Pharmacy shelves worldwide are being stocked with Paxlovid (pictured) and molnupiravir.

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WHY SCIENTISTS ARE RACING TO DEVELOP MORE COVID ANTIVIRALS

New drugs against SARS-CoV-2 will be needed to counter the looming threat of resistance.

By Max Kozlov

The roll-out of COVID-19 vaccines at the beginning of 2021 marked a key turning point in the fight against the global pandemic. Another major milestone was reached at the end of the year, with the approval of two oral antiviral treatments — molnupiravir and Paxlovid — that promise to reduce the number of COVID-19 hospitalizations and deaths. But as these pills slowly make their way into pharmacies worldwide, researchers are already looking ahead to the drugs that could supersede them.

"These are our first-generation antivirals against coronaviruses," says Sara Cherry, an immunologist at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. Our experience with antivirals against other diseases proves that "we can do better and better over time", she adds.

Clinical-trial data showed that molnupiravir, developed by the pharmaceutical firm Merck, based in Kenilworth, New Jersey, and the biotechnology company Ridgeback Biotherapeutics in Miami, Florida, cut hospitalizations and deaths by 30%, compared with placebos. Meanwhile, Paxlovid (nirmatrelvir and ritonavir), made by Pfizer, based in New York City, cut hospitalizations and deaths by 89%.

It's too soon to tell whether SARS-CoV-2 is likely to develop any resistance to these first-generation antivirals, says Tim Sheahan, a coronavirologist at the University of North Carolina at Chapel Hill. Although its sky-high rate of replication is a breeding ground for mutations, he says, the virus also causes acute infections that offer relatively little time for resistance-causing mutations to accumulate.

But the threat of resistance is particularly severe for 'monotherapies' such as molnupiravir and Paxlovid that each target only one part of the virus. That's why it's imperative to develop new antivirals aimed at different targets, or ones that can be combined into a single treatment to attack the virus on multiple fronts, says Sheahan.

Successful antivirals have typically targeted two key pieces of a virus's biological machinery — a polymerase and a protease, both of which are essential for viral replication. The current COVID-19 pills are no exception: Paxlovid inhibits SARS-CoV-2's main protease, whereas molnupiravir tricks its RNA polymerase into incorporating part of the drug into the virus's RNA, creating so many errors that it cannot survive.

Molnupiravir's mode of attack means that it might not be wise to include it in a combination therapy, says Luis Schang, a virologist at Cornell University in Ithaca, New York. If the treatment does not completely wipe out the virus in a patient, some of the RNA errors it creates might inadvertently give the virus resistance against the other drug in the combination. That's why it's a key priority for researchers to find an accessible drug that effectively blocks the virus's RNA polymerase, he says, which could be used in partnership with a protease inhibitor such as Paxlovid.

Other antiviral drug candidates are slowly working their way through the clinical-trial pipeline, says Carl Dieffenbach, director of the division of AIDS at the US National Institute of Allergy and Infectious Diseases (NIAID). He says that one promising candidate is a protease inhibitor that is currently in phase II/III clinical trials in Asia. The candidate targets the same protease as Paxlovid but would require patients to take only one pill each day, compared with Paxlovid's twice-daily dosage. That simpler regimen could help to avert the rise of resistance, Cherry says.

Target practice

Researchers should also develop treatments that target other parts of the virus, Schang says. "We really have to identify and validate new targets for antivirals so that when the next [pandemic] happens, we have a much broader pipeline to choose from," he says.

Other potential targets include a different protease in SARS-CoV-2 called PL_{pro}, and an enzyme called methyltransferase that stabilizes the virus's RNA, says Matt Hall, director of the early translation branch at the US National Center for Advancing Translational Sciences (NCATS) in Bethesda, Maryland. Clear Creek Bio, a biotechnology firm based in Cambridge, Massachusetts, announced on 6 January that it will collaborate with NCATS to develop an oral drug targeting the PL_{pro} enzyme.

Dieffenbach says that researchers would ideally like to identify targets that are common to entire families of viruses and inhibit them with a single drug. Developing such broad-spectrum drugs will take significant public and private investment, says Hall. Last year, the United States appropriated US$1.2 billion to NIAID to launch the Antiviral Drug Discovery Centers for Pathogens of Pandemic Concern, which will fund basic research on developing antivirals for seven virus families.

But all antivirals face an inherent limitation, says Dieffenbach: they must be taken within days of infection to stop a virus from proliferating. Antivirals are effective only if people acknowledge that they might be ill, and can access diagnostic tests. "We can build the best drugs in the world, but if people don't understand that they have to get on board quickly, they're not going to do any good," says Dieffenbach. "Pills do not take themselves."