Increased Severity of *Pseudomonas aeruginosa* Corneal Infection in Strains of Mice Designated as Th1 versus Th2 Responsive

Linda D. Hazlett, Sbaron McClellan, Byungsuk Kwon, and Ronald Barrett

**PURPOSE.** Mice favoring Th1 (C57BL/6, C57BL/10, and B10.D2/nSn) versus Th2 (BALB/c, BALB/cBy, BALB.B, and BALB.K) response development were infected with *P. aeruginosa*. This study addresses the question of whether Th1 versus Th2 response propensity affects the pathogenesis of bacterial keratitis in mice.

**METHODS.** Ocular disease was determined by mean clinical score, slit lamp, plate counts, and histopathology, and antigen-specific cellular responses were assessed by immunostaining and measurement of delayed type hypersensitivity (DTH).

**RESULTS.** Strains of mice favoring Th1 (B6, BL10, and B10.D2) versus Th2 (BALB/c, BALB/cBy, BALB.B, and BALB.K) responsiveness were infected with *P. aeruginosa*. Mice favoring Th1 response development exhibited a similar course of disease and the infected eyes of all mice perforated by 7 days postinfection (p.i.). Strains (BALB/c, BALB/cBy, BALB.B, and BALB.K) favoring Th2 response development exhibited a milder course of disease, and none of the infected corneas perforated at 7 days p.i. In a Th1-responsive strain (B10.D2), positive immunostaining for CD4+ and CD8+ T cells was observed in the cornea by 3 days p.i. and by 5 days p.i., respectively, some cells stained positively for IL2-R, indicating that the cells were activated. In contrast, in a Th2 responder strain (BALB/c), there was no detectable positive immunostaining in cornea for any of the T-cell markers tested and DTH was significantly elevated in B10.D2 versus BALB/c mice.

**CONCLUSIONS.** These studies are the first to provide evidence that in *P. aeruginosa* ocular infection, mouse strains favoring development of a Th1-type response are susceptible (cornea perforates), whereas strains favoring Th2 response development are resistant (no corneal perforation). (Invest Ophthal Vis Sci. 2000;41:805–810)

Keratitis caused by *Pseudomonas aeruginosa* is one of the most rapidly developing and destructive diseases of the cornea. Once the bacteria infect the cornea, complex host tissue reactions occur, including inflammation, cellular and humoral immune responses, and degradation of stromal proteins. During inflammation, leukocyte adhesion to the endothelium is enhanced by adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and by cytokines such as interleukin (IL)-1 and tumor necrosis factor,1 products of both T cells and macrophages. With regard to T lymphocytes, their role in susceptibility versus resistance to ocular bacterial infection has been investigated recently in C57BL/6 (B6) mice.4 Data from that study were the first to provide evidence that CD4+ (type 1, Th1) T cells were important in the pathogenesis of corneal disease and perforation. That the tissue destructive stromal inflammation involved T cells was evidenced by the decreased stromal inflammation in mice that were depleted by specific monoclonal antibody (MAb) of CD4+, but not CD8+ T cells or in which interferon gamma (IFN-γ) was neutralized by MAb before corneal infection. Similarly, many studies of Th1 versus Th2 responses have shown that in C57BL/6 and related inbred strains, Th1 responsiveness is predisposed in response to a wide variety of infectious pathogens and antigens.3–5

Recently, the influence of the genetic background of the T-cell on T-helper (Th) phenotype development has been reported.6 Some mouse strains (e.g., B10.D2) were shown to favor Th1, whereas other strains such as BALB/c6 and related strains,7–9 favored Th2 T-cell response development. Others have already begun to examine T-cell response profiles as a potential basis for susceptibility to other ocular diseases, such as experimental autoimmune uveitis,5 using some of these naturally resistant versus susceptible animal models. In contrast, except for a recent abstract,10 no other studies have used these natural models to directly test whether T-cell response profiles are important in determination of susceptibility versus resistance to ocular bacterial disease caused by *P. aeruginosa*. Therefore, the purpose of the present study was to test the hypothesis that after corneal infection with *P. aeruginosa*, Th1- versus Th2-responsive mouse strains will evidence a susceptibility (cornea perforates) versus resistance (less corneal disease, no perforation) phenotype, respectively.
MATERIALS AND METHODS

Mice

Female mice of strains that favor either Th1 or Th2 responsiveness (Table 1), including C57BL/6 (B6), B10.D2/nSnJ (B10.D2), C57BL/10J (BL10), BALB/cByJ, and BALB/c were purchased from the Jackson Laboratory (Bar Harbor, ME) at 8 weeks of age. Additionally, BALB/ByOlaHsd and BALB.K/OlaHsd female mice were purchased from Harlan Sprague–Dawley (Indianapolis, IN) at 8 weeks of age. Animals were housed on a 12-hour light/dark cycle and given unrestricted access to rodent chow (Ralston-Purina, St. Louis, MO) and acidified water. Animals were housed in accordance with the National Institutes of Health guidelines, and all procedures in this study conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Bacteria

P. aeruginosa strain 19660 was purchased from the American Type Culture Collection (ATCC, Rockville, MD). Strain 19660 is proteolytic, hemolytic, and lipolytic and under appropriate growth conditions will produce exotoxin A.11 The stock culture was maintained on Peptone Tryptic Soy broth (PTSB) slants (PTSB solidified with 1.7% agar; Difco Laboratories, Detroit, MI) at 4°C. Fresh slants were prepared every 2 weeks using frozen stock cultures as the inoculum. Cultures were grown in PTSB at 37°C on a rotary shaker at 150 rpm for 18 hours to an approximate OD of 1.6 at 540 nm. Cultures were then centrifuged at 6000g for 10 minutes at 15°C, washed once with sterile saline (0.85% NaCl, pH 7.2), and resuspended in saline to a concentration of 2.0 × 10^10 colony forming units (CFU)/ml.

Infection and Ocular Response

To assess the ocular disease response, mice were challenged with P. aeruginosa strain 19660. Briefly, mice were anesthetized with Aerrane (Anaquest Inc., Liberty Corner, NJ), and the left cornea was scarified with a 25-gauge needle. Three 1-µm incisions were made to the corneal surface, which penetrated partially or fully covering the pupil;+1, slight opacity, fully covering the anterior segment; +2, dense opacity, partially or fully covering the pupil; +3, dense opacity, covering the entire anterior segment; +4, corneal perforation or phthisis. Mean clinical scores were calculated by summation of the scores for each group (n = 5/group, repeated 3 times) of mice divided by the total number of mice scored at each time point.

Quantitation of Viable Bacteria

Individual corneas (n = 3/group) were removed from the eyes of B6 and BALB/c mice at days 1, 5, and 9 postinfection (p.i.) using a sterile razor blade and homogenized with glass tissue grinders (Fisher Scientific, Itasca, IL) in 1 ml of sterile phosphate-buffered saline (PBS) containing 0.5% bovine serum albumin (BSA). To quantitate viable bacteria per cornea, a 0.1-ml aliquot of the corneal homogenate was serially diluted 1:10 in sterile PBS-BSA. Serially diluted samples were plated in triplicate (0.1 ml/plate) onto Pseudomonas isolation agar (Difco) plates and incubated for 24 hours in a water-jacketed CO2 incubator (American Scientific Products, McGaw Park, IL) at 37°C and 5% CO2. The lower limit of detection of this method is 100 CFU/cornea. For corneas with less than 100 CFU of viable bacteria, a value of 0 CFU was assigned and used to calculate the mean number of CFU. The values of CFU/cornea are expressed as log_{10} and shown as the mean CFU ± the SEM.

Histopathology

Infected eyes from Th1 (B6, BL10, and B10.D2) and Th2 (BALB/c, BALB.B, and BALB.K) mice (n = 3/strain) were enucleated on the day before perforation (6 days, p.i.) in the Th1-responsive mice. The procedure for embedding eyes in resin and sectioning for light microscopy has been previously described.12 In brief, mice were killed by cervical dislocation, and the infected and contralateral (control) eye was enucleated. Eyes were fixed in cold acetone at −20°C overnight and then fixed in cold acetone at −20°C for 2 minutes after fixation, slides were rinsed several times with 0.1 M PBS containing 1.0% BSA and 0.05% Tween 20 and incubated at room temperature (RT) in a moist chamber for 30 minutes. Sections were cut with a Micron cryostat (Fisher Scientific, Itasca, IL) and mounted to poly-l-lysine–coated slides (Polysciences Inc., Warrington, PA). Before immunostaining, slides were stored at −30°C overnight and then fixed in cold acetone at −20°C for 2 minutes. After fixation, slides were rinsed several times with 0.01 M PBS. To block nonspecific binding, each section was covered with 20 µl PBS containing 1.0% BSA and 0.05% Tween 20 and incubated at room temperature (RT) in a moist chamber for 30 minutes. Sections were incubated for 1 hour with primary Mabs specific for CD4 (rat IgG2a, clone H129.19, 1:10), CD8 (rat IgG2a, clone 53-6.7, 1:25), and CD25 (IL-2R, rat IgM, clone 7D4, 1:50) (all from Pharmingen, San Diego, CA). Sections were incubated with 0.3% hydrogen peroxide for 30 minutes to block endogenous peroxidase activity. They were then incubated for 1 hour with the appropriate biotinylated secondary Ab, anti-rat IgG2a (CD4, 1:25 and CD8, 1:50) and

### Table 1. Th1 or Th2 Responsiveness

<table>
<thead>
<tr>
<th>Mouse Strains</th>
<th>Th Response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6</td>
<td>Th1</td>
<td>6</td>
</tr>
<tr>
<td>B10.D2</td>
<td>Th1</td>
<td>6</td>
</tr>
<tr>
<td>C57BL/10</td>
<td>Th1</td>
<td>5</td>
</tr>
<tr>
<td>BALB/c</td>
<td>Th2</td>
<td>6</td>
</tr>
<tr>
<td>BALB/cBy</td>
<td>Th2</td>
<td>6</td>
</tr>
<tr>
<td>BALB.B</td>
<td>Th2</td>
<td>7, 8</td>
</tr>
<tr>
<td>BALB.K</td>
<td>Th2</td>
<td>9</td>
</tr>
</tbody>
</table>

---

Downloaded From: http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933587/ on 06/25/2017
anti-rat IgM (IL-2R, 1:100) (Pharmingen). Horseradish peroxidase–conjugated avidin (1:25 to 1:100 concentration; Zymed, San Francisco, CA) was then incubated with the sections for 30 minutes Color was developed with 3,3′-diaminobenzidine tetrahydrochloride (10–15 minutes) containing cobalt and nickel chloride (Pierce, Rockford, IL) to visualize positively reacted cells. Control sections were similarly treated after incubation with an irrelevant rat anti-human MAb (HLA-DR5, clone SFR3-DR5, IgG2b; ATCC).

**Delayed Type Hypersensitivity**

For this assay, B10.D2 and BALB/cj mice (n = 5/group, repeated once) were infected ocularly, as described above. At 6 days p.i., 2.0 × 10^7 CFU of heat-killed *P. aeruginosa* cells (10 μl in 0.01 M PBS) were injected SC into the ear pinna ipsilateral to the infected eye. PBS was injected into the contralateral ear as a control. Ear thickness was measured with an engineer’s micrometer (Mitutuyo, Tokyo, Japan) just before injection and at 24 and 48 hours after antigen challenge. Delayed type hypersensitivity (DTH) was calculated using the following equation: ([24- or 48-hour measurement – 0-hour measurement]Ag challenged ear) − ([24- or 48-hour measurement – 0-hour measurement]PBS-challenged ear)^1.4.

**Statistical Analysis**

χ^2^ analysis was used to determine the significance of the ocular disease response (mean clinical score) data and an unpaired, two-tailed, Student’s t-test was used to analyze differences in the plate count and in DTH. Data are presented as the means ± SEM. A P ≤ 0.05 confidence interval was used to determine the level of significance of differences.

**RESULTS**

**Infection in Th1 and Th2 Responder Strains**

The scarified corneas of Th1- versus Th2-responsive mice were infected with *P. aeruginosa*, the ocular disease response was graded, and from these, mean clinical scores were calculated. These data are shown in Figures 1A and 1B. From 24 hours to 7 days p.i., all three of the Th1 responder strains tested were virtually indistinguishable with regard to disease response. At 24 hours, mice exhibited a +2 response, which progressed to a +3 disease grade by 3 days p.i., and by 7 days p.i., all the infected corneas had perforated (Fig. 1A). From 24 hours to 9 days p.i., all Th2 responder strains exhibited less severe disease, and more variation in the response grades was observed than seen in Th1 responder mice (Fig. 1B). At 24 hours p.i., light (+1) to dense central opacity (+2) was observed in all the Th2 strains tested. In +1 graded eyes, disease progressed to a +2 score and in all mice did not worsen through 7 days p.i. By 6 to 9 days p.i., the corneas of Th2 responder mice began to show evidence of disease resolution and restoration of corneal clarity. A typical example of disease responsiveness in Th1 versus Th2 responder mice is shown macroscopically at 7 days p.i. (Figs. 2A–2D). Although the corneas of Th1 mice had obviously perforated (Figs. 2A, 2B), the corneas of Th2 responder mice exhibited either a +2 (Fig. 2C) grade or had only slight opacity (Fig. 2D) in the cornea. The degree of vascularization in the cornea of Th2 strains also was quite striking when compared with the minimal vascularity observed in the cornea of Th1 responder mice.

**Viable Bacteria in Cornea**

Because of the marked difference in the ocular disease response (mean clinical scores) between the Th1 versus Th2 responder groups of mice, the number of viable bacteria recovered from the infected corneas of BALB/c and B6 mice was quantitated at 1, 5, and 9 days p.i. Those results are summarized in Table 2. No significant difference in bacterial load was detected between the two mouse strains at 1 day p.i. At 5 days p.i., the number of viable bacteria recovered from the corneas of B6 mice was approximately 1 log greater than in BALB/c mice. At 9 days p.i., B6 mice exhibited approximately 2 logs more bacteria in the cornea than BALB/c mice. These differences in bacterial load were significant at both 5 (P = 0.0041) and 9 (P = 0.0023) days p.i.

**Histopathology**

The histopathology of the corneal disease response in Th1 versus Th2 responder mice was examined, and data representative of the response at 6 days p.i. are shown in Figures 3A–3F. At this time, the corneas of all Th1-responsive mice (B6, BL10, and B10.D2) exhibited extreme thinning of the corneal stromal
tissue and numerous inflammatory cells in the peripheral cornea, in the thinned central corneal stroma, and within the anterior chamber (Figs. 3A, 3B, 3C, respectively). In contrast, at the same time period, the corneas of Th2 responder mice (BALB/c, BALB.B, and BALB.K) showed evidence of less severe corneal stromal disease. The corneal epithelium and the endothelium also were intact in these mice (Figs. 3D, 3E, 3F, respectively). Although some variation in histopathology was observed in Th2 responder mice, none of the corneas of these mice perforated. Nonetheless, resolution of the inflammatory response was not complete by 6 days p.i. in all Th2 responder strains tested. Inflammatory cells were present (Figs. 3E, 3F) and corneal vascularization also was evident (Fig. 3F) in some of the murine corneas sampled. The histopathology complemented and was consistent with the mean clinical score grades.

Immunostaining

Although the cellular infiltrate after *P. aeruginosa* infection consists predominantly of polymorphonuclear leukocytes (PMN), previous studies have shown that T lymphocytes also infiltrate the cornea of B6 mice and are activated at 5 days p.i. Therefore, the spatial distribution and kinetics of T-cell infiltration into the infected corneas of other Th1 and for the first time, in Th2 responder mice was determined. Representative

![Figure 2](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933587/ on 06/25/2017)

**FIGURE 2.** Photomicrographs of ocular disease typically observed in Th1 (A, B) versus Th2 (C, D) responder mice at 6 days p.i. Corneal perforation (+4) is evident in the eyes of B10.D2 (A) and B6 (B) mice. In contrast BALB/c (C) and BALB/c (D) corneas are either at a grade of +2 (C) or +1 (D). Note increased vascularity in the eyes of Th2 versus Th1 responder mice. Each at ×60 magnification.

![Figure 3](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933587/ on 06/25/2017)

**FIGURE 3.** Corneal histopathology in Th1 versus Th2 responder mouse strains at 6 days p.i. with *P. aeruginosa*. At this time, the corneas of Th1 responder mice (B6, BL10, and B10.D2, A through C, respectively) had perforated; the central corneal stroma was thinned and cellular infiltrate was evident in the cornea and anterior chamber. In contrast, the corneas of Th2 responder mice showed a lesser degree of corneal inflammation, with fewer cells in the anterior chamber. The cornea of a BALB/c mouse is illustrated in (D) and has only modest stromal inflammation. Corneas shown in (E) (BALB.B) and (F) (BALB.K) are shown to illustrate the variation in the inflammatory response at this time. Magnification, (A through F) ×54.

![Figure 4](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933587/ on 06/25/2017)

**FIGURE 4.** Immunostaining of T-cell infiltrate in infected corneas at 6 days p.i. Positive immunostaining for (A) CD4, (B) CD8, and (C) IL-2R surface markers was seen in the cornea of the Th1 responder B10.D2 mouse strain. In contrast, no positive immunostaining for these markers was detected in the cornea of the Th2-responsive BALB/c mouse strain (D). The section shown in (D) was immunostained with a specific CD4+ T-cell MAb and is negative. The negatively stained section appeared similar to tissue stained with a nonspecific (anti-HLA-DR5) primary MAb (data not shown). Magnification, (A through D) ×1000.

---

**TABLE 2.** Number of Viable Bacteria in Cornea at 1, 5, and 9 Days p.i.

<table>
<thead>
<tr>
<th>Mouse Strains</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALB/c</td>
<td>5.3 ± 0.20*</td>
<td>5.9 ± 0.22**</td>
<td>1.85 ± 0.54***</td>
</tr>
<tr>
<td>C57BL/6</td>
<td>5.7 ± 0.03</td>
<td>6.8 ± 0.09</td>
<td>4.70 ± 0.44</td>
</tr>
</tbody>
</table>

The data are expressed as log10 CFU/cornea of *P. aeruginosa* ± SEM, n = 3 cornea/strain/time.

* P = 0.07, ** P = 0.0041, *** P = 0.0023.
examples of positive staining for CD4, CD8, and IL-2R cell markers at 7 days p.i. are shown in Figures 4A–4C. Similar to B6 mice, B10.D2 and BL10 (data not shown) strains of mice showed no T cells in the cornea until 3 days p.i. By 7 days p.i., the number of cells expressing surface markers for CD4+ T cells appeared increased, and cells were mainly observed para-centrally, clustered beneath the epithelium. The T cells were activated by 5 days p.i., as they positively stained for IL2-R surface marker. Immunostaining of BALB/c or BALB/c by (data similar and not shown) cornea for the same T-cell markers failed to detect any T cells in the cornea of these mice at all the times tested. A representation of the lack of positive cell staining in BALB/c mice is shown in Figure 4D, using an anti-CD4+ T-cell-specific MAb. This negative immunostaining for CD4+ T-cell detection resembled control corneal tissue (data not shown) immunostained with a rat anti-human HLADR-5 MAb. Further confirmation of these immunostaining data were provided by testing the DTH response, an indicator of systemic cell-mediated immune responsiveness. Using heat-killed P. aeruginosa as antigen, DTH was significantly enhanced in B10.D2 versus BALB/c mice at both 24 and 48 hours after antigen challenge (Fig. 5).

**DISCUSSION**

*P. aeruginosa* is capable of producing a rapid and severe corneal stromal keratitis, which often results in perforation of the cornea. A higher incidence of disease occurs in contact lens wearers, particularly those who use extended wear lenses. In rodent models such as the mouse, which share many features of human disease, host factors such as genetic background, immune status, and age have been shown to modulate disease outcome. In mice, PMNs are the major inflammatory cells that migrate into the corneal stroma early after the onset of infection. These cells are implicated in the extensive stromal damage, which is the hallmark of this disease, but also in the resolution of disease, as suggested by studies with leukopenic mice. Outbred young adult mice are resistant to bacterial ocular challenge and consistently mount a significantly greater inflammatory response than susceptible animals at 24 hours p.i. These mice are then able to decrease this response after clearance of bacteria from the cornea. In contrast, susceptible aged outbred mice initially experience a delayed inflammatory response after infection. Numerous inflammatory cells such as PMN persist in the cornea at later times after infection, consistent with tissue damage and the perforation response in aged mice. On the basis of these past observations, we predicted that, similar to outbred animals, inbred Th2 responder mice such as BALB/c, if resistant to *P. aeruginosa* infection, would be able to clear the bacterial infection more effectively and have a lesser inflammatory cell response at later times after infection. Both plate count and histopathologic results confirmed this prediction. PMN and other inflammatory cells remained plentiful at 6 days p.i. in Th1 responder mice whose corneas perforated, whereas in Th2 responder mice in which the corneas were less severely diseased, fewer viable bacteria and inflammatory cells were evident. At 6 days p.i., the corneas of BALB/c and other Th2 responder mice had mean clinical scores between +1 to +2, consistent with a decreased number of inflammatory cells in the cornea when compared to a +4 grade (perforation) in B6 and other Th1 responder mice.

A paradigm for bacterial disease pathogenesis and the role of Th1 versus Th2 responsiveness has evolved from numerous studies using a mouse leishmaniasis model. Data using this model, although not directly applicable to a pseudomonal infection, are thought provoking, in that they indicated that the cytokines produced against the parasite during the primary infection controlled differentiation of CD4+ T lymphocytes and the quality of the subsequent immune response. According to this paradigm, CD4+ Th1 (type 1) cell-mediated immunity confers protection against parasitic infection, whereas the development of a CD4+ Th2 (type 2) humoral immune response is associated with disease progression. In BALB/c mice, *Leishmania major* infection causes a progressive disease that ultimately results in death, with the predominant expression of IL-4 and relatively little IFN-γ production being detected. Parasitic infection in other strains of mice such as B10.D2, C3H, C57BL/6, C57BL/10, and 129 produces self-healing lesions associated with a strong Th1-cell-mediated immune response with production of high levels of IFN-γ and other inflammatory cytokines. In contrast, in the ocular model of infection used in a previous study and in the work reported herein using the extracellular pathogen, *P. aeruginosa*, a Th1-type of inflammatory response eventually may contribute to a decrease in the number of viable bacteria in the cornea, but the price the susceptible host pays is dissolution of the corneal stroma and blindness. The corneas of Th2 responder mice such as the BALB/c had not been tested before for T-cell subset infiltration into the cornea. Therefore, immunostaining was used to spatially and temporally test for the presence of CD4+ and CD8+ T cells in the corneas of BALB/c mice, as had been done previously in B6 mice. Because B6 mice have been described genetically as Th1 “driven” and BALB/c mice as Th2 “driven” to many antigens, determining if CD4+ or CD8+ T cells were present in BALB/c corneas was done as a logical first step before testing for specific type 1 or type 2 cytokine profiles in the cornea. B10.D2 and BL10 corneas were used for immunostaining, and as reported before, for B6 mice, CD4+ and CD8+ T cells were first detected in the corneas of both
(B10.D2 data shown) these Th1 responder strains of mice at 3 days p.i.; by 5 and 7 days p.i. immunopositively stained cells were increased and activated, based on positive staining for IL-2R. In another murine model of disease induced by infection with Toxoplasma gondii, the presence of CD4+ T cells in B6 mice also has been demonstrated at early times after infection and has been shown to predispose these mice to rapid ileal necrosis and death within 7 days p.i. Quite surprisingly, the corneas of BALB/c or BALB/cBy mice did not express positive immunostaining for either CD4 or CD8 T-cell surface markers after infection, despite several repetitions of this experiment using a sensitive immunostaining technique. In combination, the immunostaining and the DTH data strongly suggest that resistant BALB/c (Th2 responder) mice lack a CD4+ Th1-type of T-cell response to ocular P. aeruginosa challenge. Although the mechanism of resistance in Th2 responder mice is not yet fully understood, the data presented herein are provocative and warrant further testing of the hypothesis that Th2-responsive mice, when compared with Th1 responder strains, regulate the inflammatory cellular infiltrate more efficiently. Specifically, resistance may be achieved by the ability of Th2 responder mice to downregulate the inflammatory response, resulting in less stromal damage and destruction of the corneal stroma.

References


Downloaded From: http://iovs.arvojournals.org/pdaccess.ashx?url=data/journals/iovs/933587/ on 06/25/2017