MONKEYS AND MICE ENLISTED TO FIGHT CORONAVIRUS

Animal models can reveal how infections develop, and aid drug and vaccine efforts.

By Ewen Callaway

With no sign that the coronavirus is going away, researchers are looking to animals to understand COVID-19. They are testing monkeys, mice and even ferrets to answer key questions about the disease and to fast-track potential drugs and vaccines for clinical trials.

Teams in China have reported initial findings from studies in which they infected monkeys and mice engineered to be susceptible to infection by the coronavirus, called SARS-CoV-2. And a team at the Australian Animal Health Laboratory in Geelong is studying the infection in ferrets, before testing potential vaccines. Ferrets are a popular model for respiratory infections because their lung physiology is similar to humans'.

But no animal model is perfect. "There's going to be a need not just for one animal model, but multiple," says David O'Connor, a virologist at the University of Wisconsin–Madison.

Mild illness

O'Connor and fellow University of Wisconsin virologist Thomas Friedrich are part of a network of about 60 scientists who are sharing details of their efforts to study the infection in primates and other animals. They were excited to read about experiments in non-human primates infected with COVID-19, reported in a preprint on 27 February (C. Shan *et al.* Preprint at Research Square https://doi.org/10.21203/rs.2.25200; 2020).

That research, led by virologist Chao Shan at the Chinese Academy of Sciences Wuhan Institute of Virology, found that rhesus macaques infected with the coronavirus had a fairly mild illness. None developed fevers, but X-rays of their lungs showed signs of pneumonia similar to those in humans with COVID-19. The researchers also monitored two animals for three weeks; these monkeys lost weight, but didn't have other serious symptoms.

The fact that the monkeys seemed to develop symptoms similar to those in people with mild forms of COVID-19 is an important takeaway, says O'Connor. But to find models for severe human infections, researchers will have to look at different animals and vary experimental factors such as the route by which the virus is administered, he adds.

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Rhesus macaques are used to study the virus.

Many researchers are turning to lab mice to test drugs and vaccines, and to investigate the nature of the infection. But ordinary mice seem to be resistant to infection by SARS-CoV-2. So researchers are hoping to use mice bred to produce a human version of the protein ACE2, which the virus uses to enter cells.

One lab has already begun infecting them with coronavirus. A team of researchers in China found that, like rhesus monkeys, the mice seemed to develop only mild illness, showing weight loss and signs of pneumonia but nothing more severe (L. Bao *et al.* Preprint at bioRxiv http://doi.org/dph2; 2020). Qin Chuan, a virologist at Peking Union Medical College in Beijing who co-led the study, says that, in unpublished work, his team also identified several drugs that slowed the virus's replication and limited the animals' weight loss.

Animals that develop mild infections could be useful for testing drugs and vaccines, says Stanley Perlman, a coronavirologist at the University of Iowa in Iowa City whose lab developed an ACE2 mouse strain. But he's thinking about developing other mouse models to better mimic severe cases. "Models are imperfect; we do the best we can," Perlman says.

Why does the coronavirus spread so easily?

A microscopic feature could make the virus more infectious than the SARS virus.

As the number of coronavirus infections passes 100,000 worldwide, researchers are racing to understand what makes it spread so easily.

A handful of genetic and structural analyses have identified a key feature of the virus — a protein on its surface — that might explain why it infects human cells much more readily than does the coronavirus that causes severe acute respiratory syndrome, or SARS.

Other groups are investigating the doorway through which the new coronavirus enters human tissues — a receptor on cell membranes. The cell receptor and the virus protein offer potential targets for drugs to block the pathogen, but researchers say it is too early to be sure.

To infect a cell, coronaviruses use a 'spike' protein that binds to the cell membrane. Genomic analyses of the new coronavirus have revealed that its spike protein differs from those of close relatives, and suggest that the protein has a site that is activated by an enzyme called furin.

This is significant because furin is found in many human tissues, including the lungs, liver and small intestine, which means that the virus has the potential to attack multiple organs, says Li Hua, a structural biologist at Huazhong University of Science and Technology in Wuhan, China, the city where the outbreak began.

The finding could explain some of the symptoms observed in people with the coronavirus, such as liver failure, says Li, who co-authored a genetic analysis of the virus (H. Li *et al.* Preprint at http://chinaxiv.org/abs/202002.00062; 2020).

Other groups have also identified the activation site as possibly enabling the virus to spread easily between humans.

But some researchers are cautious about overstating the role of the site. "We don't know if this is going to be a big deal or not," says Jason McLellan, a structural biologist at the University of Texas at Austin, who co-authored another structural analysis (D. Wrapp *et al. Science* http://doi.org/ggmtk2; 2020).

By Smriti Mallapaty