See How the Lab Animal Models are playing a critical role against the COVID-19 pandemic - Part II.

We continue our selection of recent important articles that emphasize the need of animal studies in allowing critical understanding of the pathogenesis and areas of intervention essential for the development of pharmaceutical products against COVID 19. Well-defined appropriate model animal studies allows accelerated research responses.

Dozens of potential treatments and vaccines for the novel coronavirus and the disease it causes, COVID-19 are being studied by scientists. Virtually all of them have one thing in common — they're the product of animal research. Medical progress is dependent on the animal research allowing critical understanding of the pathogenesis and areas of intervention essential for the development of pharmaceutical products against COVID-19 (SARS COV-2).

Animal models are helping scientists repurpose existing drugs to fight the novel coronavirus. Gilead Sciences' antiviral remdesivir has "shown promise in animal models for treating Middle East Severe Respiratory Syndrome (SARS)," according to the NIAID. This was further verified in COVID-19 mouse models (https://www.nature.com/articles/s41422-020-0282-0) and in Rhesus Macaque studies (https://www.biorxiv.org/content/10.1101/2020.04.15.043166v1.full.pdf) as well as a human clinical trial that was “leaked” from University of Chicago that showed remdesivir allowed rapid recover in fever and respiratory symptoms (https://www.statnews.com/2020/04/16/early-peek-at-data-on-gilead-coronavirus-drug-suggests-patients-are-responding-to-treatment/). No one will be able to say for certain whether remdesivir will be the panacea everyone is hoping for until Gilead reports data from phase 3 trials, one of which is designed to

compare the drug to the standard of care in treating COVID-19. Those data aren't expected until late May.

Other treatments include development of monoclonal antibodies (Regeneron Pharmaceuticals) with the help of humanized mice models. APEIRON Biologics is also studying the effect of APN01, a recombinant human angiotensin-converting enzyme treatment, on laboratory mice.

More severe treatment needs have included ventilators, which have had animal model use for ventilator safety evaluations and condition developments when ventilators are required to be used (http://rc.rcjournal.com/content/59/11/1619). Also recent continued innovative animal model use in this area was demonstrated by a research team at Auburn University, who successfully tested and converted a continuous positive airway pressure machine used to treat sleep apnea, into an emergency ventilator for a 200-pound goat (which has a similar human lung capacity)

(https://ocm.auburn.edu/newsroom/news_articles/2020/04/020930-cpap-machines-ventilators.php).

Another severe treatment modality is ECMO (Extracorporeal Membrane Oxygenation), a specialized medical treatment that uses an artificial lung to provide oxygenated blood to patients with critical respiratory issues like COVID-19. A University of Michigan researcher first developed th technique in sheep (https://animalcare.umich.edu/life-saving-ecmo-device-made-possible-sheep-research).

Genetically engineered Mice (K18-hACE2 transgenic mouse model, as discussed in part one of this series), hamsters, and ferrets are the primary small animal models currently being studied for COVID-19 pathogenesis and interventions. The Jax K18-hACE2 mouse appears to be a highly infected and translatable model for COVID-19. Scientists

found hamsters could readily be infected with SARS. Their symptoms were subtle, so they were not a good model for the disease. With COVID-19 infections, hamsters lose weight, became lethargic, and develop ruffled fur, a hunched posture, and rapid breathing. High levels of SARS-CoV-2 were found in the animals' lungs and intestines, tissues are studded with the virus' target, the protein receptor called angiotensin-converting enzyme 2 (ACE2). These clinical and pathological findings "closely resemble the manifestations of upper and lower respiratory tract infection in humans," (https://doi.org/10.1093/cid/ciaa325). Ferrets may not be as good a model, they are susceptible and get increases in body temperature, but it didn't replicate to high levels and the ferrets didn't develop other symptoms or fatalities. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7144857/).

Nearly 100 Scientists, regulators and funders are collaborating intensively via a weekly video conference (arranged by the World Health Organization) who are collectively working with a menagerie of lab animals, including mice, ferrets, and several species of monkeys. The group swaps the latest data—and tips, such as different viral transmission strategies and the most likely places to find the pathogen in animals. The goal is to get an animal model that's faithful to the human condition and reproducible. Participants have commented "this is a refreshing way to approach this problem". The wide range of species may be an asset. "You need the right model for the right question," (https://www.sciencemag.org/news/2020/04/mice-hamsters-ferrets-monkeys-which-lab-animals-can-help-defeat-new-coronavirus).

Animal research is particularly crucial to the development of vaccines. As Dr. Anthony Fauci, the head of the National Institute of Allergy and Infectious Diseases (NIAID), said in a White House briefing last month, scientists can "get a good feel … in animal models" for whether a

potential vaccine will protect someone from a dangerous pathogen or risk enhancing their infection.

MRNA-1273, the potential vaccine furthest along in the development process, developed by scientists at Cambridge, Mass.-based Moderna originally developed it to inoculate against the coronavirus that causes SARS. The vaccine has shown promise in mice and other animal models. The company hopes to launch phase 2 clinical trials in humans as early as this spring.

The potential vaccine from Pennsylvania-based Inovio Pharmaceuticals. Mice and guinea pigs that have received it have produced both antibodies and T cells against the coronavirus. The research team is also investigating the vaccine's impact in monkeys. Studies that test whether animals who have been inoculated are susceptible to infection by COVID-19 will follow.

Chinese researchers have discovered that monkeys recovered from infection with the novel coronavirus showed no signs of reinfection when exposed a second time. This discovery could have vital implications for vaccine design and animal model testing prior to human vaccine clinical trials.

More than 60 candidate vaccines are now in development, worldwide, and several have entered early clinical trials in human volunteers, according to the World Health Organization. The best candidates will need safety and efficacy testing in animal models prior to wide dissemination and use.

The critical need and development of the animal models continues in this war on this virus. The findings from these studies will benefit many lives and will be more beneficial with future pandemic concerns as we have seen from the MERS and SARS earlier studies.