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EDITORIAL

Spotlight on COVID-19: eighteen months on

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In this Editorial, we highlight the contents of *The FEBS Journal*'s second Special Issue focussed on COVID-19. The issue covers a variety of aspects related to COVID-19, ranging from the most recent improvements in therapies and the significant impact of rapidly developed COVID-19 vaccines to the emergence of variants of SARS-CoV-2, the role of the immune system in the various stages of the disease and the impact of the disease in different organs. We hope that this collection of articles will give readers an informative and critical perspective on recent advances in understanding and treating COVID-19.

It is now more than 18 months since the emergence of COVID-19, which formed the focus of a *FEBS Journal* issue that was compiled during the early stages of the pandemic [1]. In early 2020, we did not imagine that we would still be in the midst of the crisis at this stage. Whilst there are some encouraging signs on the horizon, many parts of the world remain very much at the mercy of the virus. However, the speed with which science has responded has been truly remarkable, and it is science that is leading us out of the crisis. There have been considerable improvements in existing treatments, and a number of innovative therapies have been developed, which are having a positive impact on the outcome of disease. However, the impact of the vaccines is the most important development since we discussed the emerging disease in 2020. In less than a year, multiple vaccines entered into global roll-out, some of which are based on innovative approaches that will have a major impact on vaccination strategies for many infectious agents for years to come. Therefore, in this second Special Issue focussed on the novel coronavirus and its ongoing impact on science and society, the article by Dhillon *et al.* [2] is particularly timely. In this interview-based article, two leading experts in vaccinology and immunology discuss different vaccine strategies, the nature of the immune response and the likely length of protection. Whilst many questions remain on the latter point, it is clear that the efficacy of the major vaccines that are in use is extremely high and that protection, based on several immune parameters, is likely to be long-lasting. It is also interesting to note that whilst a large number of variants of SARS-CoV-2 have emerged, many of which affect transmissibility, there is currently very little evidence to suggest that they affect the relatively robust protection conferred by the vaccines. An interesting feature of the article is that it addresses common questions raised in communities that are sceptical or hesitant in relation to the vaccines. Whether the readership of this journal belongs to these groups is something of a moot point, but some arguments in this manuscript could help scientists in formulating

Abbreviations
ACE2, Angiotensin-Converting Enzyme 2; COVID-19, Coronavirus Disease 19; SARS-CoV-2, Severa Acute Respiratory Syndrome Coronavirus 2; PBM, PDZ-binding motif.

convincing answers and comments for the lay public [2]. The article provides a valuable follow-up to an article published by *The FEBS Journal* team last year, which sought to clarify the science behind several early claims and controversies relating to COVID-19 [3].

As noted above, variants of SARS-CoV-2 have emerged with greater levels of transmissibility. The article by Seyran *et al.* [4] featured in this issue provides an excellent review of S protein structure and how it mediates virus attachment and entry. A critical element of this is an apparent lack of mutation in the regions of the Spike protein that mediate interaction with the primary entry receptor ACE2, and the authors speculate that the interaction here is most likely already at an optimal level. However, sequence variation elsewhere in Spike can affect its association with sialic acid and heparin sulfate proteoglycans, a feature which promotes the virus surfing over the cell surface, prior to encountering the primary receptor. This particular feature of SARS-CoV-2 is most likely linked to the efficiency of virus infection and could explain the emergence of more transmissible variants. The presence of both entry factors and antiviral restriction factors is known to dictate the differential permissiveness of various cell types in different organs. This is highlighted by the work from Lin *et al.* [5], who identified a subtype of tubular cells as the most vulnerable cell type to SARS-CoV-2 infection in the kidney, using single-cell RNA sequencing and urinary proteomics. Whether changes in either number or function of these cells—a feature of multiple kidney diseases—can be used to assess the risk of renal infection in COVID-19 remains an interesting, yet unproven hypothesis.

A critical feature in the eventual clinical outcome of COVID-19 is the nature of the immune response in the infected individual, which involves not only the positive role of inflammation in disease clearance early on in infection but also the corresponding detrimental role of inflammation in advanced stages of severe disease. The latter can induce additional pathologies, not necessarily linked simply to virus-induced cell death. In this Special Issue, there are two articles that address some of these aspects. Ku *et al.* [6] describe studies on SARS-CoV-2 infections in individuals with inborn errors of immunity, and how modulation of inflammation offers an excellent way of improving the outcome for COVID-19 patients. They also highlight an important role for the type I interferon response in early stages of disease, whose loss of activity, either through viral inhibition or inborn defects, results in much higher levels of inflammation and a poorer disease outcome. Indeed, modulation of the inflammatory response, both in patients with inborn errors of immunity and in immunocompetent individuals, offers important improvements to disease outcome. The article by Tong *et al.* [7] looks at the role of T-cell immunity in diabetic patients and their response to SARS-CoV-2 infection. Through an extensive literature review, the authors provide compelling evidence that a reduced level of T-cell immunity in patients with type II diabetes links to the poorer prognosis for such patients when exposed to SARS-CoV-2. The essential role of inflammation in end-stage COVID-19 is also highlighted by the work of Zeng *et al.* [8]. By performing quantitative proteomics of the bronchoalveolar lavage fluid from a series of COVID-19 patients and noninfected controls, they identified a few differentially expressed proteins, particularly involved in both inflammatory and oxidative stress responses. Although based on a small cohort of individuals, the raw data made available in this work represent a powerful source of information for further studies aimed at validating either novel biomarkers or therapeutic targets for COVID-19 [8].

Great strides have been made over an incredibly short period of time in improving the treatment of COVID-19 patients, through the development of novel treatment regimens and identification of various forms of antiviral therapy. However, a great deal remains to be done in this area, as no truly antiviral therapy has so far been identified. Within this issue, three papers investigate various aspects of the virus as a means of developing specifically targeted antiviral therapies. Chen *et al.* [9] focus their attention on the viral 3C-like cysteine proteases. These proteases are perfect targets for the development of antiviral therapeutics, as they share very little similarity with human proteases and, furthermore, they play an essential role in the viral life cycle by cleaving the viral polyprotein into its individual protein products, which are important for carrying out a whole range of essential functions. In their review, Chen *et al.* describe the structural aspects of the protease that render it particularly suitable for developing novel antiviral inhibitors and discuss their potencies and modes of action. A very large number of such inhibitors have now been identified, some of which are *de novo* inhibitors, whilst others have been repurposed from targeting other viral proteases. In many cases, the efficacy *in vitro* looks very promising, but many challenges still remain in getting these potential antiviral agents into a clinical setting. The authors speculate that combination therapies may offer the most promise, and for this reason, it is important to look at other druggable functions of the virus. In line with this, Saramago *et al.* [10] performed an elegant

biochemical characterisation of the SARS-CoV-2 nsp14/nsp10 complex. They demonstrated that complex formation is a critical requirement for optimal nsp14 exoribonuclease activity, which is, in turn, essential for completion of the viral life cycle. Using mutational analysis and subsequent biochemical assays, they defined key residues required for formation of these complex and key residues that are essential for catalytic activity. The results of this study open up new avenues for developing therapeutics that are specifically targeted against the nsp14-nsp10 complex. Caillet-Saguy *et al.* [11] performed an elegant interactome study to search for host PDZ domain-containing substrates that interact with SARS-CoV-2 proteins in a PDZ-binding motif (PBM)-dependent manner, focussing on the viral E, 3a and N proteins, all of which have classical PBMs. As a result of the screen, a large number of high-affinity cellular PDZ domain-containing substrates were identified. These all have roles linked to cell-cell junction integrity, cell polarity or immune evasion. Since PBM-PDZ interactions have been extensively studied and the structural basis underlying many of these interactions is very well defined, this study offers intriguing insights for the development of novel antiviral therapeutics for targeting these interactions [11]. However, PBM-PDZ interactions are common in human cells, so it will be challenging to develop therapeutics that can specifically block virus PBM-PDZ interactions without affecting those in host cells. Without a doubt, therapeutics that target unique viral functions are likely to offer the most hope in terms of specificity. However, targeting of key host cell functions is also a viable option for antiviral therapy that is gaining momentum. In this issue, Hari Prasad [12] reviews the role of endosomal acidification in SARS-CoV-2 infection and discuss the caveats and opportunities of using alkalinising drugs therapies for COVID-19.

This introduction provides only a snapshot of the contents of this second COVID-19 Special Issue in *The FEBS Journal*, and we encourage readers to delve into the remaining articles, which include a review focussed on the ageing immune response as a risk factor for severe disease [13] and a research paper that addresses the potential protective role of aspirin on infection [14]. The journal remains dedicated to providing a particularly fast turnaround for COVID-19 submissions and to making all such articles that are accepted for publication freely available to all. In recognition of the unique challenges faced by and efforts of early-career scientists during the pandemic, the journal also ran a cover image competition aimed at this group earlier in the year, and the winning entry by Merve Evren (Izmir, Turkey) is featured on the cover of this Special Issue.

The speed at which science has moved to combat SARS-CoV-2 is truly remarkable. We now hope that better therapies and increased levels of vaccination will mean that the world will soon be able to return to a semblance of normality. For scientists, this last year has provided a unique challenge and an opportunity. However, we all look forward to returning to the possibility of gathering at meetings, and exchanging and discussing science in the manner which is, by far and away, the most effective: in person.

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