The effects of antiviral therapy on the distribution of herpes simplex virus type 1 to ganglionic neurons and its consequences during, immediately following and several months after treatment

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Both famciclovir (FCV) and valaciclovir (VACV) are potent inhibitors of herpes simplex virus type 1 (HSV-1) in a murine cutaneous infection model. The object of the present study was to determine whether either drug had an effect on the anatomical distribution of infected neurons in the peripheral nervous system and to assess the consequences for infected cells during, immediately following and several months after a 9 day period of continuous treatment. Mice were inoculated via the neck with a recombinant strain of HSV-1 expressing the lacZ reporter gene under the immediate-early gene promoter. Sensory ganglia were sampled daily up to day 11 post-inoculation (p.i.) and infected cells were detected by means of the reporter gene product. Ganglia were also removed at 1–5 and 10 months p.i. and latency was assessed by explant co-cultivation and by using in situ hybridization to detect LAT-expressing neurons. While both drugs reduced the severity of acute infection markedly, neither compound completely prevented the relentless distribution of infection among peripheral nervous tissue. Furthermore, there was a difference between the compounds regarding the expression of the reporter gene during and after termination of treatment and in the number of residual LAT-positive neurons.

Introduction

It is well known that both acyclovir (ACV) and penciclovir (PCV) are effective inhibitors of herpes simplex virus types 1 (HSV-1) and 2 (HSV-2). The two compounds share the same general mechanism of action and are of similar potency when tested against viruses in tissue culture (Boyd et al., 1987; Bacon et al., 1994). However, they differ at the enzymatic level in that PCV has a relatively high affinity for the HSV thymidine kinase compared with ACV (Vere Hodge & Perkins, 1989) whereas PCV triphosphate has a much lower affinity than ACV triphosphate for the HSV DNA polymerase (Ilsley et al., 1995). Furthermore, the intracellular half-life of PCV triphosphate has been shown to be longer (Earnshaw et al., 1992; Vere Hodge & Perkins, 1989), all of these differences being at least one order of magnitude (reviewed by Field, 1996). Finally, PCV has been shown to share with ganciclovir the property of induction of apoptosis, while ACV did not display this property (Thust et al., 1998; Shaw et al., 1999).

In a series of experiments conducted over several years, we have compared the effects of ACV and PCV using a murine ear pinna infection model for HSV-1 or HSV-2, in order to determine whether the above biochemical differences are reflected in different effects in vivo. The compounds were administered orally in the form of famciclovir (FCV) or valaciclovir (VACV), which are rapidly metabolized in mice with similar kinetics to yield PCV and ACV, respectively (Field et al., 1995). Both compounds were effective in reducing clinical signs and infectious virus production during the acute infection. However, FCV was consistently more effective than VACV in limiting the establishment of latency, particularly when the onset of therapy was delayed for several days after virus inoculation (Thackray & Field, 1996a, 1998, 2000b). However, the difference between the compounds was not easily reconciled with their relative effects on acute virus replication in the nervous system during the acute phase of the infection. The object of the present study was to assess the...
Fig. 1. Detection of β-gal-positive neurons in cervical and trigeminal ganglia. Ganglia were stained for the presence of β-gal by using X-Gal. Left-hand panels show whole mounts, which are slightly squashed intact ganglia; right-hand panels show tissue sections cut from the same ganglion in each case. (a) Left CIII from uninfected mouse showing no positive cells. Magnification: whole mount × 30, 10 µm section × 75. (b) Left CIII from infected, untreated mouse on day 6 p.i. In the whole mount, two areas of the ganglion contain many positive cells, as indicated by the arrows, and at least 120 positive neurons were counted in this ganglion. Magnification: whole mount × 30, 10 µm section × 75. (c) Left TG from uninfected mouse. Magnification: whole mount × 75; 10 µm section × 75. (d) Left TG from infected, untreated mouse on day 6 p.i. A large mass of cells showing positive signal is evident and at least 200 positive neurons were counted in this ganglion. The right panel shows a part of the section where positive cells are visible that contain signal that is faint but clearly above background. Three typical positive neurons are indicated by the arrows; at least 180 positive neurons were counted in the entire 10 µm section. Magnification: whole mount × 30, 10 µm section × 150.
progress of infection in the relevant neural tissues by using a reporter gene to identify acutely infected cells.

Thus, the HSV-1 recombinant strain SC16 lacZ IE110, with the lacZ gene under the immediate-early gene promoter (Lachmann et al., 1999), was applied to the scarified skin of the neck and either FCV or VACC at 1 mg/ml was supplied ad libitum in the drinking water from days 1 to 9 post-inoculation (p.i.), this method for treating acute murine HSV infection having previously been shown by ourselves to be more effective than twice daily oral gavage at 50 mg/kg (Field & Thackray, 1995). By this means, we could examine the effects of continuous therapy on the distribution and fate of infected neurons. Ganglia from other mice obtained from the same experimental groups were analysed 1 to 10 months later for evidence of latent infection and these data were matched with the results obtained from acutely infected ganglia.

The results emphasize how neither compound was able to prevent completely the relentless progression of HSV through the nervous system. However, they provide further evidence for a difference between the compounds in their interactions with HSV and neural tissues in vivo.

Methods

- **Virus strain and tissue culture.** The virus used was HSV-1 SC16 lacZ IE110, a recombinant strain containing the lacZ reporter gene inserted under the control of the immediate-early 110 promoter (Lachmann et al., 1999). Virus working stocks were prepared at low m.o.i. in BHK-21 cells and stored at –70 °C until needed. The virus was a gift from Dr S. Efstathiou, Department of Pathology, Cambridge University, UK.

- **Mice and virus inoculation.** Female BALB/c mice were purchased (Harlan UK Ltd, Blackthorn, Biester, UK) at 4 weeks of age and were inoculated at 5 weeks. Anaesthetized mice were shaved on the left side of the neck 3 days before inoculation, and 10 µl virus suspension containing 1 × 10⁶ p.f.u. was placed onto a 1 cm² scarified skin site, 0.5 cm lateral to the ventral mid-line. Mice were observed twice daily and clinical signs were recorded as described previously (Field et al., 1995).

- **Antiviral therapy.** FCV and VACC powders were supplied by SmithKline Beecham Pharmaceuticals. They were dissolved in drinking water from days 1 to 9 p.i. containing 10⁵ p.f.u. virus. Vesicles at the inoculation site were visible within 2–3 days and a zosteriform distribution of lesions developed over the next few days, with maximum clinical signs at day 7 p.i. In all mice, lesions were apparent on the shoulder and then on the base of the ear and finally, in approx. 40% of the mice, the ear pinna itself by day 9 p.i. Twenty per cent of the untreated mice died from the infection between days 7 and 9 p.i.

- **Detection of LATs by in situ hybridization.** Probes for the detection of LATs were made by T7 polymerase transcription of HindIII-linearized pSLAT 2 with a digoxigenin (DIG) detection system as described previously in detail (Arthur et al., 1993). The plasmid pSLAT 2 was a gift from Dr S. Efstathiou. In situ hybridization was carried out as described previously (Thackray & Field, 1998), including the complementary strand to pSLAT 2 by way of a control. Positive neurons contained dark signal exclusively in the nucleus. A typical section is shown in Fig. 4(d).

Results

**Pathogenesis of infection**

In a preliminary experiment, we showed that SC16 lacZ 110 is slightly less pathogenic than the parental virus SC16 from which it was derived. Infection with the mutant was established in a shaved site on the left side of the neck by scarification and application of a 10 µl drop containing 10⁵ p.f.u. virus. Vesicles at the inoculation site were visible within 2–3 days and a zosteriform distribution of lesions developed over the next few days, with maximum clinical signs at day 7 p.i. In all mice, lesions were apparent on the shoulder and then on the base of the ear and finally, in approx. 40% of the mice, the ear pinna itself by day 9 p.i. Twenty per cent of the untreated mice died from the infection between days 7 and 9 p.i.

**Effects of therapy on pathogenesis**

Treatment with either VACC or FCV at 1 mg/ml in the drinking water commencing 24 h p.i. completely prevented death. Both drugs also reduced the intensity and duration of clinical signs as reflected in the zoster score, which was reduced significantly on several individual days (data not shown).

**Distribution of β-gal-expressing neurons**

The temporal appearance of signal in the ganglionic neurons (in the absence of therapy) was assessed. Representative X-Gal-treated whole mounts and 10 µm sections of CIII and TG are shown in Fig. 1(a–d). The first neurons that contained blue staining that was clearly above background were observed on day 2 p.i. in the left (ipsilateral) and right (contralateral) CIII (Table 1; Fig. 2). On day 3, while more positive neurons were detected in the right CIII, all TG neurons remained at or below background. However, on day 4, both left and right TG neurons gave positive signals, with more staining in the left than in the right.

The number of positive neurons reached a peak on days 6 and 5 for the left and right TG, respectively (Table 1; Fig. 2). It was notable that the largest number of positive neurons was...
Table 1. Detection of β-gal-positive neurons in ganglia during or after FCV or VACV therapy during the acute phase of HSV-1 infection

Data are shown as mean numbers of β-gal-positive neurons per section per group ± SD.

<table>
<thead>
<tr>
<th>Ganglion</th>
<th>Infected, untreated controls</th>
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<td></td>
<td>1</td>
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<td>LCIII</td>
<td>0 ± 0</td>
<td>10 ± 12</td>
<td>20 ± 8</td>
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<tr>
<td>RCIII</td>
<td>0 ± 0</td>
<td>6 ± 4</td>
<td>12 ± 5</td>
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<tr>
<td>LTG</td>
<td>0 ± 0</td>
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<td>RTG</td>
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Statistically significant differences are indicated as follows: between treated groups and infected, untreated controls, a, P ≤ 0.001; b, P ≤ 0.01; c, P ≤ 0.05; between VACV and FCV treatments, d, P ≤ 0.001; e, P ≤ 0.01; f, P ≤ 0.05.

detected in the left TG (Fig. 1d). Not only were there more positive neurons in TG, but the proportion of positive neurons counted was greater than for the cervical ganglia. We estimated that the proportions of ganglionic neurons positive for β-gal expression at the peak were approximately 50% and 75% for left CIII and left TG, respectively (data not shown). The mean numbers of positive neurons in the separate ganglia for each individual mouse over time are shown in Fig. 3.

There was an abrupt disappearance of positive cells, and no signal was detected in any left or right CIII on days 7–10 or in left or right TG on days 9–10.

Effects of therapy on distribution of β-gal expression

In the cervical ganglia (CIII), there was relatively little reduction in the number of β-gal-expressing neurons with either drug, and the reduction barely reached significance (Table 1). However, in the TG with treatment, there was a marked reduction in the number of positive neurons; for FCV, this was highly significant (P ≤ 0.001) on days 6 and 7 p.i. for the left TG in comparison with the untreated controls and day 4 p.i. for VACV. For the contralateral (right) side, the reduction was highly significant on days 5 and 6 for FCV but only on day 6 for VACV (Table 1; Fig. 2). Scores for individual mice are also shown (Fig. 3).

It was notable that therapy with either drug did not completely prevent the distribution of virus to any of the ganglia tested, and small numbers of positive neurons were observed in both left and right CIII with either therapy. In VACV-treated mice, the number of β-gal-expressing cells in the TG exceeded 100 and 70 neurons per section for left and right TG, respectively. The comparable numbers for FCV were 35 and 25.

After therapy was discontinued (day 9) and all ganglia had become negative for 2 days, there was a single day (day 11) on which sections from VACV-treated mice only yielded positive signal in both left CIII and left TG neurons in 5/5 and 4/5 mice for CIII and TG, respectively (a representative whole mount and section are shown; Fig. 4a). The number of positive neurons ranged from 2 to 23 per section for CIII and 20 to 53 for TG (Figs 3 and 4a; Table 1).

A few ganglia were examined for β-gal expression at 1:5 and 10 months p.i. and, in both cases, positive neurons (< 20 positive cells per section) were detected in all ganglia (Figs 4b–c and 5a). The mean numbers of positive neurons per section in the individual ganglia at 10 months for treated and untreated mice are shown (Table 2).

Latent infection (LAT expression)

Latency was examined at 1:5 months and again at 10 months p.i. by in situ hybridization with a probe for the major LAT (Fig. 4d). The mean number of LAT-positive cells per section is shown (Table 2). The mean number of LAT-positive neurons is plotted for individual mice (Fig. 5b) and this should be compared with data obtained during the acute phase (Fig. 3).
The greatest number of LAT-positive cells (81 neurons per section at 6 weeks p.i.; Table 2) was observed in the left TG. The number of LAT-positive cells was consistently and significantly reduced in ganglia obtained from mice that had received FCV. In contrast, there was less reduction in the number of LAT-positive neurons in VACV-treated mice and, for contralateral TG, the number was actually significantly higher than that seen in untreated controls, with 2.6- and 3.2-fold increases over control (untreated) mice at 1-5 and 10 months p.i., respectively (Fig. 5; Table 2).

When ganglia were tested by explant co-cultivation at 1-5 months p.i., infectious virus was reactivated from all the sampled CIII and right TG from untreated mice. However, only 4/5 of the left TG yielded infectious virus and the infectious virus titres for positive ganglia were low (geometric mean of 1.9 log_{10} p.f.u. per ganglion for the left TG compared with 2.1 for the right TG, 3.3 for the left CIII and 2.6 for the right CIII; data not shown). At 10 months p.i., additional mice were tested. In this case, all ganglia were positive except left TG (Fig. 5c). Since there may have been amplification during the 5 day culture period, the titration of infectious virus after 5 days provides only a semi-quantitative estimate of the reactivation. However, the highest titres of infectious virus were observed in the left CIII (Fig. 5c). In contrast, no ganglia from either drug-treatment group reactivated infectious virus (Fig. 5c). Thus, at 1-5 months p.i. and similarly at 10 months p.i., all ganglia from mice that had been treated with either FCV or VACV were negative for infectious virus after co-cultivation.

**Discussion**

Several important findings have emerged from this study. Firstly, both FCV and VACV showed marked antiviral activity in the murine neck inoculation model for HSV-1. This model involves the application of virus to a scarified area of skin and confirms previous data from this laboratory, which were obtained by using the ear pinna model, where virus was
Fig. 3. For legend see facing page.
Effect of antivirals on HSV neuronal infection

Fig. 3. The mean numbers of β-gal-positive neurons in CIII and TG (L, left; R, right) for individual mice during and after therapy. To obtain the mean count, 30 sections were enumerated in each case. The numbers 1–5 for each day are individual mice; i.e., LTG 1 comes from the same mouse as RCIII 1 on any day.

Inoculated as a discrete 10 µl bleb into the skin of the ear pinna. With the β-gal gene product used as a marker for infection, the present study also confirmed that treatment starting from 1 day p.i. did not eliminate the infection of ganglionic neurons in the third ipsilateral cervical ganglion (CIII), which provides direct innervation for the infected skin inoculation site. Furthermore, continuous treatment applied in the drinking water did not prevent the colonization of secondary ganglia.
Fig. 4. The detection of virus-positive cells in ganglia at late times after infection. (a)–(c) Ganglia were stained for the presence of β-gal by using X-Gal. Left-hand panels show whole mounts, which are slightly squashed intact ganglia; right-hand panels show tissue sections cut from the same ganglion in each case. (d) Two ganglionic sections stained by means of in situ hybridization for major LAT. (a) Left CIII from infected mouse that had been treated with VACV from day 1 to day 9, inclusive. The ganglion was explanted 11 days p.i. and shows a group of 36 strongly positive neurons expressing β-gal (arrow). Magnification × 75. The right panel shows a 10 µm section of part of the same ganglion where a group of strongly positive cells is clearly visible (white arrow), but further positive neurons at the centre left (arrow) were also visible under the microscope and a total of 20 positive neurons were counted in the complete section. Magnification × 75. (b) Left CIII from an infected, untreated mouse taken 1–5 months p.i. The ganglion contains one focus of β-gal positive neurons (arrow), which contained 13 positive cells. Magnification × 30. In the section from this ganglion, shown in the right panel, 10 positive neurons were counted. Magnification × 150. (c) Left CIII from an infected, untreated mouse taken at 10 months p.i. In the whole mount, 33 positive neurons were counted. Magnification × 30. In the 10 µm section (right panel), 19 positive neurons were recorded in the entire section. Magnification × 150. (d) Left CIII taken at 10 months p.i. and tested by in situ hybridization. The left panel shows a 5 µm section from an uninfected mouse stained for the presence of major LAT. No signal was detected in this section. Magnification × 75. The right panel shows a 5 µm section from an infected, untreated mouse containing 26 positive neurons (example shown by the arrow) that have signal exclusively in their nuclei. Magnification × 75.
including both left and right TG and the contralateral CIII, nor was the time of first detection of positive cells in any ganglion delayed by chemotherapy.

The TG showed the largest number of infected neurons during the acute phase, with or without treatment. The observed predominance of positive neurons in ganglia that are not directly innervated by the infection site is consistent with the previous publications of Ecob-Prince et al. (1993) and Simmons et al. (1992). They reported that the secondary sites for latency (i.e. those not directly innervated by the inoculation site) contained larger numbers of latently infected cells.

Our hypothesis to explain the failure of the antiviral compounds to prevent the spread of infection in the nervous system is that there were occasions during the treatment period when drug levels were sub-inhibitory and allowed replication to proceed, at least transiently, in some ganglionic neurons, such that axonal and trans-synaptic spread of infection was able to continue (Ecob-Prince et al., 1993). This may have resulted from uneven consumption of compound over the 24 h period (we have reported previously that mice consume most water during the night; Field & Thackray, 1995). However, in our experience, providing compound *ad lib* is superior to twice-daily oral gavage on a strictly 12 h schedule (Field & Thackray, 1995). We believe, therefore, that it is unlikely that

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**Fig. 5.** Detection of latency at 10 months p.i. by using three different techniques. (a) Mean numbers of β-gal-positive neurons per section in individual ganglia. Data are plotted on the same scale as Fig. 3 for direct comparison. (b) Mean numbers of LAT-positive neurons per section as above. Data are plotted on the same scale as Fig. 3 for direct comparison with the number of blue cells in (a) above. (c) Infectious virus titres obtained from individual ganglia following explant co-cultivation for 5 days. Empty boxes indicate negative results.
constant exposure of the target cells at or above the inhibitory concentration for the compounds can be achieved by using conventional methods for supplying drug to the animal.

Previously, we have reported a transient recurrence of infectious virus in ganglia and brain-stems of mice tested following the withdrawal of VACV (but not FCV) after a period of continuous therapy (Thackray & Field, 1996a, b, 1997, 2000a). Here, we observed expression of β-gal in ipsilateral TG and CIII neurons of 8/10 mice tested on day 11, which was 2 days after therapy was discontinued and 3 days after reporter-gene expression had fallen to below the level of detection in the ganglia of surviving mice (with or without treatment). No observations were made immediately after day 11 in the present experiment, but extensive work with different models has shown that the recurrence of infectious HSV-1 (as evidenced by infectious virus) is transient. This occurred with higher doses of VACV and did not occur with sub-optimal doses of FCV (Thackray & Field, 2000b). Previously, we followed the infection with daily observations for infectious virus for several weeks and saw no further evidence of virus activity in HSV-2-infected mice treated with either of the two drugs (Thackray & Field, 2000b). Furthermore, we have observed in pilot experiments that there is little or no detectable β-gal expression during the period 2–3 weeks p.i. Fig. 4(a) shows a representative CIII whole mount and section sampled on day 11 p.i. It was interesting that no blue cells were detected in the right TG, although this tissue contained a larger number of positive cells during the acute infection than the left CIII, which showed recurrence. We speculate that recurrence occurs in a sub-population of neurons that enter the lytic cycle on removal of the inhibitor. The fact that this does not occur on withdrawal of FCV may reflect the longer intracellular half-life of PCV triphosphate, although this seems unlikely, since in other extensive studies we have sampled ganglia from FCV-treated mice for up to 3 weeks after withdrawal of therapy, during which time no recurrences were observed (Thackray & Field, 2000a). It seems more likely, therefore, that the sub-population of infected cells involved has already undergone lysis during the acute period of virus infection in the untreated mice or in the presence of PCV. This could be related to the ability of PCV (in contrast to ACV) to induce apoptosis (Thust et al., 1998; Shaw et al., 1999).

We showed in the present study that ganglia from surviving mice were latently infected in all cases. The ganglia contained LAT-positive neurons (Figs 4d and 5b). We also observed some β-gal expression in a small number of neurons in mice from all three treatment groups (Fig. 4b–c and 5a). Although the numbers were small, there was a trend towards the highest β-gal expression among the group of mice that had been treated with VACV, and this was consistent with

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<th>Table 2. Detection of LAT-positive and β-gal-positive neurons at late times (6 weeks and 10 months) after infection and therapy with FCV or VACV</th>
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<td><strong>Ganglion</strong></td>
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<td><strong>Treatment</strong></td>
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<td>Mock-infected</td>
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Statistically significant differences are indicated as follows: between treated groups and infected, untreated controls, a, *P < 0.001; b, *P < 0.01; c, *P < 0.05; between FCV and VACV treatments, d, *P < 0.001; e, *P < 0.01; f, *P < 0.05.
the pattern of LAT expression (Fig. 5). The continued sporadic expression of β-gal at late times after inoculation with this mutant has also been reported by Lachmann et al. (1999). The latent foci in the treated mice may have been established before the onset of therapy at 24 h p.i.; however, we have shown in a recent study (Field & Thackray, 2000) that even commencing therapy 1 day before virus inoculation was unable to prevent the establishment of latently infected neurons as assessed by reporter gene or LAT expression.

Using the explant co-cultivation test for latency, all ganglia from treated mice were negative for infectious virus, and this confirms previous results: on numerous occasions, the ganglia from mice treated from 1 day p.i. or earlier have not yielded infectious virus by this test, despite the presence of LAT-positive neurons. The ganglia from control, untreated mice were positive for this test with the exception of the left TG at 10 months. This was an unexpected result and is not consistent with previous studies that used the ear pinna infection model. Furthermore, 4/5 left TG sampled at 5–5 months were positive for reactivation by means of co-cultivation, albeit with relatively low levels of infectious virus in the assay. However, we note that the left TG had the highest level of LAT-positive cells (both with and without treatment), and this may be important. We have previously observed no correlation between the number of LAT-positive neurons present in ganglia and the ability to reactivate by means of explant culture (Thackray & Field, 2000b). Others have reported that there is no clear relationship between the presence of LAT expression and the ability to reactivate. For example, Ecob-Prince & Hassan (1994), using dual labelling techniques for LAT and a β-gal reporter gene, showed that at least a proportion of the cells that reactivate are neurons that appeared to be LAT-negative. We speculate that the neurons that are not directly innervated by the inoculation site, together with those from all ganglia from mice that received early antiviral therapy, contain fewer DNA copies per neuron, as shown for ACV therapy by Sawtell et al. (1998), and that this is a more important factor in determining the success of reactivation by means of explant culture.

We also observed that the right TG from mice that had received VACV therapy contained a significant excess of LAT-positive cells over controls. We have observed similar increased numbers of latently infected neurons in VACV-treated mice previously (e.g. Table 6 in Thackray & Field, 1998). Since this appears to be reproducible, it may reflect the sparing of infected neurons in the presence of ACV such that an increased number of latently infected neurons survive the primary infection. It is unlikely that the increase simply reflects the increased survival of mice that received therapy, since the excess was observed only for VACV and not with FCV therapy.

The general conclusion of this study is that, while neither VACV nor FCV can completely prevent the establishment of latency, both compounds do clearly affect the outcome of neural infection by HSV in vivo. Furthermore, the results of the present investigation confirm our earlier assertions that these two antiviral compounds are subtly different in how they interact with HSV-infected neurons. This is consistent with the known biochemical differences that exist between these two similar guanosine nucleoside analogues.

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References


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