HIGHLIGHTS

ANTIVIRAL DRUGS

Herpes simplex Achilles' helicase

Achilles was immortal, except for the one heel that turned out to be his downfall — he was shot there by Paris' arrow. Two papers in the April issue of *Nature Medicine* identify the herpes simplex virus (HSV) helicase–primase enzyme as a potential viral Achilles' heel. They report a new class of inhibitors of this enzyme, which show superior efficacy in animal models compared with current antiherpetic drugs.

More than 80 known viruses exist within the herpesvirus family. Of these, eight are known to cause disease in humans, the most common being HSV-1 and -2. Although acyclovir — the first nucleoside inhibitor of HSV DNA polymerase — was a milestone in the development of antivirals, nucleoside drugs are not always effective, and encounter the problem of resistance.

Researchers from Bayer and Boehringer Ingelheim independently identified non-nucleoside thiazoylphenyl-containing compounds that act as inhibitors of the HSV helicase–primase enzyme. This enzyme is a good target, because it functions at several stages of the chromosomal replication process, and has intrinsic DNA helicase, RNA polymerase (primase) and single-stranded DNA-stimulated ATPase activities. Each of these actions is essential for viral replication.

In cytopathogenicity assays, the Bayer and Boehringer compounds were orders of magnitude more potent than nucleoside drugs, and, importantly, were active against acyclovir-resistant mutants. To validate the target and investigate the potency and safety of the drugs, various animal models were used. Bayer's Bay57-1293 was found to be much more potent than valacyclovir in a mouse model of disseminated HSV infection and cutaneous HSV infection. Bayer's drug also compared well with valacyclovir in a guinea-pig model of intravaginal HSV-2 infection. Boehringer's drugs showed clinical utility in mouse models of HSV-1 cutaneous disease and HSV-2 genital disease. The pharmacokinetic and safety profiles compared favourably with those of the nucleoside drugs acyclovir, valacyclovir and famciclovir.

Initial investigations of the influence of the drugs on the viral replication cycle were conducted. Boehringer showed that their drugs did not function by displacing ATP from the enzyme active sites. In the presence of Bay57-1293, expression of viral immediate-early genes was initiated, but the lack of capsids that contained viral DNA, which usually bud from infected cells, show a reduction in early and late viral gene expression. Further complementation experiments concluded that the helicase–primase complex is the target of the thiazoylphenyl drugs.

Because HSV is not usually a lethal disease, the therapeutic index of an antiherpetic drug must be high to have broad application. From the animal validation studies, the non-nucleoside thiazoylphenyl-containing compounds that are directed against the HSV helicase–primase seem to be superior to the nucleoside class of drugs in terms of potency, treating early- and later-stage disease and treating otherwise drug-resistant HSV.

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References and links

ORIGINAL RESEARCH PAPERS Kleymann, G. *et al.* New helicase–primase inhibitors as drug candidates for the treatment of herpes simplex disease. *Nature Medicine* (in the press) | Crute, J. J. *et al.* Herpes simplex virus helicase–primase inhibitors are active in animal models of disease. *Nature Medicine* (in the press)