of a nanoformulation may enable the targeting of alveolar macrophages, whilst phagocytes could be targeted at inflammation sites after intravenous administration. This could enhance clinical outcomes, allowing critically ill patients to leave intensive care earlier. Moreover, nasal sprays that can provide effective protection against the COVID-19 virus represent another approach. Preliminary reports have demonstrated the capacity of spray systems to inhibit SARS-CoV-2 infection *in vitro* [282–284]. In ferrets, a nasal spray formulation of the TLR2/6 agonist INNA-051 effectively reduced levels of viral RNA in the nose and throat [285]. Similarly, the delivery of the human IgG antibody (EU126) in a nasal spray formulation to K18-ACE mice, retained its SARS-CoV-2 neutralising activity [286]. Currently, clinical trials are being undertaken for GLS-1200 applied via nasal spray atomizer (NCT04408183) and povidone-iodine (PVP-I) containing nasal sprays (NCT04347954) to assess their safety and efficacy in COVID-19 treatment. As such, the alternative administration and reformulation of drugs, merits further studies as a useful strategy in preventing or reducing SARS-CoV-2 infection.

Generally, the use of immunomodulatory therapeutics is limited by their toxicity. However, implementing different strategies such as actively targeting nanocarriers, to overcome biological barriers, offers the possibility of directing immunomodulatory drug delivery to organ and cellular/intercellular sites involved in the pathophysiology of SARS-CoV-2 (ACE2 expressing macrophages, domains of viral S protein, IL-1 and IL-6 receptors prostaglandin D2 and group 2 innate lymphoid cells). Hence the incorporation of immunomodulatory drugs into targeted nanoformulations could improve their specificity, whilst also allowing therapeutic concentrations to be reached at viral target sites. For instance, the IL-1 inhibitor Anakinra has been previously been encapsulated in folate-targeted nanoparticles for the treatment of rheumatoid arthritis [287]. Anakinra's ability to inhibit both IL-1 subtypes and short half-life makes its use, favourable in COVID-19. Recent reports of intravenous delivery have shown it to be safe [288], however, more localised delivery to lung macrophages could show benefit in COVID-19 related hyperinflammation. Additionally, tocilizumab is also amenable to nanoformulations, as demonstrated by Lee *et al.* who developed a hyaluronate/gold nanoparticle/-tocilizumab targeted delivery system for rheumatoid arthritis [289]. A similar targeted approach could be achieved in COVID-19 to help overcome the cytokine release syndrome seen in severely ill COVID-19 patients who have extensive lung lesions and high IL-6 levels. Combinatorial strategies to modulate multiple immune axes in coordination are seen as an attractive strategy for the treatment of COVID-19, offering several advantages such as reduced dosages, achieving multiple and complimenting therapeutic targets via co-delivery and decreasing the prospect of developing resistance [290]. A nanomedicine-based strategy is thus a powerful tool in enhancing COVID-19 therapeutic management through the use of repurposed drugs.

5.1. The utility of Long-Acting formulations

Long-acting (LA) drug delivery systems involving depot injections, implants, or microarray patch-mediated delivery have attracted recent attention for the prevention of infectious diseases such as malaria and HIV [291,292]. Advantages include the ability to deliver potent antiviral combinations for several months, whilst offering sustained drug levels, lower dosage requirements and targeted drug release leading to a higher exposure of the drug at the target site.

Ivermectin is a positive allosteric modulator of the $\alpha - 7$ nicotinic acetylcholine receptor, which has been suggested to represent a target for the control of COVID-19 infection, with potential immunomodulatory activity [293]. A recent *in vivo* study in hamsters displays similarities of ivermectin's response with the anti-inflammatory action of dexamethasone and tocilizumab i.e. a reduction in IL-6 activity [294]. This corroborated with another study displaying a reduction in the inflammatory process by reducing the production of several cytokines [295,296]. Previously described nanoparticle formulations for LA ivermectin [297,298] have been shown to enhance intestinal absorption and exhibit controlled release to extend the duration of therapeutic drug levels. Current research is focusing on refining the administration of LA ivermectin formulations, developing aerosol administration [275], and considering ivermectin use in combination with other agents to enhance efficacy at low dosages [299]. Likewise, a preclinical study with a sustained release formulation of hydroxychloroquine displayed preferentially higher lung concentrations in comparison to standard intravenous administration[300].

The development of LA drug delivery platforms could also enable the use of drugs known to display harmful side effects. For example, a number of immunomodulatory biologics are known to have side effects that include serious infections, malignancy and immunogenicity [301]. Developing a LA-release formulation that exhibits suitable release kinetics to maintain the minimum effective drug concentration could mitigate adverse side effects by reducing the steady-state drug concentration with the additional

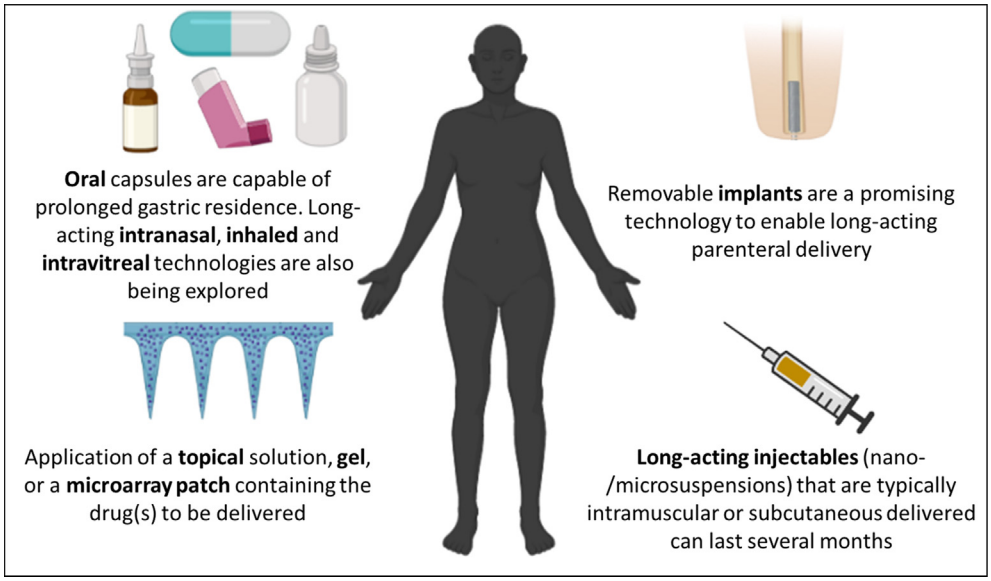

Fig. 4. Methods of administration for long-acting and extended-release drug delivery technologies.

benefit of alternative routes of administration as summarised in Fig. 4. However, not all drugs currently under evaluation for COVID-19 are likely to benefit from this approach. Importantly, nanomaterial-based delivery technologies may also make administration convenient for patients, for example, through microneedle patches and implants. In a global pandemic, in which healthcare systems are operating at the limit, such self-administration technologies in persons at risk for disease severity, may prove extremely valuable. Long-acting treatments could play a transformational role in the absence of a safe and efficacious vaccine. Challenges facing LA drug delivery systems include identifying the optimal dosing interval, appropriate timing of administration number and volume of injections per visit and effective drug combinations. However, benefits to patients include infrequent dosing and long dosing intervals making administration convenient, the possibility of directly observed therapy and better long-term adherence and use in difficult to treat populations including adolescents, pregnant/postpartum women, or those with a history of substance abuse.

The development of LA drug delivery systems may provide an alternative option to vaccines. The advent of very LA formulations may provide a further aim for immunomodulatory therapies, which is chemoprophylaxis for uninfected persons at risk, by behaving as vaccine mimetics. Furthermore, the provision of such medication to potential contacts of new diagnoses could help to control the unprecedented COVID-19 global outbreak.

6. Conclusions

The complexity of the immune response in COVID-19 has made identification of specific targets for immune modulation therapy difficult and has, so far, been restricted to anticoagulation, inhibition of plasma cytokines or more general immune suppression through corticosteroids. As a number of complex and interconnected immune/inflammatory mechanisms are involved in the pathophysiology of COVID-19, modulation of one particular component of the immune system, e.g. complement activation, will include "knock-on" effects on others, such as inflammasome activation and endothelial integrity, activation and function. Modulation of immune metabolic processes may be beneficial, especially in individuals with pre-existing metabolic conditions, who are at particular risk for SARS-CoV-2 infection and severe COVID-19. New approaches for the delivery of immune modulating agents have to be considered to achieve sufficient drug tissue levels and reduce toxicity in acute COVID-19 and PIMS-TS.

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Declaration of Competing Interest

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