Passive Transfer of Anti-Herpes Simplex Virus Type 2 Monoclonal and Polyclonal Antibodies Protect Against Herpes Simplex Virus Type 1-Induced but Not Herpes Simplex Virus Type 2-Induced Stromal Keratitis

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Purpose. To investigate whether passive transfer of antibodies to viral glycoproteins would protect against herpes simplex virus type 2-induced stromal keratitis.

Methods. Balb/c mice were infected on the scarified cornea with herpes simplex virus types 1 or 2 (HSV-1 and HSV-2, respectively), and monoclonal or polyclonal antibodies were administered intraperitoneally 24 hr later. Eyes were monitored for corneal opacity. Flow cytometry was used to examine the expression of glycoproteins on the surface of HSV-infected cells.

Results. Passive transfer of monoclonal antibodies to viral glycoproteins gB, gD, or gE or anti-HSV-2 hyperimmune serum were all highly effective (P < 0.005) at preventing blinding disease induced by HSV-1. In contrast, none of the antibody preparations could prevent stromal keratitis when the animals were challenged with various HSV-2 strains. However, antibody treatment could prevent the development of fatal encephalitis in the majority of HSV-2 infected hosts. Flow cytometry analysis revealed that gD and gB expression on the membranes of HSV-2 infected corneal epithelial cells isolated from excised corneas was substantially less (P < 0.005) than that detected on HSV-1 infected cells at both 24 and 48 hours postinfection. This antigenic difference was not due to the failure of HSV-2 to replicate in corneal epithelial cells in vivo.

Conclusions. Decreased levels of membrane glycoprotein antigen expression may be one factor contributing to the refractoriness of HSV-2-induced ocular disease to humoral immunotherapy. Invest Ophthalmol Vis Sci. 1993; 34:2460-2468.
response has not been shown to contribute to the immuneopathology. Instead, we and others have found that the timely administration of monoclonal antibody to selected viral glycoproteins is highly effective at preventing the development of blinding corneal disease.

Ten different glycoproteins have been identified on the virion surface and the plasma membrane of the infected host cell where they serve as targets of the immune response. Glycoproteins gB and gD are among the most immunogenic and constitute candidates for a subunit vaccine. The genes of HSV-1 and HSV-2 display substantial homology, and so the glycoproteins of the two serotypes share numerous cross-reactive epitopes.

HSV-2 infection of the murine cornea also can induce stromal keratitis, which is clinically indistinguishable from that induced by HSV-1. However, it is not known whether antibody immunotherapy can prevent corneal disease induced by this serotype. To investigate this question experiments were conducted with a number of monoclonal antibodies to HSV glycoproteins, and also with hyperimmune serum. In contrast to our results with HSV-1, antibody failed to protect when HSV-2 was used as the challenge virus. Studies investigating possible reasons for the inability of antibody to promote resistance against HSV-2 corneal infection are described.

MATERIALS AND METHODS

Animals

Three- to four-week-old female Balb/c mice were purchased from Charles River Breeding Laboratories (Wilmington) MA. The animals were treated and housed in accordance with the ARVO Resolution on the Use of Animals in Research.

Viruses

HSV-1(17) and HSV-2(186) were originally obtained from Bernard Roizman (University of Chicago, Chicago, IL). HSV-1(RE) was originally obtained from Ysolina Centifanto-Fitzgerald (Tulane University, New Orleans, LA), and HSV-2(333) was obtained from Fred Rapp (Hershey Medical Center, Hershey, PA). HSV-2(Av) was obtained from Richard J. Whitley (University of Alabama, Birmingham, AL). After being plaque-purified, virus stocks were grown in Vero cells and titrated by a plaque assay as previously described.

Antibodies

The anti-HSV glycoprotein D (gD) monoclonal antibody (mAb) 8D2 was prepared and purified as previously described. Anti-gD mAbs III-114-4 and III-174-1.2 raised via immunization with HSV-2(G) were donated by Patricia G. Spear (Northwestern University Medical School, Chicago, IL). III-114-4 is of the IgG2b isotype whereas 8D2 and III-174-1.2 are IgG2a as determined by radial immunodiffusion (RID). Anti-gB (F3AB) and anti-gE (H7E), both IgG2a antibodies, were prepared as described by Rector et al. Anti-HSV-2 hyperimmune mouse sera was raised via immunization with HSV-2(333). The dosages of antibody given were 200 µg of III-174-1.2 or III-114-4, a 1:2 dilution of α-HSV-2 serum, and 2000 µg of F3AB and 500 µg of H7E. Antibodies were passively transferred by inoculating a 0.2 ml volume intraperitoneally.

Corneal Infection

Mice were anesthetized with 0.2 ml of sodium pentobarbital at a concentration of 5 mg/ml, and one eye was scarified by three twists of a 2 mm corneal trephine. A 2 µl volume containing the desired challenge dose of HSV was dropped onto the scarified cornea and rubbed in with the eyelids. Eye scores were read weekly using a dissecting biomicroscope with a fiber optic light source. Corneal opacity was graded on a scale of 0 to +5 as described by Metcalf et al. The person scoring the eyes was ignorant of the treatment the mice received.

Isolation of Mouse Corneal Epithelial Cells

Corneas from HSV infected and uninfected mice were excised and incubated in 5 mmol/l ethylenediaminetetraacetic acid (EDTA) for 20 min in 5% carbon dioxide at 37°C. Using forceps the epithelial sheets were lifted off the stromal–endothelial portions of the cornea and incubated with 0.1% trypsin for 5 min in 5% carbon dioxide at 37°C. The epithelial sheets were then passed repeatedly through a 25-g needle to dissociate the cells. The cells were washed twice with buffer (phosphate buffered saline with 2% fetal bovine serum and 0.1% sodium azide) before being used in further tests. Fourteen to twenty epithelial sheets were pooled for each sample. Comparable numbers of epithelial cells were recovered from HSV-1- and HSV-2-infected corneas, and the percentage of cells recovered that were viable was > 80% for both serotypes.

Fluorescence Activated Cell Sorter

The reactivity of mAb with cultured mouse corneal fibroblasts or isolated corneal epithelial cells was analyzed by fluorescence activated cell sorter (FACS). Corneal fibroblasts were cultured as previously described. The cells (2×10^6) were seeded into 75 cm² flasks and allowed to adhere overnight. The monolayers were infected with HSV-1(RE) or HSV-2(333) at a multiplicity of infection of 3. After 45 min adsorption, fresh medium was added and the cells were incubated for various intervals. At the desired times postin-
fection the cells were harvested with trypsin/EDTA (0.25% trypsin, 1 mmol/l EDTA-4Na, Gibco BRL, Grand Island, NY).

The mouse corneal fibroblasts or epithelial cells were prepared for FACS analysis according to the protocol used by Jennings et al.29 The cells were washed twice with FACS buffer (phosphate buffered saline with 2% fetal bovine serum and 0.1% sodium azide) and underwent centrifugation. The resulting pellet was suspended at 1×10⁶ viable cells/ml and 100 μl was separated into aliquot portions into wells of a 96-well plate. The cells were centrifugated and the supernatant was removed. The pellet was suspended with 50 μl of primary antibody and incubated for 30 min at 4°C. After centrifugation the supernatant was removed and the resulting pellet was suspended in 50 μl of secondary antibody and incubated for 30 min at 4°C. The secondary antibody was fluorescein isothiocyanate-conjugated goat anti-mouse affinity purified F(ab)₂ fragments (Cappell Research Products, Durham, NC). The cells were washed twice with FACS buffer and analyzed using an FACS 440 (Becton Dickinson, San Jose, CA). The mean fluorescence intensity (MFI) was calculated by using the formula:

$$\frac{\sum \text{(Number of cells in a channel) x (channel number)}}{\text{Total number of cells analyzed}}$$

The reported ΔMFI values represent the MFI of the test samples minus the MFI of the IgG2a controls.

### HSV Growth in Mouse Corneal Cells

Three to five corneas from mice infected with the desired concentration of HSV were excised at varying time points after infection, and the epithelial layers were separated from the stromal–endothelial layers as described earlier. After separation the samples from each cornea were frozen at −70°C. The samples were subsequently thawed, sonicated for 10–20 sec using a Sonic 300 Dismembrator (Arteck Systems Incorporated, Farmingdale, NY), and titrated for infectious virus by plaque assay on Vero cell monolayers.

The infectious virus titer of infected isolated corneal epithelial cells was also determined from aliquot portions of the same samples used by FACS analysis. The corneal epithelial cells were isolated as described above. After being washed twice with FACS buffer, 5×10⁴ cells per sample were dispersed into test tubes and frozen at −70°C. The samples were then thawed, sonicated, and assayed for infectious progeny on Vero cell monolayers.

### Statistical Analysis

The Mann-Whitney U test was used to determine significant differences in the corneal opacity scores between control and test groups. Student’s t test was used to compare the MFI values between HSV-1(RE) and HSV-2(333)-infected cells.

### RESULTS

#### 8D2 mAb Treatment Fails to Prevent HSV-2-Induced Stromal Keratitis

The mAb 8D2 recognizes a type common discontinuous epitope on gD and neutralizes HSV-2 strains

<table>
<thead>
<tr>
<th>Challenge Virus</th>
<th>Viral Challenge Dose (PFU/eye)</th>
<th>8D2 MAb Treatment</th>
<th>No. Survivors/Total</th>
<th>Survivor Mean Corneal Opacity Score (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1 (17)</td>
<td>2 × 10⁴</td>
<td></td>
<td>6/6</td>
<td>0 (&lt;0.025)</td>
</tr>
<tr>
<td></td>
<td>2 × 10⁴</td>
<td></td>
<td>3/6</td>
<td>3.7</td>
</tr>
<tr>
<td>HSV-1 (17)</td>
<td>4 × 10⁴</td>
<td></td>
<td>6/6</td>
<td>0 (0.005)</td>
</tr>
<tr>
<td>HSV-2 (186)</td>
<td>2 × 10⁴</td>
<td>+</td>
<td>6/6</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>2 × 10⁴</td>
<td>−</td>
<td>6/6</td>
<td>5.0</td>
</tr>
<tr>
<td>HSV-2 (186)</td>
<td>4 × 10⁴</td>
<td>+</td>
<td>6/6</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>4 × 10⁴</td>
<td>−</td>
<td>6/6</td>
<td>4.8</td>
</tr>
<tr>
<td>HSV-2 (AV)</td>
<td>4 × 10⁴</td>
<td>+</td>
<td>4/6</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>4 × 10⁴</td>
<td>−</td>
<td>0/6</td>
<td>0 (NS)</td>
</tr>
<tr>
<td>HSV-2 (333)</td>
<td>4 × 10⁴</td>
<td>+</td>
<td>7/7</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>4 × 10⁴</td>
<td>−</td>
<td>6/7</td>
<td>5.0</td>
</tr>
</tbody>
</table>

* Mice were infected on the trephined cornea with the indicated strain and challenge dose of HSV. Twenty-four hours after corneal infection, the animals were given MAb 8D2 (55 μg) or control IgG2a (55 μg) intraperitoneally. Survivors are defined as those living at the time corneal opacity scores were determined. Corneas were examined on days 4 or 28 post-infection. NS = not significant.
to the same high titer (10^3) as HSV-1 strains. Previous studies have shown that this purified antibody is strikingly effective at preventing or significantly reducing the incidence of HSV-1-induced stromal keratitis.\textsuperscript{12} We tested whether 8D2 would also protect mice challenged on the cornea with HSV-2. Table 1 shows that a dose of 55 \(\mu\)g/mouse, which provided excellent protection against HSV-1 strain 17 corneal infection, failed to protect animals infected with any of three different HSV-2 strains. Moreover, administering the antibody 30 min before HSV-2 corneal infection, or increasing the mAb dose to 110 \(\mu\)g/mouse, that is, tenfold higher than that shown to be effective against HSV-1\textsuperscript{12}, failed to provide protection against HSV-2 challenge (data not shown).

It was possible that the failure to protect against stromal keratitis was peculiar to mAb 8D2. Therefore, an additional five mAbs that were specific for type common continuous epitopes or other discontinuous epitopes on gD were tested. None proved to be efficacious although all five had previously been shown to protect against HSV-1 strain RE corneal challenge\textsuperscript{13} (data not shown).

**FIGURE 1.** Effect of mAb and hyperimmune serum therapy on HSV-induced stromal keratitis and encephalitis. Mice were infected on the trephined cornea with 4 \(\times\) 10^4 plaque-forming units of HSV-1 strain RE (Panels A, B, C) or HSV-2 strain 333 (Panels D, E, F). The desired antibody was given intraperitoneally 24 hr later. Controls received an equivalent amount of IgG2a or phosphate buffered saline. There were initially 6–9 mice in each group. The opacity scores were determined on day 21 or 28 postinfection. Parentheses indicate the number of survivors per total number challenged. *\(P < 0.005\), †α-gD mAb III-114-4, ‡α-gD mAb III-174-1.2.

**FIGURE 2.** Titers of HSV-1 and HSV-2 in corneal epithelial and stromal–endothelial layers. The right corneas were infected with 4 \(\times\) 10^4 plaque-forming units of HSV-1 strain 17 (●) or HSV-2 strain 333 (○) on day 0. At the indicated times after infection three to five corneas were excised. The epithelial layers were separated from the stromal-endothelial portions and each was titrated for infectious virus. Panel A (top) shows infectious virus titers of individual epithelial layers while Panel B (bottom) depicts the virus titers observed in the individual stromal–endothelial layers.

**Protection Studies with Other Monoclonal and Polyclonal Antibodies**

In the forgoing experiments all of the anti-gD mAbs tested had been produced in response to HSV-1 immunization. There are data that indicate that antibodies raised against HSV-2 may be more therapeutically active against HSV-2 than antibodies raised against HSV-1.\textsuperscript{30} Therefore, two anti-gD mAbs raised through immunization with HSV-2 were tested by passive transfer intraperitoneally 24 hr after infection. We found that antibodies III-114-4 and III-174-1.2, provided excellent protection against HSV-1 strain RE challenge (Figure 1A) but neither could protect against HSV-2 strain 333 (Figure 1D) ocular infection. Similarly, a polyclonal hyperimmune mouse serum raised against HSV-2 and tested at a 1:2 dilution was therapeutically effective against HSV-1 (Figure 1B) but not against HSV-2 (Figure 1E).

Additional protection studies were performed using type common mAbs to two other major glycopro-
tein antigens, gB and gE. Anti-gB and anti-gE were highly effective in protecting against HSV-1 challenge (Figure 1C) but failed to prevent corneal disease induced by HSV-2 infection (Figure 1F). Conversely, Figure 1 (Panels D and F) also shows that 79% (27/34) of the mAb-treated hosts survived HSV-2 infection whereas only 12% (2/17) of the virus-infected controls did so. Thus, mAbs to glycoproteins B, D, and E could provide significant ($P < 0.05$) protection against type 2-induced encephalitis.

**HSV-1 and HSV-2 Growth in Murine Corneas**

Studies were initiated to determine why antibody failed to protect against HSV-2 induced stromal keratitis. One possibility was that HSV-2 replicated to higher titer in ocular tissue than HSV-1 and thereby overwhelmed the therapeutic effect of antibody. To investigate this hypothesis virus titers in epithelial (Figure 2A) and stromal–endothelial (Figure 2B) layers of individual corneas were determined at various times post infection. Although HSV-1 replicated to slightly higher titers than HSV-2 the differences were not statistically significant at any time point for either corneal layer. By day 7 postinfection only residual amounts of HSV-1 and HSV-2 were detected. Thus, HSV-2 was not found to replicate more extensively or persist longer in ocular tissue than HSV-1.

**Glycoprotein Antigen Expression on HSV-Infected Cell Membranes**

Because antibody was not administered until 24 hr after corneal infection the target in vivo was expected to be cell-associated virus antigen rather than cell-free virus. Perhaps less glycoprotein antigen was being expressed on the surface of HSV-2 infected cells compared to that found on HSV-1-infected cells. To address this possibility FACS analysis was performed using III-174-1.2, an anti-gD mAb generated by HSV-2 immunization. We first compared the levels of gD found on mouse corneal fibroblasts that had been grown in culture and then infected with HSV-1 or HSV-2. Glycoprotein antigen was readily detected on the surface of HSV-1 infected cells at 8 and 13 hr postinfection. However, the results with HSV-2 were quite comparable to those found on HSV-1 infected cells. To address this possibility FACS analysis was performed using III-174-1.2, an anti-gD mAb generated by HSV-2 immunization. We first compared the levels of gD found on mouse corneal fibroblasts that had been grown in culture and then infected with HSV-1 or HSV-2. Glycoprotein antigen was readily detected on the surface of HSV-1 or HSV-2 infected cells at 8 and 13 hr postinfection.
different. In Figure 4 (Panels C and D), little or no gD antigen could be seen. These results were consistently obtained in six independent experiments.

Analogous studies were conducted to assess gB expression in vivo. Results representative of five independent experiments are shown in Figure 5. Although gB could be detected on HSV-2 infected cells (Figure 5C and D), the amount was consistently low and significantly less ($P < 0.005$) than that expressed on HSV-1-infected cells (Figure 5A and B).

### HSV-1 and HSV-2Titers in Isolated Corneal Epithelial Cells

It was possible that the reduced HSV-2 glycoprotein expression observed in vivo reflected reduced HSV-2 replication in the epithelial cells analyzed. Therefore, aliquot portions of the same preparations used for FACS analysis were titrated for infectious virus content. The results of two such experiments are shown in Figure 6. It is evident that HSV-2 could readily replicate in mouse corneal epithelial cells although the titers tended to be approximately threefold lower than those for HSV-1. Whether the slightly lower virus yield was sufficient to account for the reduced gB and gD antigen expression on the surface of HSV-2-infected cells is not clear.

**FIGURE 5.** Cell surface expression of gB on epithelial cells isolated from HSV-infected mouse corneas as analyzed by FACS. Mice were infected on the scarified cornea with $1 \times 10^6$ plaque-forming units of HSV-1 strain RE (Panels A and B) or HSV-2 strain 333 (Panels C and D). The corneal epithelial cells were isolated at the indicated times postinfection and stained with anti-gD mAb F3AB (—) or an IgG2a control Ig (—) followed by fluorescein isothiocyanate-conjugated goat anti-mouse affinity purified F(ab')2 fragments. The ΔMFI values are (A) 21, (B) 17, (C) 8, and (D) 7.

**DISCUSSION**

The major observation in this report is that passively transferred antibody failed to prevent stromal keratitis after HSV-2 corneal infection. This was the case regardless of whether the immunoglobulin transferred was anti-HSV-2 hyperimmune polyclonal serum or mAbs to gD, gB, or gE. Whether antibodies to other viral glycoproteins would be protective remains to be determined. However, it is striking that the same monoclonal and polyclonal antibody preparations that failed to protect against HSV-2 were highly effective in preventing corneal disease induced by HSV-1.

It is important to emphasize that not all tissues infected by HSV-2 were unresponsive to antibody therapy. We found that immunoglobulin treatment consistently protected the majority of the recipients against viral encephalitis that developed as a consequence of HSV-2 spread into the central nervous system. This latter observation agrees with previously published reports. Thus, antibody transferred before or after HSV-2 footpad challenge was found to protect mice against fatal central nervous system disease. In addition, mAbs to gD$^{33}$ as well as polyclonal HSV-2 specific antibodies$^{34}$ have been shown to prevent skin and retinal lesions resulting from HSV-2 subcutaneous infections.

McDermott et al$^{35}$ reported that mice given anti-gC or anti-gD mAbs were protected against HSV-2 footpad but not intravaginal challenge. These authors suggested that antibody ineffectiveness against the latter was attributable to a lack of transudation into vaginal secretions. However, Eis-Hübinger et al, found that antibody treatment readily protected mice inocu-
lated intravaginally with HSV-1. Thus, vaginal tissue may be a body site where antibody can protect against HSV-1 but not HSV-2 lethal infection. Collectively, our experiments in the cornea and those involving intravaginal infection suggest that the capacity of immunoglobulin to prevent disease is dependent on both the tissue infected and the infecting HSV serotype.

There are a number of potential explanations for the failure of antibody to prevent HSV-2 corneal disease. One possibility is that HSV-2 replicated more rapidly and to a higher titer in ocular tissue than HSV-1, thereby overwhelming the protective effect of antibody. We investigated this hypothesis and found that the two serotypes replicated to similar levels in corneal cells. In an earlier study in rabbits Stevens and Oh\(^{37}\) reported that HSV-2 titers in the eye were 100-fold lower than those of type 1. Thus, there is no evidence to support the theory that HSV-2 replicates more extensively in ocular tissue than HSV-1.

Stevens and Oh\(^{37}\) also noted that corneal inflammation in rabbits infected with HSV-2 strains was more severe than in animals infected with HSV-1 strains. In our work blepharitis appeared to be more intense in the HSV-2-infected mice (unpublished observation). Recent studies in our laboratory have shown that interleukin 1α can be detected in HSV-1 infected murine corneal buttons, and that effective mAb immunotherapy is accompanied by decreased production of this pro-inflammatory cytokine\(^{38}\). One can speculate that the inflammatory cytokine cascade induced following HSV-2 infection differs either quantitatively or qualitatively from that induced by HSV-1 infection, and thus was insensitive to putative antibody-mediated down-regulation. A comparative analysis of cytokine expression after HSV-1 and HSV-2 infection merits investigation.

Through FACS analysis we discovered a definite disparity in gD antigen expression between HSV-1 and HSV-2 infected cells after in vivo infection. Although gD was readily detected on epithelial cells isolated from HSV-1 infected corneas it was barely demonstrable on epithelial cells isolated from HSV-2 infected corneas. Moreover, surface gB was also more abundant on HSV-1 than HSV-2 infected cells. In contrast, the amount of surface gD was similar on cultured mouse corneal fibroblasts infected in vitro with HSV-1 or HSV-2. These results are compatible with the observations of Jennings et al.\(^{39}\) They reported that the kinetics and amount of glycoprotein antigen expressed on HSV-infected cells varied according to the host cell type. Reduced glycoprotein antigen expression on the surface of one target cell type but not another could conceivably explain why antibody treatment prevents HSV-2-induced central nervous system disease but not stromal keratitis. Likewise, a difference in glycoprotein expression could account for why antibody protects against HSV-1- but not HSV-2 induced corneal disease. Although we currently favor this explanation, our conclusions are strictly tentative because a causal relationship has not been established. To explain the dichotomy in corneal protection it will be important to develop an understanding of why antibody is effective against HSV-1 challenge. The failure to detect accelerated clearance of virus from ocular tissue of antibody-treated hosts\(^{38}\) suggests that conventional antibody protective mechanisms such as virus neutralization, or antibody-mediated lysis of infected cells, are not operative.

A multiplicity of factors in addition to the extent of virus replication appear to influence how much viral glycoprotein antigen will be expressed by infected cells. Gething et al.\(^{39}\) have shown that the correct folding of the influenza virus hemagglutinin is required for it to be transported from the endoplasmic reticulum to the cell surface. Similar conclusions were reached by de Silva et al.\(^{40}\) in studies on vesicular stomatitis virus G protein. Therefore, it is possible that HSV-2 glycoproteins fail to fold in a conformation that is conducive for efficient transport to the corneal epithelial cell surface. Johnson and Smiley\(^{41}\) observed that the kinetics of intracellular transport of gD in HSV-2 infected L cells was much slower than in transformed mouse L cells. They suggested that gD interaction with viral structural components retarded its movement to the cell surface. In our study, HSV-1 replicated at least as well as HSV-2, which suggests comparable levels of viral structural components within cells infected with either of the two serotypes. Thus, it seems unlikely that inhibition in gD transport would be greater in type 2- than type 1-infected cells.

The kinetics of glycoprotein appearance on infected cell membranes as well as the amount made seems to be critical. Thus, Wachsmann et al.\(^{42}\) have found that gD-1 expressed under the control of an early but not a late promoter in vaccinia recombinant viruses could protect guinea pigs from cutaneous HSV-2 disease. Regulation of glycoprotein genes during viral infection can occur at the levels of transcription\(^{43}\) and posttranscription.\(^{44}\) Several immediate early proteins including ICP0,\(^{45}\) ICP4,\(^{46,47}\) and ICP27\(^{48}\) have been shown to play a role in regulating viral glycoprotein gene expression. Possibly the differential interaction of HSV-1 and HSV-2 immediate early gene products with components of the host cell could account for the dissimilarity in virus-infected cell surface glycoprotein expression in selected cell types. Alternatively, glycoproteins may be shed in greater abundance by HSV-2-infected cells into the corneal interstitium making it harder to eliminate stromal disease by passive immunization.

In summary, we have shown that passive transfer of antibody fails to prevent HSV-2-induced stromal keratitis, although it provides excellent protection against HSV-1 ocular infection. However, antibody
therapy is able to prevent encephalitis induced by HSV-2 spread into the central nervous system. The dissimilar protection seen in different tissues suggests that the protective mechanism is influenced by inherent properties of the infected host cell as well as the genetic makeup of the infecting HSV serotype.

Key Words
HSV-1, HSV-2, monoclonal antibodies, stromal keratitis, HSV glycoproteins

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