News in focus

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The coronavirus ravages the lungs of people with the infection.

HOW DOES COVID-19 KILL? UNCERTAINTY HAMPERS DOCTORS' ABILITY TO CHOOSE TREATMENTS

Physicians are reaching for drugs that dampen immune responses — but that can undermine the body's own fight against the coronavirus.

By Heidi Ledford

How does COVID-19 kill? Uncertainty over whether it is the virus itself — or the response of a person's immune system — that ultimately overwhelms a patient's organs, is making it difficult for doctors to determine the best way to treat people who are critically ill with the coronavirus.

Clinical data suggest that the immune system plays a part in the decline and death of people infected with the new coronavirus, and this has spurred a push for treatments such as steroids that rein in that immune response. But some of these treatments act broadly to suppress the immune system, stoking fears that they could actually hamper the body's ability to keep the viral infection in check.

"My greatest fear is that this gets taken to an extreme, where people are using whatever they can get their hands on to turn off the immune response," says Daniel Chen, an immunologist and chief medical officer at IGM Biosciences in Mountain View, California. "You can't knock down the immune system at a time when it's battling an infection."

As people with COVID-19 flood hospitals worldwide, physicians are wading through streams of incomplete data and preprints that have not been peer-reviewed, struggling to find ways to help their patients and sharing their experiences on social media. Some doctors are trying cocktails of unproven therapies in a desperate bid to save lives.

"People are watching patients deteriorate before their eyes, and there's a very strong motivation to reach for any therapy that you think could be effective," says Kenneth Baillie, an intensive-care anaesthetist at the University of Edinburgh, UK.

Some of the earliest analyses of people with the coronavirus in China suggested that it might not be the virus alone that ravages the lungs and kills; rather, an overactive immune

response might also contribute. Some people who were critically ill with COVID-19 had high blood levels of proteins called cytokines, which can ramp up immune responses. They include a small but potent signalling protein called interleukin-6 (IL-6). IL-6 is a call-to-arms for some components of the immune system, including cells called macrophages. Macrophages fuel inflammation and can damage normal lung cells. The release of those cytokines, known as a cytokine storm, can also occur with other viruses, such as HIV.

The ideal counter, then, would be a drug that blocks only IL-6 activity and so reduces the flow of macrophages into the lungs. Such drugs, known as IL-6 inhibitors, already exist for the treatment of rheumatoid arthritis and other disorders. One drug, called tocilizumab, has been approved in China to treat people with COVID-19, and researchers worldwide are working to test it and other drugs of this type.

Immune challenges

But globally there is not enough of the drug, and many clinicians are turning to steroids, says James Gulley, an immuno-oncologist at the National Cancer Institute in Bethesda, Maryland. IL-6 inhibitors might suppress only those immune responses that are governed by IL-6, allowing other immune responses that could help the body fight COVID-19 to continue. But steroids could reduce the body's ability to fight infection overall. These drugs will suppress not only macrophages, but also immune cells called CD4 T cells, which are crucial for initiating immune responses, and also CD8 T cells, which are the body's antiviral assassins, capable of destroying infected cells with more precision than macrophages. "When things get really bad, they'll throw on steroids," says Gulley. "I am a bit worried about where some people are going."

Steroids and other immune suppressants are already being tested against coronavirus in clinical trials. In March, UK researchers launched the RECOVERY study, a randomized clinical trial that will evaluate the steroid dexamethasone and other potential treatments for COVID-19. This worries rheumatologist Jessica Manson at University College Hospital in London. Evidence from previous outbreaks caused by related coronaviruses suggests that steroids deliver little benefit, and might even delay recovery, she says.

But Peter Horby, who studies infectious diseases at the University of Oxford, UK, and leads RECOVERY, notes that the trial will use relatively low steroid doses. "Higher doses are not routinely recommended, but the jury is out on lower doses," he says. "And many authorities, including the World Health Organization, recommend a trial."

A combination of damage from a virus and from an immune response is not uncommon, says Rafi Ahmed, a viral immunologist at Emory University in Atlanta, Georgia. The effects of 'hit-and-run' viruses such as norovirus, which cause illness immediately, are more probably due to the virus itself, he says. By contrast, people infected with viruses such as the coronavirus do not show symptoms until several days after infection. By then, collateral damage from the immune response has often contributed to the illness. But it's hard to work out the contribution of each, Ahmed says. "It's almost always a combination of the two."

Ahmed is hopeful that, in the absence of an answer, researchers will arrive at a combination therapy, such as an IL-6 inhibitor that does not completely suppress the immune system, combined with an antiviral drug that directly targets the virus.

CORONAVIRUS TESTS GO UNUSED IN THEIR THOUSANDS

US labs that underwent huge efforts to retool for COVID-19 testing are still facing major obstacles.

By Amy Maxmen

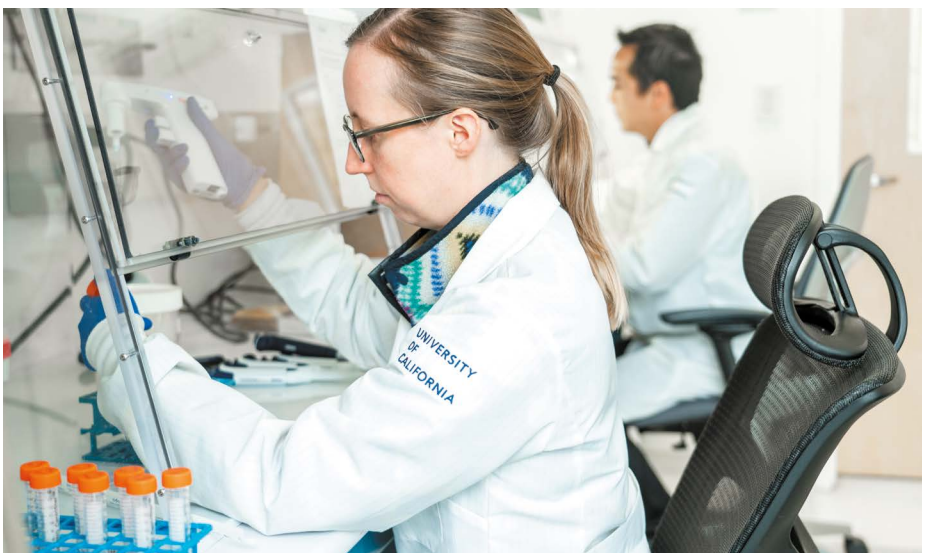
As the United States struggles to test people for the coronavirus, academic laboratories that are ready and able to run diagnostics are not operating at full capacity.

A *Nature* investigation of several university labs certified to test for the virus finds that they have been held up by regulatory, logistic and administrative obstacles, and stymied by the fragmented US health-care system. Even as testing backlogs mounted for hospitals in California, for example, clinics were turning away offers of testing from certified academic labs because they didn't use compatible health-record software or didn't have existing contracts with the hospital.

"Our capacity is 2,000 tests a day," says Stacey Gabriel, a human geneticist at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, where testing facilities were approved in March. "But we aren't doing that many. Yesterday was around 1,000. What is holding us back?" she says.

The Broad Institute and several other leading US labs spent thousands of dollars to pivot their facilities – which usually focus on topics from genome engineering to stem-cell research – to testing people for coronavirus. They navigated complex federal regulations and tweaked their molecular-biology protocols. But despite this, some say they're performing at half capacity or less because of supply shortages or because hospitals won't send them samples.

"We can give results in 12 hours – 24 at the most," says David Pride, an infectious-disease



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Academic labs face many hurdles in their push to help with coronavirus testing.