Sparing of the Ipsilateral Retina After Anterior Chamber Inoculation of HSV-1: Requirement for Either CD4⁺ or CD8⁺ T Cells

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Purpose. To determine whether CD4⁺ T cells, CD8⁺ T cells, or both CD4⁺ and CD8⁺ T cells are required for preservation of the ipsilateral retina after uniconular anterior chamber inoculation of herpes simplex virus type 1 (HSV-1).

Methods. Adult-thymectomized BALB/c mice were T cell depleted by administration of anti-CD4 monoclonal antibody (mAb), anti-CD8 mAb, or anti-CD4 mAb and anti-CD8 mAb together. Control mice were thymectomized but were not T cell depleted. HSV-1 (KOS) was inoculated in one anterior chamber. At intervals after inoculation, the injected eyes were examined histopathologically or homogenized to determine the kinetics of infectious virus recovery. Additional groups of in vivo depleted mice were injected with wild type KOS and RH116 (a mutant of KOS containing the Escherichia coli β-galactosidase gene) to determine whether viral genes were expressed in the retina in any of the mice.

Results. In the inoculated eyes of mice depleted of both CD4⁺ and CD8⁺ T cells, there was a significantly higher incidence of acute destructive retinitis at days 9 and 14 postinoculation (PI), and the titer of virus recovered at day 14 PI was significantly higher. Viral gene expression in the retina and the optic nerve was observed after day 7 PI only in the group of mice depleted of both CD4⁺ and CD8⁺ cells. In contrast, acute destructive retinitis was not observed in nondepleted mice or in mice depleted of either CD4⁺ or CD8⁺ T cells alone, and virus recovery was not significantly different among these three groups of mice. No virus-infected cells were observed in the optic nerve or the sensory retina of nondepleted mice, of mice depleted of only CD4⁺ cells, or of mice depleted of only CD8⁺ cells.

Conclusion. The results of these studies suggest that either CD4⁺ or CD8⁺ T cells can spare the retina of the injected eye after uniconular anterior chamber inoculation of HSV-1. Because virus appeared after day 7 PI in the ipsilateral optic nerve and retina only in mice depleted of both CD4⁺ and CD8⁺ T cells, these results suggest that spread of virus to the ipsilateral retina occurs via the optic nerve and that either CD4⁺ or CD8⁺ T cells can prevent spread of virus to the inoculated eye resulting in sparing of the ipsilateral retina. Invest Ophthalmol Vis Sci. 1994;35:3251-3259.

Inoculation of herpes simplex virus type 1 (HSV-1 [KOS]) into euthymic BALB/c mice via the anterior chamber route induces acute retinal necrosis in the uninoculated contralateral eye within 2 weeks of inoculation, whereas the ipsilateral retina is morphologically spared.¹ In contrast, inoculation of HSV-1 into one anterior chamber of athymic BALB/c (nu/nu) mice or euthymic mice BALB/c mice in which T cells have been depleted results in retinitis in the injected eye of a majority of the mice by day 14 PI.²-⁴ Together, these latter studies support a role for T cells in preservation of the retina of the injected eye, although the exact mechanism by which T cells participate in sparing of the ipsilateral retina is unknown.⁵

Recent studies in euthymic mice have elucidated the pathway by which virus gains access to the retina of the uninoculated eye. Tracing studies in which wild type HSV-1 (KOS strain) and RH116, a mutant of
KOS containing the Escherichia coli β-galactosidase (β-gal) gene under control of an early gene promoter, were coinjected into one eye of a BALB/c mouse revealed that virus spread from the injected eye through the central nervous system to the optic nerve and retina of the uninoculated eye by synaptically related neurons. Sequentially, the route (and timing) of virus spread from the injected eye to the retina of the un.injected eye is as follows: iris and ciliary body of the ipsilateral (injected) eye (day 1 PI); ipsilateral ciliary ganglion (day 2 PI); ipsilateral Edinger–Westphal nucleus and nucleus of the ipsilateral oculomotor nerve (day 3 PI); ipsilateral sylvian optic nerve and retina in euthymic mice. When taken together with the previous studies demonstrating that lack of T cells correlates with development of retinitis in both eyes, the tracing studies support the idea that sparing of the ipsilateral retina is a T cell-dependent process and is due to the inability of the virus to spread from the contralateral SCN to the ipsilateral optic nerve and/or retina in non-T cell-depleted mice. To determine whether both CD4+ and CD8+ T cells are required for sparing of the ipsilateral retina, we performed experiments in which BALB/c mice were depleted of CD4+ T cells only, CD8+ T cells only, or both CD4+ and CD8+ T cells and injected in the anterior chamber of one eye with HSV-1. The incidence of retinitis in the injected eye was assessed histopathologically, and the titer of virus in the injected eye was determined by plaque assay. In addition, T cell-depleted and -nondepleted control mice were coinjected with KOS and RH116 to correlate the presence of virus in the optic nerve and retina of the injected eye with development of retinitis.

METHODS

Animals

Female inbred euthymic BALB/c mice (4 to 5 weeks old) and male outbred athymic mice (5 to 6 weeks old) were purchased from Taconic, Inc. (Germantown, NY) and maintained in our animal facility before and during the experiments in accordance with the recommendations of the National Institutes of Health Guide for the Care and Use of Laboratory Animals. All animals were maintained on a 12-hour light cycle alternating with a 12-hour dark cycle. All animal treatments in this study conformed to the ARVO Resolution on the Use of Animals in Research. Sodium pentobarbital (0.65 mg/10 g body weight) was used as the anesthetic agent for all intraocular injections, thymectomies, and clinical observations.

Virus

The KOS strain of HSV-1 and RH116, a thymidine kinase-negative mutant of KOS containing the E. coli β-gal gene, were used in these experiments. Stocks of both strains of HSV-1 were prepared as described previously. The titer of each stock was determined by plaque assay and was 2.5 × 10^8 plaque-forming units (PFU)/ml for wild type KOS and 3.5 × 10^8 PFU/ml for RH116.

Monoclonal Antibodies

The hybridomas GK1.5 and 2.43 (American Type Culture Collection, Rockville, MD) were used to obtain rat anti-mouse L3T4 (CD4) mAb and rat anti-mouse Lyt2 (CD8) mAb, respectively. These monoclonal antibodies were obtained in ascites fluid by propagation of the hybridoma cells in the peritoneal cavity of outbred, pristane-primed athymic male mice. The concentration of each mAb was determined by enzyme-linked immunosorbent assay and was: anti-CD4 mAb, 7.0 mg/ml; anti-CD8 mAb, 3.0 mg/ml. Flow cytometry was used to determine the in vivo depletion efficiency of each monoclonal antibody. On day 14 PI, the spleen cells from thymectomized mice that had been injected intravenously with 0.1 ml of either antibody on day -2, 0, 6, and 11 PI and injected in the anterior chamber with KOS on day 0 were collected, stained with the appropriate fluorescein-isothiocyanate-conjugated rat anti-mouse antibody, and analyzed by flow cytometry. The average percentage of CD4+ T cells in the spleen of a mouse treated with anti-CD4 mAb was 0.86% and that of CD8+ T cells in a mouse treated with anti-CD8 mAb was 0.51%. The percentages of these two T cell subsets in a control mouse treated with phosphate-buffered saline (PBS) were: CD4+ T cells, 19.6%; CD8+ T cells, 10.7%.

EXPERIMENTAL DESIGN

All mice were thymectomized at least 2 weeks before injection of virus into the anterior chamber. Thymectomy does not affect development of retinitis in the uninoculated eye of otherwise normal BALB/c mice after anterior chamber inoculation of HSV-1 but does allow for more complete and long-lasting depletion of CD4+ and CD8+ T cells. This study consisted of three experiments.

Experiment 1

Histopathologic examination was used to evaluate the extent of retinitis in the injected eye of mice after anterior chamber inoculation of HSV-1. Anti-CD4 and/or
anti-CD8 mAb(s) or PBS were intravenously adminis-
tered to the mice at day –2, 0, 6, and 11 PI. All mice
were inoculated with $2 \times 10^4$ PFU of HSV-1 (KOS) in
one anterior chamber on day 0. Mice were examined
clinically for retinitis in the uninoculated eye as de-
scribed previously,$^{14}$ and only mice with retinitis in the
contrateral eye were sacrificed at days 9 and 14 PI.
Both eyes were removed, fixed in buffered formalin,
sectioned, stained with hematoxylin and eosin, and ex-
amined microscopically. Significant differences be-
tween treatment groups were determined by chi-
square analysis.

**Experiment 2**

To determine whether development of ipsilateral reti-
nitis in T cell-depleted mice correlated with recovery
of virus in the injected eye, the kinetics of virus recov-
ery in the injected eye was determined. As described
for experiment 1, thymectomized mice were treated
with anti-CD4 and/or anti-CD8 mAb(s) or PBS and
inoculated with $2 \times 10^4$ PFU of HSV-1 on day 0. Four
or five mice from each treatment group were sacri-
ficed at days 1, 3, 5, 7, 9, 10, and 14 PI. The ipsilateral
eyes were removed and homogenized in serum-free
tissue culture medium, and the titer of infectious virus
was determined in duplicate plaque assays on mono-
layer cultures of Vero cells. All mice sacrificed on days
9, 10, and 14 PI had clinical evidence of retinitis in the
uninoculated eye. The Kruskal–Wallis test was used to
determine the significance of the virus recovery results
among the four independent treatment groups. When
the Kruskal–Wallis test demonstrated significant dif-
ference, the Bonferroni-adjusted Mann–Whitney tests
were used to assess significant differences between
two treatment groups.$^{15}$

**Experiment 3**

To investigate virus replication and location in the
eyes, mice were thymectomized 2 weeks before inocu-
lation, followed by mAb(s) or PBS treatment at day –2,
0, and 6 PI. All mice were inoculated with a mixture
containing $2 \times 10^4$ PFU of KOS and $2 \times 10^5$ PFU of
RH116 in 2 µl. Replication of wild type KOS comple-
ments the thymidine kinase deficiency of RH116 and
allows the mutant virus to replicate and spread
through nervous tissue.$^{7,16}$ At days 3, 5, 7, and 9 PI,
three to five mice were sacrificed, and both eyes were
removed, embedded in OCT compound (Miles, Na-
TABLE 1. Frequency of Retinitis in the Inoculated Eye

<table>
<thead>
<tr>
<th>mAb Treatment</th>
<th>Day 9 PI</th>
<th>Day 14 PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>αCD4 + αCD8</td>
<td>8/10*</td>
<td>9/10*</td>
</tr>
<tr>
<td>αCD4</td>
<td>2/10</td>
<td>0/10</td>
</tr>
<tr>
<td>αCD8</td>
<td>1/10</td>
<td>1/10</td>
</tr>
<tr>
<td>PBS only</td>
<td>1/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>

* Significantly different than PBS-treated control, $P < 0.05$ (chi-square analysis).

RESULTS

Histopathologic Findings in the Injected Eye (Experiment 1)

Destructive retinitis characterized by disorganization of the sensory retina, inflammatory cell infiltration, and cytopathic effects characteristic of HSV-infected cells was observed in the inoculated eye of 8 of 10 mice at day 9 PI and in 9 of 10 mice at day 14 PI in the group depleted of both CD4+ and CD8+ T cells (Fig. 1A, Table 1). In contrast, only 2 of 10 mice (day 9 PI) and 0 of 10 mice (day 14 PI) in the CD4-depleted group and 1 of 10 mice (day 9 PI and day 14 PI) in the PBS-treated control group had evidence of acute retinitis. Irrespective of the time after inoculation, none of the 20 mice in the CD8-depleted group developed acute retinitis. In the CD4-depleted group, the CD8-depleted group, and the PBS-treated group, inflammatory cells were observed in the vitreous cavity, and there were occasional folds in the retina as have been described previously in the inoculated eye, but the architecture of the retina was maintained (Figs. 1B to 1D).

Recovery of Virus From the Injected Eye (Experiment 2)

Before day 10 PI, there was no significant difference in the titer of infectious virus recovered from the injected eye after anterior chamber inoculation of HSV-1. Each point represents the median titer of virus recovered from four or five mice in each group at each time point. □□ CD4- and CD8-depleted, ▲▲ CD4-depleted, ▼▼ CD8 depleted, •• nondepleted. *Significantly different from PBS-treated control mice by Bonferroni-adjusted Mann-Whitney test, $P < 0.02$. 

![Figure 2](image-url) Viral recovery from the injected eye after anterior chamber inoculation of HSV-1. Each point represents the median titer of virus recovered from four or five mice in each group at each time point. □□ CD4- and CD8-depleted, ▲▲ CD4-depleted, ▼▼ CD8 depleted, •• nondepleted. *Significantly different from PBS-treated control mice by Bonferroni-adjusted Mann-Whitney test, $P < 0.02$.

![Figure 3](image-url) (top set) Photomicrographs illustrating β-gal staining in ciliary body (arrowhead) of the injected eye of a CD4- and CD8-depleted mouse (A) and of a nondepleted mouse (B) 5 days after inoculation of wild type KOS and RH116 into the anterior chamber. Note the lack of β-gal staining in the retina. Although only results from the CD4- and CD8-depleted group and the nondepleted group are shown, the pattern of β-gal staining in mice depleted of only CD4+ T cells or CD8+ T cells was identical. Original magnification ×122.

![Figure 4](image-url) (bottom set) Photomicrographs illustrating β-gal staining in the optic nerve (A) and retina (B) of the injected eye of a CD4- and CD8-depleted mouse 7 days after inoculation of wild type KOS and RH116 into the anterior chamber. β-gal staining was not observed in the optic nerve and retina of CD4-depleted mice (C, D), CD8-depleted mice (E, F), and nondepleted mice (G, H). Original magnification ×122.
ject ed eye of mice in any of the four treatment groups (Fig. 2). At day 10 PI, the titer of virus was greater than 3 log$_{10}$ PFU/ml in CD4- and CD8-depleted mice, and at day 14 PI, the amount of virus recovered from the injected eye of CD4+ and CD8-depleted mice was significantly higher ($P < 0.02$) than that recovered from PBS-treated control mice. In CD4-depleted mice, CD8-depleted mice, and PBS-treated mice, the titer of virus in the injected eye decreased after day 10 PI, and virus was cleared from the injected eye by day 14 PI. The titer of virus recovered from the injected eye of CD4-depleted mice or CD8-depleted mice were not significantly different from the titer of virus recovered from PBS-treated control mice at any time after infection.

**Staining for β-Galactosidase (Experiment 3)**

Studies were performed to determine whether development of acute destructive retinitis in the inoculated eye correlated with detection of virus in the sensory retina. Up to and including day 5 PI, there was no difference in β-gal staining among the four treatment groups. Although the anterior segment of the inoculated eye of all mice in all groups was severely inflamed and the iris and ciliary body contained many β-gal positive virus-infected cells (Figs. 3A and 3B), the optic nerve (not shown) and the sensory retina were virus negative. Occasionally, a few cells in the peripheral retina were β-gal positive without evidence of accompanying destructive retinitis. The frequency of detection of virus-infected cells in the peripheral retina in any of the three T cell-depleted groups was not significantly different than the frequency of such staining in the PBS-treated control group (data not shown).

By day 7 PI, the amount of β-gal staining in the anterior segment had decreased in all treatment groups. At this time, both the optic nerve and the sensory retina of the injected eye in mice depleted of both CD4+ and CD8+ T cells contained many β-gal positive cells (Figs. 4A and 4B). β-gal positive cells were not observed in the optic nerve and central retina of CD4-depleted mice (Figs. 4C and 4D), CD8-depleted mice (Figs. 4E and 4F), or PBS-treated control mice (Fig. 4G and 4H). One mouse in the CD4-depleted group had a few β-gal positive cells in the peripheral retina only (see Table 2). On day 9 PI, acute retinitis was observed only in CD4- and CD8-depleted mice, and the sensory retina of these mice contained many β-gal positive cells. The optic nerve and sensory retina of CD4-depleted mice, CD8-depleted mice, and PBS-treated control mice were negative for β-gal staining.

The staining results from days 7 and 9 PI are summarized in Table 2; β-gal positive cells were observed in the sensory retina of all mice (5/5) depleted of both CD4+ and CD8+ T cells. A small number of β-gal positive cells were observed in the peripheral retina of 1 of 5 mice in the CD4-depleted group; however, the optic nerve of the injected eye of this mouse was virus negative. Virus-infected β-gal positive cells were not observed in the sensory retina and optic nerve in any of the CD8-depleted mice or in any of the PBS-treated control mice.

**DISCUSSION**

After uniocular anterior chamber inoculation of the KOS strain of HSV-1 in euthymic BALB/c mice, acute retinal necrosis is observed in the uninoculated contralateral eye, whereas the retina of the ipsilateral eye is spared.1 In contrast, bilateral retinitis is observed in athymic BALB/c mice,2-4 and virus spreads to the retina of both the injected and the uninjected eye.7,17,18 Tracing studies have demonstrated that spread of virus from the injected eye to the central nervous system in euthymic and athymic mice occurs via the same neuronal pathways,7,18 but in euthymic mice, virus does not spread to the optic nerve and retina of the injected eye from the contralateral SCN.7 In athymic mice, both SCN become virus positive by day 5 PI and both optic nerves are virus positive by day 7 PI.18 Comparison of the results from euthymic and athymic tracing studies suggest that an intact T cell immune system correlates with prevention of virus spread from the contralateral SCN to the optic nerve and retina of the injected eye.

In these studies, we report the effect of depletion of CD4+, CD8+, or both CD4+ and CD8+ T cells on development of retinitis in the injected eye. CD4-depleted mice, CD8-depleted mice, and PBS-treated mice did not develop acute destructive retinitis. Only mice depleted of both CD4+ and CD8+ T cells developed retinitis. The frequency of such staining in the PBS-treated control mice was significantly higher than that observed in mice depleted of both CD4+ and CD8+ T cells ($P < 0.02$). This is consistent with previous work showing that CD8+ T cells are required for the development of bilateral retinitis following a single anterior chamber inoculation of KOS strain of HSV-1 in euthymic mice.12,13 The development of retinitis in mice depleted of both CD4+ and CD8+ T cells suggested that, like CD8+ T cells, CD4+ T cells are also required for the development of bilateral retinitis following a single anterior chamber inoculation of KOS strain of HSV-1 in euthymic mice.12,13 This result is consistent with previous work showing that CD4+ T cells are required for the development of bilateral retinitis following a single anterior chamber inoculation of KOS strain of HSV-1 in athymic mice.2-4 The development of retinitis in mice depleted of both CD4+ and CD8+ T cells suggested that, like CD8+ T cells, CD4+ T cells are also required for the development of bilateral retinitis following a single anterior chamber inoculation of KOS strain of HSV-1 in euthymic mice.12,13 This result is consistent with previous work showing that CD4+ T cells are required for the development of bilateral retinitis following a single anterior chamber inoculation of KOS strain of HSV-1 in athymic mice.2-4

**TABLE 2. Summary of β-Galactosidase Staining in the Injected Eye**

<table>
<thead>
<tr>
<th>mAb Treatment</th>
<th>Number of Mice†</th>
<th>Retina Positive</th>
<th>Optic Nerve Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>αCD4 + αCD8</td>
<td>5</td>
<td>5†</td>
<td>5†</td>
</tr>
<tr>
<td>αCD4</td>
<td>5</td>
<td>1§</td>
<td>0</td>
</tr>
<tr>
<td>αCD8</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PBS only</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

† Combined staining results from days 7 and 9 postinoculation.
§ The contralateral retinas of all mice in each group were β-gal positive.
Significantly different than PBS-treated control, $P < 0.02$ (chi-square analysis). $β$-gal staining only in the peripheral retina.
Sparing of the Ipsilateral Retina

op ed acute retinitis in the injected eye, which correlated with a significantly higher titer of virus at day 14 PI. The results suggest that either CD4+ or CD8+ T cells prevent virus spread to or replication in the retina of the injected eye, which, in turn, prevents development of retinitis in this eye.

Although depletion of both CD4+ and CD8+ T cells correlated with increased virus replication and development of retinitis in the inoculated eye, by themselves these results do not provide information about the route by which HSV-1 reached the retina of the injected eye in this group of mice. The two most likely routes are by direct spread from the anterior segment and by traveling to the central nervous system and then returning to the eye via the optic nerve. The finding that there was no β-gal staining in the ipsilateral retina at days 3 and 5 PI in any of the mice while the anterior segment was strongly positive favors the second route of spread. Additional support for the second route of spread is provided by the result that the virus infected the ipsilateral retina in mice depleted of both CD4+ and CD8+ T cells beginning at day 7 PI. Because all mice in these experiments also had β-gal staining in the retina of the contralateral eye beginning at day 7 PI (confirming virus spread to the central nervous system), the finding that both the ipsilateral optic nerve and the retina were positive at this time in mice depleted of CD4+ and CD8+ T cells suggests that virus spread through the central nervous system to the optic nerve and retina. Because HSV-1 did not spread from the anterior to the posterior segment in any of the T cell-depleted mice, prevention of anterior-to-posterior spread of the virus cannot be T cell dependent. It is unclear why virus cannot spread from the infected anterior segment of the injected eye to the retina. The anatomy of the mouse eye may prevent direct anterior-to-posterior spread of HSV-1 or, because previous studies have demonstrated that the ipsilateral retina is functionally damaged19 and there are inflammatory cells in the vitreous of the injected eye after anterior chamber inoculation,2 a T cell independent mechanism such as secretion of α- and β-interferon from infiltrating inflammatory cells may prevent direct anterior-to-posterior spread of HSV-1.

Because the ipsilateral optic nerve and the retina of nondepleted mice and of mice depleted of either CD4+ or CD8+ cells alone remained virus negative throughout the infection, it appears that T cells or their products prevent virus spread by acting at a site proximal to entry of virus into the ipsilateral optic nerve. In euthymic mice, development of acute retinitis correlates with spread of virus to the contralateral retina from the ipsilateral SCN by day 7 PI;2 therefore, the most likely site at which T cells exert their effect to protect the retina of the injected eye would be near the contralateral SCN or at the level of the interconnec-

tions between the ipsilateral and the contralateral SCN.

Little is known about how T cells or their products limit virus spread, replication in the central nervous system after anterior chamber inoculation of HSV-1, or both. T lymphocytes are observed in the trigeminal ganglion during primary corneal infection with HSV-1,20,21 but the role of these T cells in limiting virus infection in this ganglion was not addressed. Both CD4+ and CD8+ T cells have been observed in the brains of mice with HSV-1 encephalitis.22 T cells have also been seen in the brains of mice infected with mouse hepatitis virus strain JHM.23 In these mice, CD4+ T cells function as helpers, and virus-specific, class I restricted CD8+ T cells mediate clearance of virus from the central nervous system.23 In mice chronically infected with Theler’s murine encephalomyelitis virus, demyelination in the central nervous system appears to result from lysis of virus-infected glial cells by virus-specific CD8+ T cells.24 Aggregate evidence from inflammatory demyelinating disorders suggests that cytokines such as interleukin-1, interferon-γ, and tumor necrosis factor-α play a role in inflammatory and immune reactions in both the central and peripheral nervous system.25 Similar mediators may also play a role in influencing virus spread, replication in T cell-depleted after following anterior chamber inoculation of HSV-1, or both. In addition, because both CD4+ and CD8+ T cells can protect the retina of the injected eye from virus infection, it is possible that the mechanism by which each T cell subset protects might be different. For example, CD4+ cells might protect by elaboration of cytokine, by class II-restricted killing of virus-infected cells,26 or by allowing production of HSV-1-specific antibody. Although antibody that might contribute to protection (for example, by neutralizing virus at synapses) is made in CD8-depleted mice, it is unlikely that antibody contributes to protection in either CD4-depleted or CD4- and CD8-depleted mice because little, if any, virus-specific neutralizing antibody is produced in CD4-depleted mice infected with HSV-1.27 CD8+ cells might protect by class I restricted cytotoxic killing of virus-infected neurons and surrounding glial elements.

After anterior chamber inoculation of HSV-1, the T cell immune system appears to be both protective and destructive. As previously demonstrated, T cells, especially those of the CD4+ subset,11 are required for development of fulminant acute retinal necrosis in the uninoculated eye. However, as shown in these studies, T cells are also beneficial in that the presence of either CD4+ or CD8+ T cells correlates with sparing the retina of the injected eye from virus infection. The difference between the ability of CD4+ or CD8+ cells to protect the injected eye and the ability of CD4+ cells to produce fulminant retinal necrosis in the contralateral


18. Atherton SS, Vann VR. Immunologic control of neural spread of herpes simplex virus type 1 (HSV-1) following anterior chamber inoculation. In: Dermouchamps JP, Verougstraete C, Caspers-Velu L, Tassig-
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