How the Lab Animal Models are playing a critical role against the COVID-19 pandemic in developing potential treatments and potential vaccines.

FBR released on March 20th an interesting list of treatments and preventions in the battle against COVID 19, from antivirals, to Monoclonal Antibody Treatments and Vaccines. Respectable science sources such as Forbes, ABC News, Genetic Engineering and Biotechnology News were used for this information.

These articles emphasized how animal studies have allowed critical understanding of the pathogenesis and areas of intervention essential for the development of pharmaceutical products against COVID 19. In many of the articles, fast tracking has been shown as a critical component, a component that can be supported easily by well-defined appropriate model animal studies, accelerating the response of the research.

1. Antivirals

The first category of Drugs taken in considerations are Antivirals. Researchers have taken in consideration many options, from old to new Antivirals. The list has taken particular attention among those studies:

Leading this list is *Gilead Sciences' remdesivir.* It is being rushed to patients with infections from the novel coronavirus in hopes that it can reduce the intensity and duration of Covid-19 and ease the burden of the pandemic on health systems. Much of this is based off data of effectiveness in SARS and MERS cases, and animal studies that have shown effective outcomes. Five clinical trials have been initiated based on results from one successful patient in Washington State. The apparent success in one patient does not prove the drug is effective. There appears to be a second patient from California that has been successful as well (https://www.sciencemag.org/news/2020/03/did-experimental-drug-help-us-coronavirus-patient). This has initiated the larger human clinical trials that will compare remdesivir to placebos. Studies with mice and rhesus macaques have proven effective as well and are on-going.

Chloroquine phosphate, an 85-year-old antiviral drug that has previously been used for the treatment of malaria, has recently shown promising in-vitro results in primate cells infected with SARS-CoV. "The way that it worked against SARS was by preventing of the attachment of the virus to the cells. "Chloroquine interfered with the attachment to that receptor on the cell membrane surface, so it's disrupting a lock and key kind of mechanism of attachment." (https://abcnews.go.com/Health/chloroquine-malaria-drug-treat-coronavirus-doctors/story?id=69664561).
There are more than 20 ongoing human clinical trials in China and more scheduled to start in England, Thailand, South Korea and the United States. Due to higher in-vitro activity against SARS-CoV-2 and its wider availability in the United States compared with chloroquine, *hydroxychloroquine* has been administered to hospitalized COVID-19 patients on an uncontrolled basis in multiple countries, including in the United States. One small study reported that hydroxychloroquine alone or in combination with *azithromycin* reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with

a non-randomized control group but did not assess clinical benefit. (https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html)

Based on PBPK mouse models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance (note work done at Peking University Third Hospital Beijing (https://watermark.silverchair.com/ciaa237.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAmswggJnBgkqhkiG9w0BBwag).

APN01 is a recombinant human Angiotensin Converting Enzyme produced by APEIRON Biologics that successfully blocked viral spread of SARS-CoV-2 and minimized lung injury when tested in laboratory mice. APN01 is now entering the clinical trial phase with COVID-19 patients in China. This enzyme is what is being heavily studied to better understand how to prevent entry into the cells. Regular mice do not have the receptors for COVID-19 and only transgenic mice (K18-hACE2 transgenic mouse from Jax as an example) have these receptors. Mouse models play a critical role in both vaccine and drug development. Studies have shown that SARS-CoV enters the human body by binding to human angiotensin-converting enzyme 2 (ACE2). However, due to structural differences in mouse ACE2 compared to human ACE2 proteins, the SARS coronaviruses exhibit poor tropism characteristics for mouse tissues and are inefficient at infecting mice. A recent article published in Nature by Shi Zhengli's team showed that, like SARS-CoV, SARS-CoV-2 also enters human cells through ACE2. This supports the use of the K18-hACE2 transgenic mouse model for COVID-19 research. (https://www.jax.org/news-and-insights/2020/february/introducing-mouse-model-for-corona-virus).
It is also proven that NHP Macaques (Rhesus and Cynos) and marmosets have the ACE2 structurally similar receptors to the human ACE2 proteins and are good models.

Lopinavir and ritonavir (Kaletra made by Abbive) are anti-retroviral drugs commonly used with other medications to treat HIV/AIDS. In 2015, researchers discovered that lopinavir and ritonavir improved outcomes in marmoset monkeys infected with the MERS coronavirus (MERS-CoV). An inconclusive clinical trial of lopinavir and ritonavir in patients with COVID-19 has been conducted in China. A recent New England Journal of Medicine Article (https://www.nejm.org/doi/10.1056/NEJMoa2001282) has indicated there was no improvement in 199 patients. This doesn't appear to be a successful approach in general.

2. Monoclonal Antibody Treatments

Researchers are taking in consideration some Monoclonal Antibody Treatments as potential treatments against COVID 19. Those are the first evaluations.

Regeneron has developed hundreds of monoclonal antibody drugs that show potential for treating SARS-COV-2. These drugs work by boosting the immune system with antibodies to neutralize viruses. Regeneron's antibodies are produced in mice that have been genetically modified to have human-like immune systems. Regeneron recently announced that human clinical trials of some of their monoclonal antibody drugs could begin as early as this summer. Regeneron's antibodies are made in mice that have been genetically modified to have human-like immune systems, which means that, when they are given to a patient, his or her immune system will not attack the antibody. Regeneron said in a press release that its scientists have isolated hundreds of virus-neutralizing antibodies from its mice, and more from patients who have recovered from Covid-19. It will choose two of these based on their potency and other

"desirable qualities" like specificity, ability to be manufactured easily, and durability in the body. If all goes perfectly, human clinical trials could begin by early summer. Those studies would then have to show that the antibodies are effective. Regeneron plans to test its antibody study both to treat people who have Covid-19, and as a prophylactic that would prevent people from being infected with the SARS-CoV-2 virus. It's possible, if everything goes right, that an antibody could be available for some uses by the fall. "Things have never been done this fast before," (https://www.statnews.com/2020/03/17/regeneron-covid-19-trials-summer/)

3. Vaccines

The last category taken in consideration in the race against COVID 3 are the Vaccines.

This currently is the longer reach but much investment is being put forward for this. *Moderna* (first in this space) and *NIAID* are currently investigating a potential messenger *RNA vaccine* for the new coronavirus. A clinical trial in humans has begun in Seattle for the mRNA-1273 vaccine. Despite reports to the contrary, the clinical trial began after *mRNA-1273* was tested in mice. According to NIAID, mRNA-1273 produced a potent antibody response when testing mice. Testing in mice as well as in nonhuman primates will continue in parallel with the human clinical trial. Other vaccine approaches are being investigated. According to World Health Organization, there are approximately 42 pharmaceutical and biotech companies, including academic institutions who persistently are rushing to create a coronavirus vaccine & treatment. (https://gineersnow.com/industries/medical/list-companies-covid19-vaccines).