

An electron micrograph showing several large, spherical herpesviruses with a textured, orange-yellow surface. They are surrounded by a complex network of pink and purple filaments, likely representing the cell's internal structure. The background is a mix of blue and green, representing the cytoplasm and nucleus respectively.

Successfully controlling herpes

# Outwitting the viruses

Viruses are regarded as man's smallest enemies but their tiny size does not mean that they are any less harmful. Pathogens from the family of herpesviruses, usually known merely as the causative agents of painful cold sores, can even be fatal in newborn babies and patients with compromised immune systems. Bayer HealthCare researchers are now getting to grips with these viruses in a radically new way.

This electron micrograph provides a snapshot of the activation process. Herpesviruses (orange) can be seen making their way out of the cell nucleus (green) into the cell (blue).



Combating herpes is a tricky business. Dr. Guy Hewlett must remain one step ahead of the viruses.

It starts with an itching or burning sensation. Hours later, small red dots are visible on the skin. These then develop into blisters filled with clear fluid. It may only be a small area on the lips but it hurts like hell. The person feels generally unwell and sometimes even has a temperature. After a couple of days, the blisters burst and the sore weeps. By the time it starts to crust over, the attack of herpes has almost run its course, bringing relief – until the next outbreak.

In Germany, around twelve million men and women suffer from cold sores, a series of recurrent eruptions around the mouth. The condition itself has been around since antiquity but the causative agent was not identified until the 1930s. The culprit is a virus by the name of herpes simplex. In fact, it is anything but “simple”.

Herpes simplex may be a mere 150 to 200 nanometers ( $10^{-9}$  m) in size. It nevertheless dwarfs other viruses such as those that cause flu, yellow fever or the common cold, which are much smaller. The genetic material (DNA) of the virus is protected by a capsid, a type of capsule made up of proteins with a structure like a regular 20-sided crystal. But this is just the inner shell. It is enclosed in another protective membrane made up of fats or “lipids” in which more than a dozen other proteins are stored. They provide the human immune system with a vast array of targets. Some of these proteins are antigens that enable the body to recognize an enemy invader.

“The good thing about the herpes simplex virus is that the virus-induced inflammation is self-limiting,” says Dr. Guy Hewlett, a Bayer HealthCare virologist in the herpes team working on anti-infectives research at the Pharmaceutical Research Center in Wuppertal. “In other words, an immunologically competent being will rid itself of the virus within a couple of days.” The only snag is that the virus is not gone forever, as it is not dead but merely dormant. “It travels along the nerve fibers until it reaches certain knot-like masses of nerves where it goes into latency.” Latency is a mysterious state of viral inactivity. It has barely been touched upon by research but is considered to be virology’s “Holy Grail”.

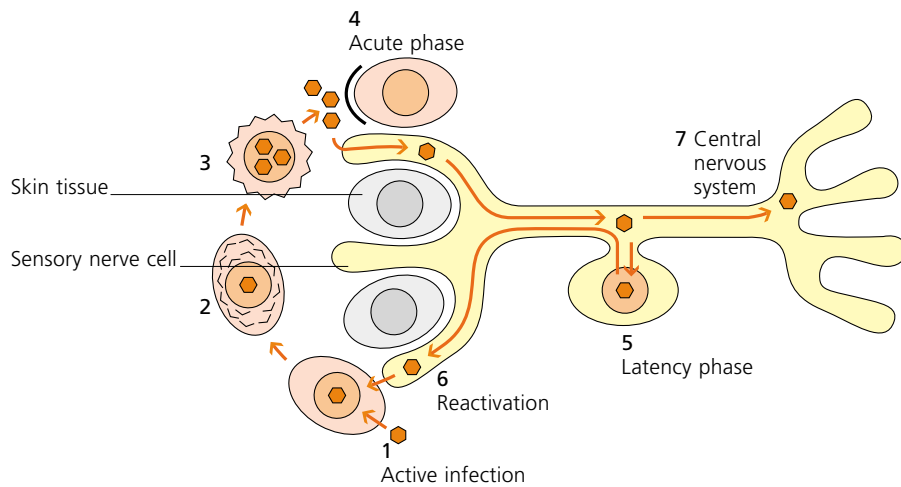
### 85 percent of adults infected with herpesviruses

Yet viruses know precisely which of these knot-like structures or “ganglia” are the best sites in which to lie dormant. HSV-1, the herpes simplex virus responsible predominantly for cold sores, hides away in the trigeminal ganglion in the temple region of the face. HSV-2, which causes a burning rash on the genitals, lingers in the sacral ganglia near the spinal cord. This distinction again shows that the “herpes” virus is not as simple as its name would suggest. For it exists in two forms. Infection with one of these forms unfortunately does not afford any protection against the other. In the most romantic scenario, HSV-1

is transmitted through kissing. Teenagers, for example, are very frequent consumers of herpes medication. Antibody tests show, however, that most of us already have the virus in our blood or in the trigeminal ganglion long beforehand – even in childhood. Babies and toddlers are constantly being kissed and cuddled by adults and so pick up infection. Up to 85 per cent of all adults are believed to carry the virus. Two thirds of them are fortunately blissfully unaware of this, however. Their immune systems are strong enough for them never to develop cold sores. The usual route of transmission of HSV-2 is sex. U.S. studies have shown that over 70 percent of prostitutes are infected with the virus. It is estimated that one in five ordinary adults in the USA and Europe is infected. “Numbers are rising, however,” says Dr. Hewlett.

Since the early 80s, a treatment has been available for both types of herpes simplex: the antiviral agent aciclovir. It is available as an ointment, a tablet or an intravenous infusion. Aciclovir and a few subsequently developed similar substances have a structure that resembles that of the building blocks of DNA known as nucleosides. They inhibit viral replication by getting themselves incorporated into viral genetic material as “defects”. The molecular chains then simply break at these points. “Predetermined break-points are incorporated, so to speak,” explains Dr. Hewlett. “But in many patients who suffer fre-

HSV-1



### Pathway followed by the herpes simplex virus

The virus infects cells of the oral or genital mucous membranes (1), forcing them to replicate the genetic material of the virus (2). At the command of the virus, the host cell also produces the virus' packaging (3) and releases a mass of new virus particles. If the immune system manages to shield the cells from invasion by new viruses (4), some viruses migrate into sensory nerve cells and accumulate in a knot-like mass of nerve cells (5). There they go into latency, a mysterious state of inactivity in which only special viral genes remain active. If the immune system is compromised, viruses migrate back to the site of infection (6) and painful sores develop. Some viral DNA also reaches the central nervous system (7) but does not do any damage there.

quently from herpes, it no longer has any effect at all." In severe cases, such as in babies infected by their mothers at birth, in AIDS patients or in patients whose immune system is compromised following a transplant, the available treatment options are insufficient. In spite of treatment, herpesviruses may cause severe tissue damage and in some cases even death.

Reason enough for Bayer's researchers to adopt a new approach. "For over 20 years, there have been no real innovations in herpes research," ex-

plains Professor Helga RübSamen-Waigmann, Head of Anti-Infectives Research at Bayer HealthCare (see Interview Box). "That's why we are looking for substances with completely new mechanisms of action."

Bayer is relying heavily here on a systematic approach – and on its library of compounds containing around a million chemicals. Bayer researchers have let these potential active ingredients loose on virus-infected cell cultures to see what effect they have. Explains Professor RübSamen-Waigmann: "When a virus replicates in a human cell, various genes are involved." Use of the virus-infected cell cultures therefore allows the Bayer researchers to target the virus with compounds in various ways. The vast majority of the substances have no effect at all – or destroy the cells rather than the viruses. Some, however, prove to be "hits", to use the scientific jargon.

### New anti-herpes active substance thanks to genetic engineering

Thiazole urea was one such "hit". In a long series of stages, the researchers optimized the compound. They substituted chemical groups and tested efficacy, tolerability and bioavailability in living beings. At the same time, they clarified the mechanism of action using molecular biological and genetic engineering methods. The Bayer researchers now have at their disposal BAY 57-1293, an optimized substance with a new mechanism of action. "We

aim to help combat life-threatening HSV infections and to reduce mortality. A further goal is to reduce latency development and the likelihood of recurrences," says Dr. Hewlett. For the 59-year-old virologist, this would be one of the high points of a long career in research. His colleague, Dr. Holger Zimmermann, and the HCMV team at Bayer HealthCare also have reason to be confident. The compound on which this biologist is working, a sulphonamide, is effective against another, by no means less threatening virus from the herpesvirus family: human cytomegalovirus or HCMV for short.

Serum tests suggest that 40 to 80 per cent of all young people are infected with this virus. And, as with HSV, it is the immune status of the carrier that determines whether the virus is activated or not. If it is allowed to gain the upper hand, it causes devastating damage to various body tissues, particularly the kidneys and the adrenal glands, by fusing cells together and tearing down the dividing walls. The "giant cells" from which the virus gets its name are then discernible in tissue specimens. Pneumonia caused by HCMV viruses used to be one of the most common causes of death in patients who had undergone bone marrow transplants. The virus is also a threat to fetuses and newborn babies. Without treatment, infection may lead to deafness and severe brain damage. Bayer now hopes to send a new compound into battle against this killer herpesvirus. It is currently being es-

Dr. Holger Zimmermann uses simulation to test a new active substance.





## “We have to be quicker than the viruses”

**Professor Helga Rübsamen-Waigmann is Head of Anti-infectives Research at Bayer. This chemist, who also holds a professorship at the University of Frankfurt am Main, made a name for herself in particular with research into AIDS. *research* asked her about strategies in virology.**

**AIDS and SARS are two viral diseases that are currently in the media spotlight. Why, then, is Bayer concerned with the comparatively harmless herpesviruses?**

We certainly are concerned with AIDS. HIV is one of the main focuses of viral research at Bayer. We are also engaged in research into treatments for hepatitis C and two viruses from the herpes family. HCMV or human cytomegalovirus is the virus most commonly transmitted from mother to child. It may prove extremely harmful or even fatal in newborn babies and the immune-deficient. And herpes simplex viruses cause genital herpes in addition to cold sores. In that respect, they too are therefore harmful. Infection with genital herpes, for example, promotes the transmission of HIV.

**Does HSV-1 also have its harmful side?**

In someone with a compromised immune system, undoubtedly. In newborn babies, even the cold sore virus may cause meningitis, resulting in mental handicap or even death. In AIDS patients, the infection is not confined to the lips and may spread all over their faces.

**Which class of viruses currently poses the greatest risk to man?**

HIV still. SARS is naturally also a problem, as airborne transmission is possible. And there is evidence of a second mode of transmission via cockroaches or other insects. It is hoped, nevertheless, that this lung

disease can be controlled. For, unlike AIDS, the symptoms appear within days. The AIDS virus goes to ground, however. Those infected appear healthy and may infect others unwittingly. In India, six million people are now reported to be infected. In other words, HIV has spread from Africa, a continent with a low population, to the most populous continent, Asia. And the epidemic is still only in the early stages there.

**Will man ever win the race against viruses?**

I don't think so. But we are getting better and better. The good thing about viruses is that they have little genetic material. HIV, for example, has a million times fewer genes than humans. Even if it changes, this is rapidly discernible. But as SARS has shown, a new virus can emerge anywhere in the world at any time. The threat posed by viruses is greater nowadays than it was in the era before air travel became common. A company that is engaged in the development of treatments for infectious diseases must adapt accordingly. In order to overcome resistance, here in Virology we are working almost exclusively on new mechanisms of action, as witnessed by the two development candidates for herpes and HCMV and our candidate for licensing out for the treatment of hepatitis B, BAY 41-4109. These mechanisms of virus inhibition are so innovative that we have been able to publish our research in respected international journals such as Nature Medicine, Science or the Journal of Virology. We hope that they will also lead to greater therapeutic success and we now eagerly await the results of clinical trials.

corted through its preclinical studies by Dr. Zimmermann and it too has a new mechanism of action. “The compound acts exclusively and very effectively against the HCMV virus,” explains Dr. Zimmermann. “We presume that the compound will be well tolerated in humans and will not harm the kidneys or the bone marrow.” An adverse effect on bone marrow is the main problem with the currently available agent, ganciclovir, a nucleosidic compound. Like the herpes simplex drug, aciclovir, it inhibits viral replication by simulating a DNA building block. Viruses may be “masters of disguise and deception”, as Dr. Hewlett and Dr. Zimmermann unanimously confirm. Human researchers occasionally manage to outwit their little enemies, however. Perhaps not forever but at least until the next time.

[www.herpes.org](http://www.herpes.org)

A frequently visited website run by doctors for herpes sufferers. It also displays the latest research findings.

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