Dr. Choudhary is a board-certified toxicologist and translational research scientist specialized in cancer biology and vaccine research with organ system expertise in nephrotoxicity, hepatotoxicity, and dermal toxicity. In this ASIO-hosted webinar on “Modeling SARS-CoV-2 infection in animals”, Dr. Choudhary talked about ongoing efforts in developing new modalities such as mRNA vaccines against the Sars CoV2 virus. He shared his research and its outcome and spoke to the advances and refinement in efficacy and safety testing animal models that has led to success and build confidence in the recent vaccines technologies to enable scientific breakthroughs.

There were several thought provoking and important questions that were discussed during this webinar. Following are detailed answer to few questions along with references that covers the essential aspect of the webinar.

1. Can you please kindly comment on SARS-CoV-2 replication in neural tissues in the K18-hACE2 Mice model in relation to human infection where neural replication is reported to be limited?

In my view it is premature to say that in humans SARS-Cov-2 infection or replication is limited in the neural tissues. The focus of earlier studies was limited to the lungs and acute phase of disease; extrapulmonary manifestations and effects of chronic disease (Long COVID) were not studied in detail. A growing body of evidence suggests that SARS-CoV-2 infection is associated with changes in brain structure and function (Douaud et al. 2022; Chou et al 2021); such impacts on the brain structure and function is not possible without active infection and replication of virus in the neural tissues. Animal models (both wild type and hACE2 expressing) may provide a good platform to study neurological disease observed in humans. In addition to K18-hACE2 mice, brain lesions are also observed in K18-hACE2 hamsters (Golden 2022). It is possible, however, that neurological manifestations observed in K18-hACE2 mice model may be related to preferential expression of K18 promoter in the brain (in addition to lungs).

References


2. Any impact of mutation and variants of SARS CoV2 on relevance of the animal models presented in the talk?
No. Since both the original strain and variants of SARS-Cov-2 virus use the same receptor (e.g., ACE2) for their entry into the cell, animal models for studying these strain/variants are same. In an infection disease model, an infection or a disease state is caused by an infectious agent (e.g., virus). Disease manifestations caused by the original strain of SARS-Cov-2 virus was studied using the original strain of the virus, whereas disease manifestations caused by variants are now being studied using virus variants on the same animal models (which have compatible ACE2).

3. Is disease severity also predictable/ translatable between these models and what is observed in clinical trials?
We do have animal models which mimic disease severity observed in humans. In humans’ disease severity varies from little or no infection to severe disease and death. We have disease models such as NHPs and wild type mice which develop minimal to mild diseases whereas transgenic mice and hamsters develop moderate to severe disease. Having said this, we do have several limitations among currently available animal models and researchers are trying best to develop new or optimize currently available animal models to achieve optimal translatability.

References

4. How is the “dose of challenge” selected in a prevention model?
This question can best be answered by a virologist. I believe for each animal species/model an optimal dose is selected from various test doses. Initial testing is done on cell/tissue cultures to get minimum infective dose and 50% tissue culture infectious dose (TCID_{50}). This dose is then optimized in animals to detect viral replication in the respiratory tract (in case of respiratory viruses) and disease manifestation.

5. What variant of concern was used to investigate the pathogenesis and vaccine efficacy in your studies?
The data shared during presentation was from SARS-CoV-2 USA-WA1/2020 isolate.

6. Do you analyze IgG/IgM titre in prevention models? Do you consider serum IgG titre for vaccine efficacy along with survival endpoint?
For these questions the readers can see publications on vaccine (one reference below).

References

7. There are few different genetically modified mouse models available to study SARS-CoV-2, which one specifically used in your research?
The data shared during presentation was from Syrian hamsters and rhesus macaques.

8. **Lung fibrosis is one of the main causes for lung failure and poor recovery in Covid-19. Have you seen pulmonary fibrosis in animal models; if so in which animals model?**

   We did see minimal interstitial fibrosis in our hamster model. Lung fibrosis has been reported by others in various animal models.

9. **Was lung function (FEV1 or FVC?) studied in these models? If so, what kind of declined lung function have you seen in these models?**

   Not evaluated in the studies shared during presentation.

10. **It was interesting to see that thrombosis is not manifested in animal models despite vaculities, however, in humans we do see it. Any thoughts on differences in this pathogenesis?**

    Thrombosis is observed in animal models, but severity and incidences are limited. More investigations are needed. One reason may be that disease is never allowed to progress to a stage that causes mortality (ethical reasons). Tissue samples from human patients are mostly from COVID-19 patients who were terminally ill and died from the disease.

11. **Any reason why NHP’s don’t show full pathology despite closer compatibility to humans especially ACE2 expression and viral entry?**

    ACE2 is an important viral determinant (related to viral entry). However, there are other host determinants, both pro-viral and antiviral (related to virus transport after entry into the cell, virus replication and translation), which eventually determine the course of disease following a virus infection. In other words, disease pathogenesis is dependent upon successful viral entry as well as successful transport of virus into the cells and replication. It is possible that antiviral host determinants of the virus are more effective in NHP as compared to hamsters. Species specific expression of pro- and/or antiviral determinants can determine the species susceptibility to any viral infection.

**References**


12. **A Philosophical question - does this current body of work for Covid prepare us better for future sars outbreak or similar pathogen**

    I THINK SO. Pharmaceutical companies have developed several effective vaccines and antiviral drugs in a record time to fight current pandemic. Technologies and platforms have been optimized; this will surely help to develop future therapies quickly. In fact, previous work related to SARS-CoV (following 2002–2004 outbreak of SARS), including identification of animal models and drugs, helped researchers move quickly in studying the COVID-19 and develop suitable preventive vaccines and therapeutic drugs. The readers are encouraged to read the publications below on how researchers leveraged works on previous coronavirus diseases (SARS in 2002-2003 and Middle East Respiratory Syndrome in 2012) to develop suitable animal models and an efficacious antiviral drug in record time.
References


Additional References: The content of the talk by Dr. Choudhary was based the following open access manuscripts


Organizer and Moderator
Pankajini Mallick, PhD
Principal Scientist
Neurocrine Biosciences
ASIO, Secretary/Treasurer