

It's the Big Day tomorrow. Is it your dream job interview? Or are you getting married to the love of your life? Deep down, you know it's going to be perfect, but every time you think about it, your stomach cramps, you can feel your palms sweat. And, as if that wasn't enough, you feel that unnerving tingling in your upper lip. You can already tell, what it means, but it just can't be, not now... In the morning you wake up with your mouth covered with hideous blisters. You try to hide it under your make-up, but let's be honest, everyone will know it's there... You've got a cold sore.

If anything can be said to make you feel better, you are not alone with this problem. It is estimated, that even 90% of people in the world is infected with herpes simplex (HSV), the virus responsible for the unsightly lesions on your lips. The disease is easily transmitted from person to person by direct contact, such as kissing or sexual intercourse. Once the virus enters human body, it establishes a lifelong infection in neural cells and may be reactivated by stress factors, such as fever, menstruation, sunlight... or your mother-in-law visiting. The symptoms, though unpleasant, are usually mild, although if you're unlucky enough to get herpes in your eye, the infection might leave you blind, or even be fatal if it makes its way to your brain.

The anti-herpes drugs available in pharmacies all rely on the use of acyclovir or one of its derivatives, all of them employing the same mode of action. They interrupt viral DNA synthesis by adding a defective "block" to its structure. This way new virus particles cannot be created, and the infection is no longer spreading. These medicaments can help contain the outbreak and alleviate the symptoms, they cannot, however, cure the latent infection. Some strains of HSV have evolved to evade inhibition by acyclovir by acquiring resistance mutations. Also, still no vaccine against herpes simplex is available.

The proposed project aims to develop novel anti-herpes agents that are designed to target a viral protein, called VP24 protease. A protease is a type of enzyme, whose job is to cleave other proteins according to a specific pattern. During viral replication VP24 is responsible for correct formation of viral capsid, a kind of protein shell surrounding the viral genetic material. During a capsid assembly a kind of scaffolding is used to help establish its shape. The scaffolding is then removed when the DNA is packaged inside the capsid. If the scaffolding is not released, the capsid cannot be fully formed and generate a new infectious herpes simplex particle. It has been shown, that a HSV-1 virus genetically engineered to be deficient in the VP24 protease is incapable of efficient infection. Similar strategies have been proven effective against other viruses, such as hepatitis C, human rhinovirus and SARS coronavirus, and, last but not least, are one of the core ingredients of a combined HIV therapy (HAART).

The activity of proposed VP24 protease inhibitors will first be evaluated with biochemical tests relying on the use of a protein produced in bacteria thanks to genetical engineering. Then, if the results prove satisfying, their effectivity will be verified in a system more closely resembling the natural infection conditions, using an immortalized cell line and a fully functional herpes simplex virus. The mechanism of antiviral activity and the capability of the virus to develop resistance towards the inhibitors will also be studied. Finally, the compounds will be assessed for possible toxicity in human skin cells.

If the suggested herpes simplex inhibitors prove effective in hampering viral infection, in the future they might be considered as a supplement to conventional anti-HSV therapy or an alternative to treat acyclovir-insensitive infection cases.