WHO R&D Blueprint
COVID-19 Animal Models
ad hoc working group

Summary of progress made by the
WHO COVID-19 modelling ad hoc Expert working Group

Covering period 26MAR-1JUN 2020

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Participants

More than 120 participants globally are actively contributing to the Expert Group.

Chairs of the R&D Blueprint Cross-Reactivity expert group

William Dowling, Simon Funnell and César Muñoz-Fontela

WHO Secretariat

Pierre-Stéphane Gsell, Ximena Riveros

Background

In response to the current COVID-19 pandemic, the WHO Blueprint team established several ad hoc Expert working Groups including one focused on COVID-19 disease modelling (COM). The goal of the disease modelling group is to advance the development of COVID-19 medical countermeasures (vaccines, therapeutics and/or drugs). This is being achieved by providing a platform to share data to help reduce duplication of effort and to accelerate learning by sharing outcomes in a secure and confidential workspace. In addition, the principles of reduction, refinement and replacement are being addressed by this international effort. The group is co-chaired by Drs. William Dowling (CEPI), Simon Funnell (PHE) and César Muñoz-Fontela (BNITM) who are seconded to WHO for this task.

Progress to date

As of 01JUN 2020, the group includes 174 experts representing 19 countries and more than 60 research, regulatory or funding entities. The group currently meets weekly to share updates on live studies and to discuss advances in the following areas;

1. COVID-19 comparative pathogenesis in animal models: Which models recapitulate human disease with suitable accuracy?

2. COVID-19 vaccines: Accelerate preclinical testing of all vaccine candidates with a sound scientific rationale. Provide developers and regulators with confidence to proceed with Phase I vaccine studies through


Outcomes to date

(1) Despite digital modelling predictions based on ACE2 genetic analysis, some animal species predicted to be susceptible are seemingly resistant, whilst others are susceptible when not expected to be. Pathogenesis studies have, however, been conducted mainly in human ACE2 transgenic mice, hamsters, ferrets and various NHP models, including Rhesus macaques, cynomolgus macaques and African green monkeys. Across many laboratories in the world, using different SARS-CoV-2 isolates, the results in these species have been remarkably reproducible and indicate mild to moderate disease with pulmonary pathology, virus shedding in upper and lower respiratory tract and, in some studies, rectal swabs, some variable weight loss and in all cases, full recovery.

(2) Different methods are being utilized to achieve expression of human ACE2 in laboratory mice including transgenesis under the control of different promoters and vectored delivery prior to infection. These methods have resulted in a pathogenesis range from either mild or severe disease, depending on the promotor utilised. These findings indicate that the levels and pattern of expression of human ACE2 in mice are a key modulator of SARS-CoV-2 pathogenicity in this model.

Other studies in mice have suggested that induced immune suppression can render a fully resistant wild strain of mouse susceptible to infection with SARS-CoV-2. This suggests that although ACE2 receptor affinity is an important factor in susceptibility, immune suppression is also pivotal in host susceptibility.

(3) Several therapeutics have been tested in animal models. Some monoclonal antibodies and antibody fragments have demonstrated protection in mouse and hamster models. A study evaluating remdesivir in non-human primates was also presented. Chloroquine and hydroxychloroquine failed to show any therapeutic effect in NHP and hydroxychloroquine has not been found to be effective in a complex human model system of respiratory epithelium.
(4) Several vaccines have been shown to be immunogenic and protective, by reducing lower respiratory tract virus burden in NHPs. Some members of the working group have suggested that an added value of vaccine candidates would be the ability to generate mucosal immunity, including IgA, to improve protection of the upper respiratory tract.