Potential new herpes therapy studied

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A new therapy being developed at the University of Florida could, in time, produce another weapon for the fight against herpes.

The gene-targeting approach uses a specially designed RNA enzyme to inhibit strains of the herpes simplex virus. The enzyme disables a gene responsible for producing a protein involved in the maturation and release of viral particles in an infected cell. The technique appears to be effective in experiments with mice and rabbits, but further research is required before it can be attempted in people who are infected with herpes.

"If things worked out the best they could, I think this could be a measure to prevent recurrence, and that would help a lot of people — and even if it just reduced severity, it would give us another therapy in cases where there is drug resistance," said David Bloom, Ph.D., a virologist at the UF College of Medicine who leads the interdisciplinary research team investigating the new therapy.

The work was published in the *Journal of Virology* in August.

The HSV-1 strain of the herpes virus causes cold sores or fever blisters around the mouth, genital herpes, a deadly but rare type of encephalitis, and keratitis, a scarring of the cornea that leads to vision loss. HSV-2 is the more common cause of genital herpes.

Existing herpes treatments work because the active ingredients target viral building blocks, and become incorporated into the virus' genetic

material and shut down its ability to make copies of itself. In so doing, the drugs limit the severity of herpes lesions.

"They work pretty well, and they keep the disease in check, but there's no real cure," said Alfred Lewin, Ph.D., a molecular geneticist on the research team.

Current treatments also can cause inflammation, and in many people the virus becomes resistant and there is no back-up medication. In HSV keratitis, even after a corneal transplant the virus can hide out in nerve cells and cause re-infection.

"Our approach would keep it from popping up again," Lewin said.

The UF team — which also includes researchers and clinicians from obstetrics and gynecology, orthopedics and ophthalmology and the university's Genetics Institute — came up with a way to cut the virus' RNA to prevent reactivation.

By designing special enzymes called hammerhead ribozymes, the researchers were able to target a so-called "late" gene that releases its protein product relatively late after infection. With late genes, partial corruption of the genetic material is sufficient to shut down virus production, as opposed to "early" genes, which would require total inactivation to hinder the process.

"What I think is remarkable with the technology is its versatility — you can design ribozymes that will be effective against any pathogenic virus you're interested in inhibiting," said John M. Burke, a professor of microbiology and molecular genetics at the University of Vermont, who has studied the use of ribozymes for treating viral infections.

Burke, who is not affiliated with the research at UF, said that finding the

way to get the ribozyme into an infected cell or animal or person in such a way that it can be active once inside is "the hard part" of these types of experiments.

The University of Florida team packaged the enzyme inside an adenovirus — the type of virus that causes the common cold — and injected it into the mice. Afterward, the animals were infected with potentially lethal doses of the HSV-1 virus. As a control, other mice were injected with green fluorescent protein before being exposed to the virus.

Ninety percent of the mice that were treated with the ribozyme survived, whereas the survival rate was less than 45 percent in mice not given the special enzyme.

Analysis of tissue from treated mice revealed lower viral DNA levels in the feet, nerve cells called dorsal root ganglia and the spinal cord than in mice not treated with the ribozyme.

The approach has also been tested in mouse tissue and in rabbits.

"They have found a very good experimental system in which they can convincingly show significant antiviral activity," Burke said.

But the researchers still need to do more checks to see whether it is safe to move to human testing. Also, they want to develop more than one ribozyme, because having enzymes that attack different places on the viral RNA during replication helps prevent the virus from successfully mutating to resist treatment. They are also trying different ways of delivering the enzyme to the host cells.

One delivery technique for the eye is called iontophoresis, in which a low current pushes the treatment into the cells. The ribozyme could also

be formulated into a cream to be used topically on other parts of the body.

"I would like to have it where you put it on once and forget about it," Lewin said.

The work is funded by University of Florida Office of Translational Research, Research to Prevent Blindness and The Burroughs Wellcome Fund.

"I think we've gotten it to the point where it looks promising," Bloom said.

Source: University of Florida