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A researcher in Nigeria uses a CRISPR diagnostic test to look for Lassa virus in a blood sample.

EPIDEMIOLOGY

CRISPR tools help to detect illnesses

Researchers turn to powerful gene-editing method to diagnose diseases and curb the spread of infections.

BY AMY MAXMEN

An epidemic of Lassa fever in Nigeria that has killed 69 people this year is on track to be the worst ever recorded anywhere. Now, in the hope of reducing deaths from Lassa in years to come, researchers in Nigeria are trying out a new diagnostic test based on the gene-editing tool CRISPR.

The test relies on CRISPR's ability to hunt down genetic snippets — in this case, RNA from the Lassa virus — that it has been engineered to find. If the approach is successful, it could help to catch a range of viral infections early so that treatments can be more effective and officials can curb the spread of infection.

Scientists in Honduras and California are testing CRISPR diagnostics for dengue viruses, Zika viruses and strains of human papillomavirus (HPV) associated with cancer. And a study to explore a CRISPR test for the Ebola virus is pending in the Democratic Republic of the Congo (DRC).

A user-friendly test could reduce the death rates from Lassa fever, which can be as high as 60%, says Jessica Uwanibe, a molecular biologist developing a Lassa diagnostic at Redeemer's University in Ede, Nigeria. "I'm working on something that could save a lot of lives."

For most infectious diseases, diagnosis requires specialized expertise, sophisticated equipment and ample electricity — all of which are in short supply in many places where illnesses such as Lassa fever occur. CRISPR tests offer the possibility of diagnosing infections as accurately as conventional methods, and almost as simply as a home pregnancy test. And because CRISPR technology is built to target specific genetic codes, researchers hope to develop tools that can identify whatever viral strain is circulating, within a week of it being sequenced.

"This is a very exciting direction for the CRISPR field," says Jennifer Doudna, a biochemist at the University of California, Berkeley, who is developing some of these tools.

Uwanibe and her team are running trials of a CRISPR diagnostic developed by researchers at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, who had paired CRISPR with the Cas13 protein. Unlike Cas9 — the enzyme originally used in CRISPR gene editing — Cas13 cuts its target genetic sequence, and then starts slicing up RNA indiscriminately. This behaviour is problematic when editing genes, but it's a boon for diagnostics because all that cutting can serve as a signal.

In 2018, the Broad team updated its test, called SHERLOCK, by adding RNA molecules that signal when they've been sliced by Cas13. The cut RNA triggers the formation of a dark band on a paper strip — similar to the visual cues in a pregnancy test — that indicates the presence of whatever genetic sequence CRISPR was engineered to find (J. S. Gootenberg *et al. Science* **360**, 439–444; 2018).

The team in Nigeria is now testing how accurately a version of this diagnostic, modified to find the Lassa virus, flags people whose infections have already been confirmed with the conventional approach, which uses polymerase chain reaction (PCR).

SHERLOCK is roughly half the price of PCR tests in Nigeria, and takes half the time to return results — around two hours compared with four, says Kayla Barnes, a geneticist at the Broad who is collaborating with the group in Nigeria. Both diagnostics require electricity to process samples, but SHERLOCK isn't as sensitive to power outages — which are ubiquitous across Nigeria — as PCR is.

Other CRISPR tests developed by Doudna and her team at Berkeley use Cas proteins with different properties to target various illnesses. Their diagnostic for HPV uses the Cas12a protein, which targets DNA, instead of Cas13 (J. S. Chen *et al. Science* **360**, 436–439; 2018). The test distinguishes between two types of HPV that have been linked to cervical or anal cancer.

Doudna hopes that it will help to curb the rising death toll from cervical cancer in African countries where the disease is frequently diagnosed too late for treatment. She co-founded a start-up called Mammoth Biosciences in San Francisco, California, last year to further develop CRISPR diagnostics. The company is now running studies of its HPV test.

The Berkeley and Mammoth researchers are looking to expand their CRISPR toolkit with the newly discovered Cas14 and CasX proteins, whose small size makes them easier to incorporate into diagnostic technologies.

"These are exciting innovations," says Dhamari Naidoo, a technical officer at the World Health Organization, who is based in Nigeria. But she adds that for CRISPR tests to be of use in low-income countries, researchers must ensure that the technology is licensed, manufactured and priced affordably.

Researchers often fail to think about this side of the equation, Naidoo says. For instance, about 12 diagnostic tests for Ebola have been developed, but only 2 are in use in the DRC's current outbreak. The rest have been held up for reasons including the lack of a market large enough for manufacturers to justify the expense of making and distributing the tests.

In light of the ongoing CRISPR patent battles between Berkeley and the Broad, diagnostics based on the technology could be troublesome from an economic standpoint. But Doudna and Pardis Sabeti, who leads the SHERLOCK project at the Broad, say they're committed to licensing their tools so that the people who need these diagnostics can use them.

For Uwanibe, that day cannot come soon enough. "I wish we could do this even faster," she says. ■