

Antiviral agents against HHV-6 and HHV-7

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I am afraid and sorry to say, that my short speech will bring you only disappointment: I can't present you neither guidelines nor the real scheme of HHV-6/7 infections treatment. There are several reasons for this:

- I am not a medical practitioner;*
- There are still not universal, "easy to use" HHV inhibitory compounds;*
- Several of the well-known antiviral agents are toxic to the organism level;*
- During the last few years hardly appeared principally new antiherpes compounds: just search between already-known nucleoside analogue lines.*

Sorry!

Overview

- *Antiviral compounds specifically inhibit one or more steps of virus replication without causing unacceptable side effects.*
- *Specific events in virus replication identified as targets for antiviral agents are:*

viral adsorption, penetration, uncoating , viral nucleic acid synthesis ,viral protein synthesis as well as virus maturation.

Specificity for infected cells may occur when virus-specified enzymes activate drugs (thymidine kinase-induced by HSV or VZV activated by antiviral agent (acyclovir). There are potential advantages to targeting very early stages because inhibitors of these steps do not have to enter cells to exert activity.

Limitations of Antiviral Agents: **narrow antiviral spectrum, ineffectiveness against the latent virus, emerging of drug resistance, toxic side effects.**

WARNING

At the same time at the very start it is important to stress that the term “antiviral agent” does not mean a patient’s treatment or therapy of infectious disease, which is a complex process by itself, depending on the disease manifestations and including symptomatic therapy with painkillers, anti-inflammatory, antipyretic or immunity stimulating agents.

Approved Antiviral Drugs

Approved Antiviral Drugs :

The approved antiviral drugs and the viruses and diseases they treat are **amantadine, rimantadine, Relenza and Tamiflu** (influenza A and B virus), **ribavirin** (respiratory syncytial virus), **idoxuridine and trifluridine** (topical treatment of herpetic keratitis), **vidarabine and acyclovir** (systemic treatment of herpes simplex virus and varicella-zoster virus infections), **amciclovir and valaciclovir** (oral treatment of varicella-zoster virus infections), **ganciclovir and foscarnet** (cytomegalovirus), and **zidovudine, didanosine, zalcitabine and stavudine** (human immunodeficiency virus).

Antiviral compounds that have been formally licensed for clinical use are amantadine, rimantadine, ribavirin, relenza, tamiflu, idoxuridine, trifluridine, vidarabine, acyclovir, ganciclovir, foscarnet, zidovudine, didanosine, zalcitabine, stavudine, famciclovir and valaciclovir. Their activity spectrum and mechanism of action are outlined in the next slide.

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Antiviral Drugs

MicrobiologyBytes: *Latest Updates*

Drug:	Viruses:	Chemical Type:	Target:
Vidarabine	Herpesviruses	Nucleoside analogue	Virus polymerase
Acyclovir	Herpes simplex (HSV)	Nucleoside analogue	Virus polymerase
Gancyclovir and Valcyte™ (valganciclovir)	Cytomegalovirus (CMV)	Nucleoside analogue	Virus polymerase (needs virus UL98 kinase for activation)
Nucleoside-analog reverse transcriptase inhibitors (NRTI): AZT (Zidovudine), ddI (Didanosine), ddC (Zalcitabine), d4T (Stavudine), 3TC (Lamivudine)	Retroviruses (HIV)	Nucleoside analogue	Reverse transcriptase
Non-nucleoside reverse transcriptase inhibitors (NNRTI): Nevirapine, Delavirdine	Retroviruses (HIV)	Nucleoside analogue	Reverse transcriptase
Protease Inhibitors: Saquinavir, Ritonavir, Indinavir, Nelfinavir	HIV	Peptide analogue	HIV protease
Ribavirin	Broad spectrum: HCV, HSV, measles, mumps, Lassa fever	Triazole carboxamide	RNA mutagen
Amantadine / Rimantadine	Influenza A strains	Tricyclic amine	Matrix protein / haemagglutinin
Relenza and Tamiflu	Influenza strains A and B	Neuraminic acid mimetic	Neuraminidase Inhibitor
			Blocks attachment and
Pleconaril	Picornaviruses	Small cyclic	uncoating
Interferons	Hepatitis B and C	Protein	Cell defense proteins activated

Inhibition of Viral Genome Replication

Most antiviral agents inhibit viral genome replication, and nearly all of these inhibit a DNA polymerase. Those viruses include certain human herpesviruses, HIV and HBV. Most of these drugs are nucleoside analogues.

A number of antiviral nucleoside analogues, including vidarabine, idoxuridine, and trifluridine, were developed and used against HSV infections. **Now these drugs have been replaced by more selective compounds.**

Antiherpetics

- **Genome Replication**

Many viruses have evolved their own specific enzymatic mechanisms to preferentially replicate virus nucleic acids at the expense of cellular molecules. There is often sufficient specificity in virus polymerases to provide a target for a specific antiviral agent, and this method has produced the majority of the specific antiviral drugs currently in use.

The majority of these drugs function as polymerase substrate (i.e. nucleoside/nucleotide) analogues. The toxicity of these drugs varies considerably from some which are well tolerated (e.g. acyclovir) to others which are highly toxic (e.g. IdU/TFT/AZT). There is a serious problem with the pharmacokinetics of these nucleoside analogues, e.g. typically short serum half lives of 1-4h. Nucleoside analogues are in fact **pro-drugs**, since they need to be phosphorylated before becoming effective. This is the key to their selectivity:

- **Acyclovir** is phosphorylated by HSV *tk* 200 times more efficiently than by cellular enzymes. The cell DNA polymerase is less sensitive to it than the viral DNA polymerase.
- **Gancyclovir** is 10 times more effective against CMV than acyclovir since it is specifically phosphorylated by a CMV-encoded kinase encoded by gene *UL97* :

More recently, a series of other nucleoside analogues derived from these drugs and active against herpesviruses have been developed:

Penciclovir, Famciclovir, BYDU, Broavir, FIAC, FIAU, (S)-HPMPA, (S)-HPMPC, AZT, ddC, ddI.

HHV-6, like CMV, has been increasingly recognized as an important pathogen in immunocompromised patients (in which it might cause life-threatening complications); however, unlike for CMV infections, no compounds have been formally approved for the treatment of HHV-6 infections. The drugs clinically used against HHV-6 are the same as those used in CMV therapy (or prophylaxis) and consist of ganciclovir, valganciclovir, and, to a lesser extent, acyclovir, valaciclovir, cidofovir and foscarnet. All these compounds are targeted at the viral DNA polymerase and can be considered (following phosphorylation) as substrate analogues (except for fos- carnet, which acts as a pyrophosphate analogue

Another class of compounds, the 4-oxo-dihydroxyquino- lines, act as non-nucleoside inhibitors of herpesvirus DNA polymerases. They exhibit broad-spectrum anti- viral activity against most human herpesviruses (including HCMV), with the exception of HHV-6 and HHV-7. Their lack of activity against HHV-6 is owing to a single amino acid change in the conserved domain III of the HHV-6 DNA polymerase .

There are recently discovered a new antiviral agent, CMV423 (2-chloro-3-pyridin-3-yl-5,6,7,8-tetrahydroindo- lizine-1-carboxamide;Figure 1), which demonstrated potent and selective in vitro activity against all three human β -herpesviruses — CMV, HHV-6 and HHV-7. Compared to ganciclovir and foscarnet, CMV423 showed a higher potency and lower cytotoxicity. However, its anti- viral action appeared to be cell-dependent. CMV423 must be targeted at an event that follows viral entry but that precedes viral DNA replication. CMV423 was also found to inhibit total cellular protein tyrosine kinase activity. It was concluded that CMV423 exerts its activity against HHV-6 through inhibition of a cellular process that is crucial in the early stage of viral replication and that might involve protein tyrosine kinase activity.

Conclusion

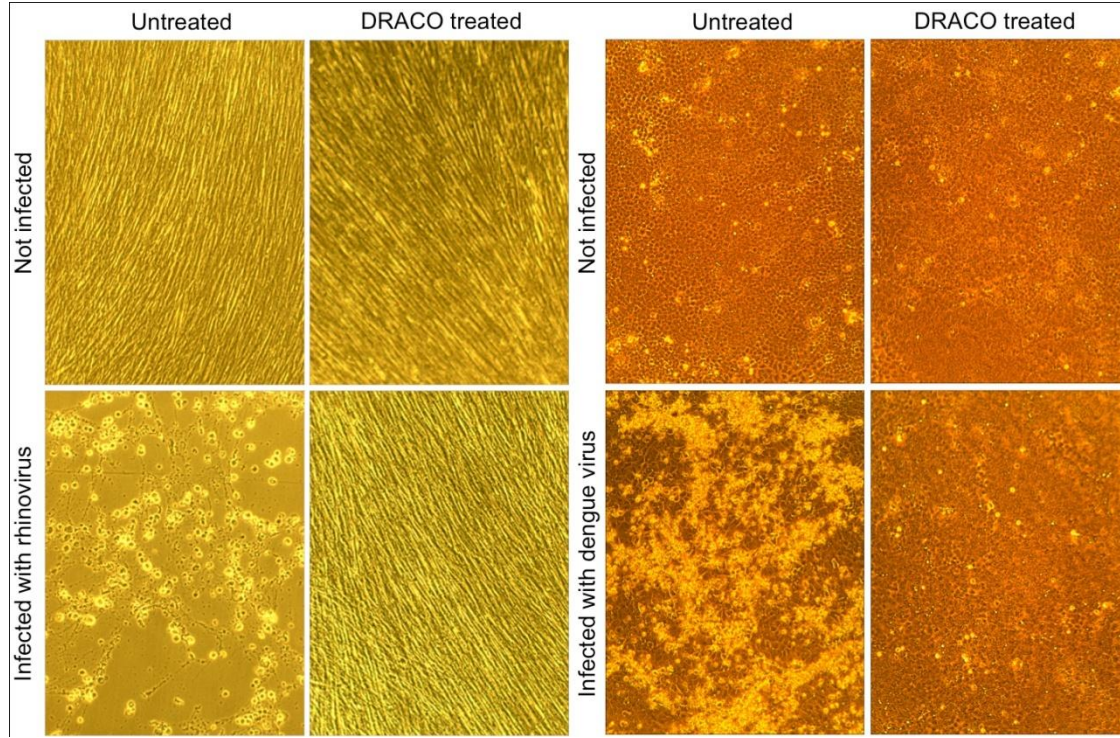
- The currently licensed anti-herpetic compounds may be effective against HHV-6 and HHV-7, but treatment strategies need to be formulated through appropriate clinical protocols : **ganciclovir, phosphonoformate (foscarnet) and cidofovir** are potent inhibitors of HHV-6 and HHV-7 replication *in vitro*; **acyclovir (ACV)** and **other thymidinkinase-dependent drugs** are marginally effective. The sensitivity of HHV-7 to the guanine analogues was different from HHV-6, **suggesting a difference in selectivity of specific viral enzymes.**
- As with other herpesviruses, HHV-6 and HHV-7 establish latent infections in monocyte-macrophages and CD4+ T lymphocytes, respectively. The mechanisms by which latency is established and reactivated are not yet known, but it is out of the question that using of virus specific antivirals in this stage does not cure the disease. The future use of immunotherapeutic approaches may complement the current management strategies.

About Future

News from MIT Lincoln Laboratory

Now, in a development that could transform how viral infections are treated, a team of researchers at MIT's Lincoln Laboratory has designed a drug that can identify cells that have been infected by any type of virus, then kill those cells to terminate the infection.

According to this information, it is a new approach to virus infections chemotherapy studies which would bring to fundamentally new solution of problem.



DRACO

The microscope images above show that DRACO successfully treats viral infections. In the left set of four photos, rhinovirus (the common cold virus) kills untreated human cells (lower left), whereas DRACO has no toxicity in uninfected cells (upper right) and cures an infected cell population (lower right). Similarly, in the right set of four photos, dengue hemorrhagic fever virus kills untreated monkey cells (lower left), whereas DRACO has no toxicity in uninfected cells (upper right) and cures an infected cell population (lower right).

In a paper published July 27 , 2011, in the journal *PLoS One*, the researchers tested their drug against 15 viruses, and found it was effective against all of them — including rhinoviruses that cause the common cold, H1N1 influenza, a polio virus, HSV, dengue fever and several other types of hemorrhagic fever.

The drug works by targeting a type of RNA produced only in cells that have been infected by viruses. “**In theory, it should work against all viruses,**” says Todd Rider, a senior staff scientist in Lincoln Laboratory’s Chemical, Biological, and Nanoscale Technologies Group who invented the new technology.

Because the technology is so broad-spectrum, it could potentially also be used to combat outbreaks of new viruses, such as the 2003 SARS (severe acute respiratory syndrome) and others.

Rider had the idea to try developing a broad-spectrum antiviral therapy about 11 years ago, after inventing **CANARY** (Cellular Analysis and Notification of Antigen Risks and Yields), a biosensor that can rapidly identify pathogens. Rider drew inspiration for his therapeutic agents, dubbed DRACOs (Double-stranded RNA Activated Caspase Oligomerizers), from living cells own defense systems.

When viruses infect a cell, they take over its cellular machinery for their own purpose — that is, creating more copies of the virus. During this process, the viruses create long strings of double-stranded RNA (dsRNA), which is not found in human or other animal cells.

Most of the tests reported in this study were done in human and animal cells cultured in the lab, but the researchers also tested DRACO in mice infected with the H1N1 influenza virus. When mice were treated with DRACO, they were completely cured of the infection. The tests also showed that DRACO itself is not toxic to mice.

The researchers are now testing DRACO against more viruses in mice and beginning to get promising results. Rider says he hopes to license the technology for trials in larger animals and for eventual human clinical trials.

Thank you for your attention !



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