Treatments for poxviruses—including those causing mpox and smallpox—may already exist in licensed drugs

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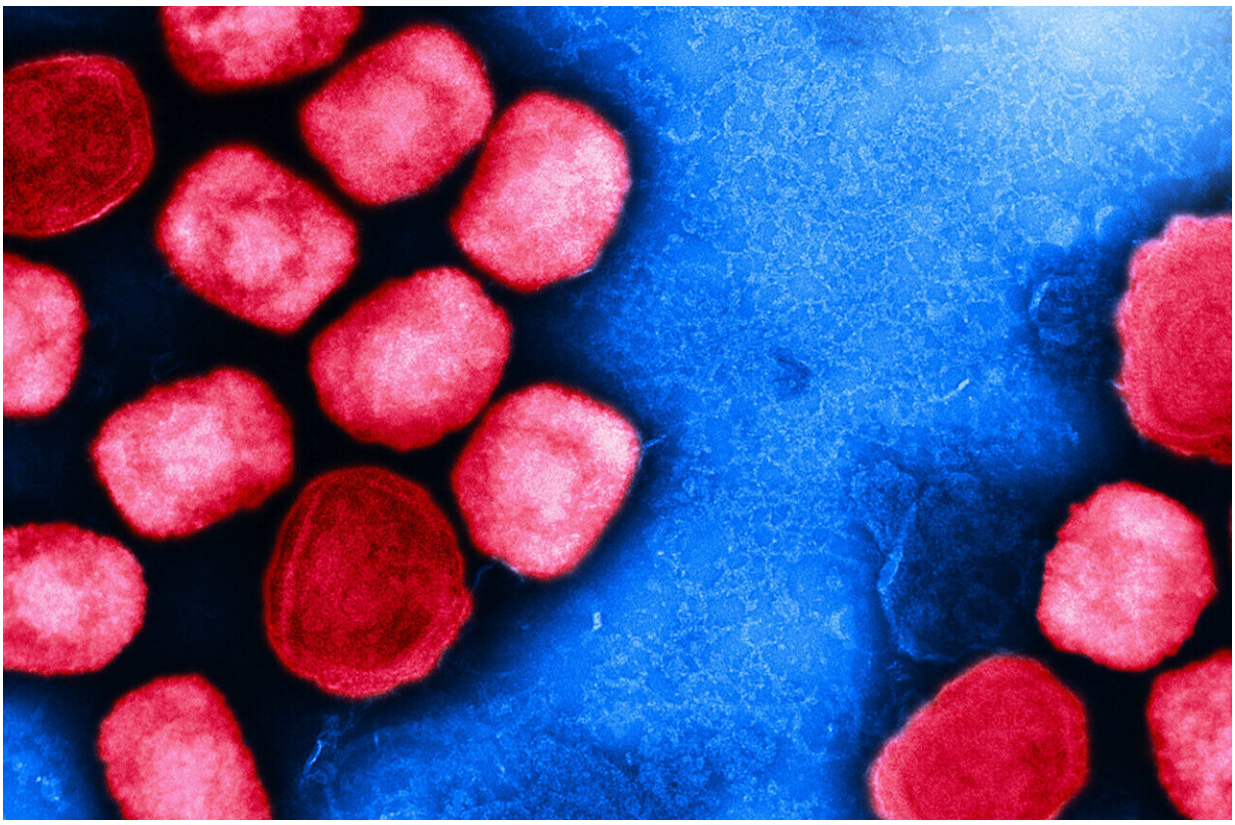

Colorized transmission electron micrograph of mpox virus particles (red) cultivated and purified from cell culture. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

Scientists studying how poxviruses evade natural defenses in human cells have identified a new approach to treatment that may be more durable than current treatments.

This follows their discovery of how poxviruses exploit a cellular protein to evade the host cell defenses, and thereby replicate and spread effectively.

Existing drugs developed to be immunosuppressive, or treat other viral infections target this cellular protein. The team found that these drugs can also restrict the replication and spread of poxviruses.

This approach to treatment, in which the drug does not directly target the virus, means that it will be much more difficult for the virus to evolve drug-resistance.

And because this hijacking mechanism is the same across many poxviruses, the drugs will be effective in treating a range of diseases such as mpox and smallpox. The research was published in the journal *Nature*.

Despite the fact that smallpox has been eradicated as a disease since 1979, the virus that causes it, variola, is still held in two high security labs—one in the United States, and one in Russia. The threat of variola virus being used in bioterrorism has led to a drug, tecovirimat, being licensed to treat smallpox.

There is an ongoing epidemic of mpox (caused by monkeypox virus), although the number of infections has dropped in the UK it is still present, particularly in London, and in many other nations.

Tecovirimat has been used to treat severe cases of mpox over the last year, but this has resulted in the emergence of multiple drug-resistant

strains of the monkeypox virus.

"The drugs we identified may be more durable than the current treatment for monkeypox—and we expect will also be effective against a range of other poxviruses including the one that causes smallpox," said Professor Geoffrey L. Smith, who conducted the work in the Department of Pathology at the University of Cambridge, the Dunn School of Pathology, University of Oxford and the Pirbright Institute.

Once a poxvirus infects a host cell, it has to defend itself from attack by cellular proteins that would restrict virus replication and spread. Researchers identified a specific cell protein, called TRIM5α, that restricts virus growth—and another cellular protein called cyclophilin A that prevents TRIM5α doing so. Existing drugs target cyclophilin A, and so make the virus more sensitive to TRIM5α.

"There are various drugs that target cyclophilin A, and because many of them have gone through clinical trials we wouldn't be starting from scratch but repurposing existing drugs, which is much quicker," said Smith.

Many other poxviruses affect animals, for example a global pandemic of "lumpy skin disease" is currently affecting cattle—and can be fatal.

Smith added, "Our results were completely unexpected. We started the research because we're interested in understanding the basic science of how poxviruses evade host defenses and we had absolutely no idea this might lead to drugs to treat monkeypox virus and other poxviruses."

Professor Guy Poppy, Interim Executive Chair at the Biotechnology and Biological Sciences Research Council (BBSRC), said, "The national monkeypox consortium was borne out of an urgent need for the UK to respond to an emerging threat of disease caused by this virus. It is

critical that public funders and policy makers are able to act with agility and coordination to support a swift scientific response.

"Taking a One Health approach, the rapid response by BBSRC and the Medical Research Council (MRC), in collaboration with policy makers via the UKRI Tackling Infections strategic theme, enabled leading researchers from across the UK to pool their expertise and deliver impactive results at pace."

The science behind the discovery

The project started with the simple observation that vaccinia virus infection causes a reduction in the level of TRIM5α in human cells. To find out why, the team engineered human cells to lack TRIM5α and found that in these cells the virus replicated and spread better. This shows that TRIM5α has anti-viral activity.

Next they identified the vaccinia virus protein that TRIM5α targets. They also discovered that the virus has two defenses against attack by TRIM5a: first, it exploits another cellular protein, cyclophilin A, to block the antiviral activity of TRIM5α, and second it makes a protein, C6, that induces destruction of TRIM5α.

Existing drugs target cyclophilin A. When the team tested a series of these drugs against a range of poxviruses, including monkeypox, they had antiviral effects in all cases. The drugs work by making the virus more sensitive to TRIM5α.

More information: Geoffrey Smith, TRIM5α restricts poxviruses and is antagonized by CypA and the viral protein C6, *Nature* (2023). DOI: 10.1038/s41586-023-06401-0.
www.nature.com/articles/s41586-023-06401-0

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