

## Discovery explains how cold sore virus hides during inactive phase

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Now that Duke University Medical Center scientists have figured out how the virus that causes cold sores hides out, they may have a way to wake it up and kill it.

Cold sores, painful, unsightly blemishes around the mouth, have so far evaded a cure or even prevention. They're known to be caused by the herpes simplex virus 1 (HSV1), which lies dormant in the trigeminal nerve of the face until triggered to reawaken by excessive sunlight, fever, or other stresses.

"We have provided a molecular understanding of how HSV1 hides and then switches back and forth between the latent (hidden) and active phases," said Bryan Cullen, Duke professor of molecular genetics and microbiology.

His group's findings, published in *Nature*, also provide a framework for studying other latent viruses, such as the chicken pox virus, which can return later in life as a case of shingles, and herpes simplex 2 virus, a genitally transmitted virus that also causes painful sores, Cullen said.

Most of the time, HSV1 lives quietly for years, out of reach of any therapy we have against it. It does not replicate itself during this time and only produces one molecular product, called latency associated transcript RNA or LAT RNA.

"It has always been a mystery what this product, LAT RNA, does,"



Cullen said. "Usually viral RNAs exist to make proteins that are of use to the virus, but this LAT RNA is extremely unstable and does not make any proteins."

In studies of mice, the team showed that the LAT RNA is processed into smaller strands, called microRNAs, that block production of the proteins that make the virus turn on active replication. As long as the supply of microRNAs is sufficient, the virus stays dormant.

After a larger stress, however, the virus starts making more messenger RNA than the supply of microRNAs can block, and protein manufacturing begins again. This tips the balance, and the virus ultimately makes proteins that begin active viral replication.

The new supply of viruses then travels back down the trigeminal nerve, to the site of the initial infection at the mouth. A cold sore always erupts in the same place and is the source of viruses that might infect another person, either from direct contact, or sharing eating utensils or towels, Cullen said.

The approach to curing this nuisance would be a combination therapy, Cullen said. "Inactive virus is completely untouchable by any treatment we have. Unless you activate the virus, you can't kill it," he said.

Cullen and his team are testing a new drug designed to very precisely bind to the microRNAs that keep the virus dormant. If it works, the virus would become activated and start replicating.

Once the virus is active, a patient would then take acyclovir, a drug that effectively kills replicating HSV1.

"In principle, you could activate and then kill all of the virus in a patient," Cullen said. "This would completely cure a person, and you



would never get another cold sore."

He and the team are working with drug development companies in animal trials to begin to answer questions about how to deliver this drug most effectively.

Source: Duke University

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