# Topical treatment wipes out herpes with RNAi

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Whether condoms or abstinence, most efforts to prevent sexually transmitted diseases have a common logic: keep the pathogen out of your body altogether. While this approach is certainly reasonable enough, it doesn't help the countless people worldwide who, for a number of reasons, are not in a position to control their sexual circumstances.

Now, Harvard Medical School professor of pediatrics Judy Lieberman, who is also a senior investigator at the Immune Disease Institute, has overseen the development of a topical treatment that, in mice, disables key genes necessary for herpesvirus transmission. Using a laboratory method called RNA interference, or RNAi, the treatment cripples the virus in a molecular two-punch knockout, simultaneously disabling its ability to replicate, as well as the host cell's ability to take up the virus.

What's more, the treatment is just as effective when applied anywhere from one week prior to a few hours after exposure to the virus. In that sense, the basic biology of this prophylactic enables a real-world utility.

"People have been trying to make a topical agent that can prevent transmission, a microbicide, for many years," says Lieberman. "But one of the main obstacles for this is compliance. One of the attractive features of the compound we developed is that it creates in the tissue a state that's resistant to infection, even if applied up to a week before sexual exposure. This aspect has a real practicality to it. If we can reproduce these results in people, this could have a powerful impact on preventing transmission."

These findings will be published in the January 22 issue of *Cell Host and Microbe*.

The World Health Organization estimates that approximately 536 million people worldwide are infected with herpes simplex virus type 2 (HSV-2), the most common strain of this sexually transmitted disease. Women are disproportionately affected. This is especially serious, since the virus can easily be passed from mother to child during birth, and untreated infants face risks of brain damage and death. While HSV-2 alone isn't life-threatening in adults, infection does increase a person's vulnerability to other viruses such as HIV.

In order for the herpesvirus to infect the host, two conditions must be met. First, the virus must be able to enter and take over host cells. Second, the virus must then reproduce itself. Lieberman's topical treatment uses RNAi to foil both these events.

RNAi, a biological process that was identified barely a decade ago, has transformed the field of biological research. A breakthrough that earned the Nobel Prize in 2006, RNAi is a natural cellular process that occurs in all cells of all multicellular organisms to regulate the translation of genetic information into proteins. This natural process can be manipulated by researchers to switch off specific genes, and there is much research and development work to harness RNAi for therapeutics.

Many in the field think RNAi-based drugs may be the next important new class of drugs.

By introducing tiny RNA molecules into cells, researchers can target a gene of interest and, in effect, throw a wrench into that gene's ability to build protein molecules. For all intents and purposes, that gene is now disabled.

While RNAi has profoundly accelerated the ability of scientists to probe and interrogate cells in the Petri dish, therapeutic breakthroughs have proved far more problematic. Researchers have had a difficult time delivering these tiny RNA molecules and ensuring that they actually penetrate the desired cells and tissues in a living organism.

Modifying a delivery technique that Lieberman developed in 2005, she and postdoctoral fellow Yichao Wu and junior researcher Deborah Palliser (who now heads her own laboratory at Albert Einstein College of Medicine) treated mice with strands of RNA that were fused to cholesterol molecules, which made it possible for the molecules to pass through the cell membranes. When applied in the form of a topical solution, these RNA molecules could then be fully absorbed into the vaginal tissue, protecting the mice against a lethal dose of administered virus.

One RNA molecule in the topical solution targeted a herpes gene called UL29, which the virus needs to replicate. Knocking out UL29 inactivates the virus.

Another RNA molecule targeted Nectin-1, a surface protein found on cells in the vaginal tissue. Nectin-1 acts as a kind of host gatekeeper to which the virus binds to pass into the cell. Without Nectin-1, the virus simply can't infect cells.

Either RNA molecule delivered by itself would be sufficient to block the virus, but together in this RNAi cocktail, the host tissue becomes like a fortress that pulls up the drawbridge to block the enemy's entrance, and also has a full-fledged battle plan to slaughter the enemy if they make it through.

"As far as we could tell, the treatment caused no adverse effects, such as inflammation or any kind of autoimmune response," says Lieberman.

"And while knocking out a host gene can certainly be risky, we didn't see any indication that temporarily disabling Nectin-1 interfered with normal cellular function."

Paper: *Cell Host & Microbe*, January 22, 2009, Vol 5 No. 1 "Durable Protection from Herpes Simplex Virus-2 Transmission Following Intravaginal Application of siRNAs Targeting Both a Viral and Host Gene"

Source: Harvard Medical School