Call for Papers: The pathophysiology of COVID-19 and SARS-CoV-2 infection

Rory E. Morty[1,2,*] and John Ziebuhr[3]

[1]Department of Lung Development and Remodeling, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany. [2]Department of Internal Medicine (Pulmonology), University of Giessen and Marburg Lung Center (UGMLC), Justus Liebig University Giessen, member of the German Center for Lung Research (DZL), Giessen, Germany. [3]Institute of Medical Virology, Justus Liebig University Giessen, member of the German Center for Infection Research (DZIF), Giessen, Germany.

Correspondence to: Rory E. Morty
Department of Lung Development and Remodeling
Max Planck Institute for Heart and Lung Research
Parkstrasse 1
D-61231 Bad Nauheim
Germany
Tel: +49 6032 705 271
Fax: +49 6032 705 360
e-mail: rory.morty@mpi-bn.mpg.de

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The world now finds itself in the grip of a coronavirus pandemic. This is our third brush with a newly emerging zoonotic coronavirus since the turn of the millennium. The first of these three episodes started as an epidemic of severe respiratory disease of zoonotic origin that emerged in November 2002 in Foshan, Guangdong Province, People's Republic of China (41, 42). During the ensuing epidemic, the disease, subsequently named severe acute respiratory syndrome (SARS) (6), was diagnosed in 8,422 patients, and caused 774 deaths in 26 countries spanning five continents. The etiological agent of SARS was identified as a novel coronavirus (18, 23, 24), the SARS coronavirus (SARS-CoV), which is a member of the species *Severe acute respiratory syndrome-related coronavirus* in the genus *Betacoronavirus* (15, 19). The SARS epidemic ended on 5 July 2003 (5), and since 2005, no human cases of SARS have been reported (17).

The current virus classification collects 39 species into the family *Coronaviridae*, with 10 more coronavirus species expected to be recognized shortly (19). Coronaviruses are enveloped positive-strand RNA viruses that infect vertebrates (25). Coronaviruses have been known since the 1930s, when infectious bronchitis virus was identified (12) as the cause of an earlier outbreak of highly contagious respiratory disease in chickens in 1931 (32). Subsequently, coronaviruses were identified in mice and pigs in the 1940s (26), and then in humans, when in 1965, 1966 and 1967 three groups of investigators isolated or passaged viruses isolated from human adults with common cold (20, 27, 35, 36). Electron microscopy studies revealed the similarity of these agents associated with common cold in humans to the infectious bronchitis virus of chickens (11) and mouse hepatitis virus (10). Based on the crown ("corona")-like appearance of the surface projections of the virions visualized by electron microscopy, this group of viruses was then named coronaviruses (10, 34). The four endemic human coronaviruses (229E, NL63, OC43, HKU1) are generally associated with upper (rarely, also lower) respiratory tract disease (37).

Since the SARS epidemic of 2002-2003, coronaviruses have gone on to cause other severe respiratory disease in two separate outbreaks in humans. The first of these emerged in June 2012 in an adult patient in Jeddah, Saudi Arabia, who died of progressive respiratory and renal failure 11 days after hospital admission for respiratory symptoms (39). A novel coronavirus was subsequently isolated from that patient (39), and was named Middle East respiratory syndrome coronavirus (MERS-CoV) (16) by the *Coronaviridae* Study Group (CSG), a working group of the International Committee on Taxonomy of Viruses (ICTV) that bears responsibility for the taxonomy and classification of viruses in the family *Coronaviridae* (19). MERS-CoV is the prototype of the species *Middle East respiratory syndrome-related coronavirus* (44). Within three years of the appearance of the first MERS patient (thus, by 31 May 2015), 1,180 cases of MERS and 483 deaths had been reported to the World Health Organization (WHO) (45). By the end of 2019, 2,499 MERS cases and 858 deaths had been reported to the WHO since the start of the epidemic, from a total of 27 countries (29). The MERS epidemic remains ongoing.

In December 2019, a number of pneumonia cases of unknown cause emerged in Wuhan, Hubei province, People's Republic of China, which exhibited a clinical presentation indicative of viral pneumonia (21). The causative agent was identified as a novel coronavirus that was provisionally named 2019-nCoV (43), which was subsequently allocated as another member of the species *Severe acute respiratory syndrome-related coronavirus* (19). Based on its close genetic relationship to SARS-CoV (and a large number of "SARS-like" animal coronaviruses isolated primarily from bats), the novel coronavirus was named SARS-CoV-2 by the CSG-ICTV (19). The disease caused by SARS-CoV-2 in humans was named by the WHO as "coronavirus disease 2019", in short, COVID-19 (2). Within three months of the appearance of the first COVID-19 clinical cases in Wuhan, the epidemic rapidly spread to include 143 countries, leading the WHO to declare the COVID-19 situation as a pandemic on 11 March 2020 (13). By 2 April 2020, 896,450 COVID-19 cases and 45,525 deaths had been

reported globally (3). MERS and SARS (28), and now also COVID-19 (4), appear on the list of 12 diseases identified by the WHO as priority diseases that are considered to pose the greatest public health risk, either due to their epidemic potential, or where there is (also) insufficient available countermeasures.

Whilst closely related to SARS and MERS, COVID-19 exhibits a number of peculiar epidemiological, clinical, and pathogenesis characteristics that remain poorly understood. Whilst SARS-CoV-2 appears to be more easily transmitted than SARS-CoV or MERS-CoV, the fatality rate of COVID-19 (≈2.3%) is lower than that of SARS (≈9.5%) or MERS (≈34.4%) (31). Furthermore, early data suggest that the elderly and those with underlying health conditions including diabetes mellitus, chronic lung disease, and cardiovascular disease, are at higher risk (14). Thus, the rapidly developing COVID-19 pandemic has underscored the need for accelerated research at several levels, including public health, behavior and education, as well as basic, clinical, and translational science.

To address this, the WHO convened a two-day meeting on 11-12 February 2020, the primary (immediate) goal of which was to "accelerate research that can contribute to containing the spread of this epidemic and facilitate that those affected receive optimal care". A secondary (mid-long term) goal was to "support research priorities in a way that leads to the development of global research platforms, aiding preparedness for the next unforeseen epidemic and encouraging accelerated research, development and equitable access, based on public health needs, to diagnostics, therapeutics and vaccines". As a conclusion of that meeting, the WHO published a report in the form of a global research roadmap (1), which highlighted research priorities to respond to the current COVID-19 pandemic. This roadmap highlighted a number of research areas of interest to contributors to our *Journal*, including studies on SARS-CoV-2 natural history (host species restriction and transmission, environmental stability of viruses, virus compartments of replication, and the duration of shedding). Additionally, studies on clinical aspects of COVID-19 were also recommended

(delineation of clinical characteristics of disease; pathophysiology of severe disease; and identifying patient risk groups as well as biomarkers and surrogate markers of infectivity). Further recommendations included preclinical studies on the development of appropriate animal models, the development of vaccines, studies on the immune modulation of disease, as well as the development of therapeutics.

The *American Journal of Physiology – Lung Cellular and Molecular Physiology* – together with our American Physiological Society sister journals– has already begun contributing scientific reports and thoughtful discussion to these pressing issues. These contributions include reports on virus-host interactions, such as those mediated by angiotensin-converting enzyme 2 (7, 8, 22, 33, 38); as well as consideration of elevated plasmin(ogen) as a risk factor for COVID-19 susceptibility. Additionally, how diabetes modulates the host-viral interactions and host-immune responses in COVID-19 and other coronavirus infections (30), and related renal injury and COVID-19 (40) have received attention, together with the use of artificial intelligence and machine learning to fight COVID-19 (9). However, to accelerate these efforts, the *American Journal of Physiology – Lung Cellular and Molecular Physiology* together with our sister journal *Physiological Reports* is issuing a joint Call for Papers on any aspect of COVID-19 pathophysiology as well as SARS-CoV-2-encoded factors affecting disease progression and outcome. This Call particularly encourages the submission of manuscripts on the following themes:

- The development of *in vitro*, *ex vivo*, and *in vivo* (animal) models of SARS-CoV-2 (and other coronavirus) infection(s). These studies may be submitted to our *Journal*'s Innovative Methodology category of manuscripts.
- The identification of biomarkers that reveal or allow the monitoring of physiological processes at play during SARS-CoV-2 (and other human coronavirus) infections, either in clinical disease, or in experimental disease models.

- The identification of pathophysiological processes relevant to viral replication, viral infection; either in clinical disease, or in experimental disease models.
- The identification of pathophysiological pathways and processes relevant to the onset, maintenance and progression of disease; either in clinical disease, or in experimental disease models.
- Studies that explore the impact of sex or gender, as well as young or advanced age on COVID-19 pathophysiology; either in clinical disease, or in experimental disease models.
- Studies specifically addressing coronavirus-host interactions, including the physiology of virus receptors on host cells, and the nature of the immune response of the host to SARS-CoV-2 and other human coronaviruses.
- Studies on genetic aspects of SARS-CoV-2 and other coronaviruses that relate to modulating the infectivity and other aspects of virus pathogenicity in *in vitro*, *ex vivo*, and *in vivo* (animal) models.
- Preclinical studies on the targeting of pathophysiological pathways relevant to onset, maintenance and progression of disease, to reveal potential candidate novel disease management strategies.
- Preclinical studies exploring the impact of comorbidities that are modelled in experimental systems –including *in vitro*, *ex vivo*, and *in vivo* (animal) models– on the onset, maintenance and progression of disease. Such comorbidities may include, but are not limited to, obesity, diabetes, combustible and e-cigarette smoking, and pre-existing airways and other lung disease, as well as cardiovascular, renal, and hepatic disease.
- Clinical reports on unusual and interesting clinical observations in patients with COVID-19 that highlight unique or noteworthy physiological aspects of clinical disease.

Manuscripts may be submitted as regular Research Articles or Rapid Reports. Additionally, Reviews, Mini-Reviews, or shorter Perspective articles, together with Case Reports and

Letters to the Editor will be considered. All manuscripts will receive expedited handling. Furthermore, all published articles addressing COVID-19 and its etiological agent SARS-CoV-2 are immediately made freely accessible by the American Physiological Society to everybody upon online publication. Please address any questions related to this call to *American Journal of Physiology – Lung Cellular and Molecular Physiology* Editor-in-Chief, Dr. Rory E. Morty, at rory.morty@innere.med.uni-giessen.de, and *Physiological Reports* Editor-in-Chief, Dr. Thomas R. Kleyman, at kleyman@pitt.edu.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.E.M. and J.Z. drafted the manuscript; R.E.M. and J.Z. edited and revised the manuscript; R.E.M. and J.Z. approved the final version of the manuscript.

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