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Researchers develop new compound to fight cytomegalovirus

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A Retro94-based compound may prevent a common and sometimes fatal virus—human cytomegalovirus (CMV)—from reproducing and help to protect immunocompromised patients, such as those with HIV, on chemotherapy, with transplants, and infants from the effects of the disease, according to Penn State College of Medicine researchers.

New therapies for CMV are needed, said Nicholas J. Buchkovich, assistant professor of microbiology and immunology and lead researcher. The current treatments for CMV in immunosuppressed patients can have toxic side effects, and emerging mutations in the virus are developing resistance to existing therapies.

The Retro94-based compound effectively stops the virus from making copies of itself. This means that immunocompromised patients with active CMV infection could be treated with anti-viral medication or even protected from the virus reactivating in the body before it occurs. The results were recently published in the *Journal of Virology*.

While about 50 percent of Americans have been infected with CMV, in developing countries this number can approach 100 percent of the adult population. Although the virus is generally harmless, it can cause serious health problems in people with suppressed immune systems.

CMV also is the most common infection present from birth, and infants born with CMV can suffer from hearing loss, vision problems, microcephaly—a condition that involves an abnormal smallness of the

head—and intellectual deficits. CMV is the leading nongenetic cause of deafness and results in the deaths of hundreds of children annually. CMV also has a major impact on morbidity and mortality of transplant patients and is often associated with transplant rejection.

After CMV infects a human cell, it creates a compartment where proteins are assembled into infectious viral particles. These virus particles then escape the cell to invade new ones, spreading infection. A key goal for the researchers is to understand how this assembly compartment forms. The level of Syntaxin 5 protein is increased in CMV-infected cells. The virus appears to recruit this protein from the host cell to generate the assembly compartment.

When the researchers used a genetic technique called miRNA knockdown to decrease this protein in CMV-infected cells, the compartments formed irregular shapes and produced fewer new virus particles.

Previous work suggested that the Retro94 molecule interferes with Syntaxin 5. Knowing this, the researchers then developed, in collaboration with Dhimant Desai and Shantu Amin in the department of pharmacology, a Retro94-based compound and tested its effect in CMV-infected cells in the laboratory.

"We knew of a compound that modulates Syntaxin 5," Buchkovich explained. "We tested to see if that would inhibit the formation of the assembly compartment and, in turn, inhibit the actual production of the virus. That is, in fact, what we found."

The CMV assembly compartments also formed irregularly in the presence of the compound. Importantly, the compound did not harm the host cells.

The findings suggest that Retro94 should be studied further as a potential effective and safe therapy against human CMV that interferes with the viral assembly compartment.

Buchkovich is now planning to test the compound in an animal model.

Provided by Pennsylvania State University