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COVID-19 therapy, from lung disease to systemic disorder

We are delighted to bring together a special issue focused on 'COVID-19 therapy, from lung disease to systemic disorder' in this issue of Current Research in Pharmacology and Drug Discovery (CRPHAR). The SARS CoV-2 infection has brought medical and scientific challenges that experts in the various fields have discussed and brought to our attention using reviews, research papers and short communications to illustrate numerous topics ranging from understanding how the unique disease pathology affects lung mechanics and health, identification and appraisal of pharmacological targets for anti-viral and anti-inflammatory therapy, to the development of novel technology platforms for synthetic chemistry and biologic approaches to possibly treat COVID-19 patients, recognizing that the clinical management of this disease requires a nimble and multifaceted approach.

In this regard, some unique (or particular) pathologies are discussed: the effects of the 'cytokine storm' on skeletal muscle diaphragm mechanics is explored with regard to opportunities for diagnosis and associated considerations for patients requiring mechanical ventilation (Mittal et al., 2021); whilst Grieb and colleagues discuss the hypothesis that early characterization of hypoxia induced by sleep apnea or blunted respiratory responses to chemical stimuli can be used to determine disease progression and hospitalization, and pharmacological approaches to reverse these events are then identified (Grieb et al., 2021). A common symptom of COVID-19 is the loss of the senses of smell and taste, and an understanding of the mechanism by which this may happen in the context of COVID-19 pathology may benefit from comparisons to other olfactory and gustatory disorders, especially when considering treatment options (Neta et al., 2021). Sometimes, SARS CoV-2 infection has been associated with chronic breathing difficulties due to the development of lung fibrosis, well after the initial infection has resided. Possible causes of lung fibrosis and treatment options have therefore been discussed (Vitiello and Ferrara, 2021).

There is also interest in how SARS CoV-2 may be targeted directly using both existing and novel anti-viral drugs, suitably informed by targets that emerge at different stages of the viral live cycle (Chen et al., 2021; Smith et al., 2022; Basu et al., 2022); and the search for appropriate chemical entities might be beneficially influenced by structure-based drug design (Bajad et al., 2021). Host directed therapies (HDTs) might provide an important adjunct to this avenue of research to target SARS CoV-2, through the identification of host pathways that have otherwise become hijacked by the virus causing infection persistence and propagation (Tripathi et al., 2021). Rao and colleagues reviewed existing drugs used against Sars-CoV-2 infection, mainly focusing their attention on ongoing clinical trials and particularly on specific treatment strategies in COVID-19 patients with comorbidities (Rao et al., 2021). Tao and colleagues compared the activity of remdesivir and its main metabolite

GS-441524 against Sars-CoV-2 in several human cell lines, showing that remdesivir exhibited greater potency (Tao et al., 2021). Rhazouani and colleagues proposed nanomaterials based on graphene oxide, an oxidized derivative of graphene, as antiviral agent against Sars-CoV-2 infection (Rhazouani et al., 2021). Artificial intelligence (AI) and machine learning (ML) may be used for drug studies. Prasad and Kumar systematically reviewed and discussed AI- and ML-based methods used for drug repurposing and discovery to treat COVID-19, for the study of viral protein structure determination and for vaccine development against Sars-CoV-2 (Prasad and Kumar, 2021). Molecular docking studies on existing and novel anti-viral drugs against Sars-CoV-2 proteins may indeed help to identify new anti-COVID-19 therapeutic molecules: Verma and colleagues identified natural components of medicinal plants as potential ligands and inhibitors of viral proteases (Verma et al., 2021); Rabie proposed the antirheumatic drug teriflunomide as strong inhibitor of viral RNA dependent RNA polymerase (Rabie, 2021); while Solo and Doss described further potential anti-viral natural compounds targeting the spike protein of the virus (Solo and Doss, 2021).

Lastly, an understanding of the immune response, and ensuing inflammation might lead to the identification of novel targets to improve on the exist pharmacopoeia. One such target is the NLRP3 inflammasome, and whether the selective inhibition of NLRP3 might improve on the modest efficacy of dexamethasone without the liabilities associated with high dose systemic corticosteroid administration (Hooftman and O'Neill, 2021). Other targets of the immune response, for example the Toll Like Receptors 7 (TLR7) and 8 (TLR8), have warranted attention and it is interesting to consider that either the activation or conversely the inhibition of these receptors (in combination with other immunomodulatory or anti-inflammatory drugs) might provide therapeutic value, dependent on a patient's immune profile, or stage of infection (Khalifa and Ghoneim, 2021). Furthermore, the use of existing biologics to target the cytokine release syndrome, especially in patient groups with poor immune responses has been brought to our attention (Migo et al., 2021).

There is therefore a diversity of opinion collected within this special issue, that hopefully stimulates imagination and creativity. We hope you enjoy reading this selection of topics, which are expansive and open up the many challenges and opportunities we face in controlling the COVID-19 pandemic.

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