



## Validation Study: Melanin Associated Antigen-Induced Anterior Uveitis in Lewis Rats

**Robin Dean • Robert Sukhu • Leslie Nemeth • Qin Zhang • Isaac Hakim  
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Comparative Biosciences, Inc., Sunnyvale, CA 94085

### **Abstract:**

**Melanin-Associated Antigen is administered to Lewis Rats leading to a consistent, strong immune-mediated anterior uveitis.**

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CBI offers a validated model of MAA-induced anterior uveitis in Lewis rats. In this model, melanin-associated antigen is administered to Lewis rats leading to a consistent, strong immune-mediated anterior uveitis. The inflammation is visible by about Day 12 and continues for about 3 weeks. It peaks at about Day 16. The inflammation is clearly visible in the anterior segment and characterized by increased vascularity, corneal opacity, fibrono-cellular exudate in the anterior chamber, pinpoint pupils. The inflammation is responsive to corticosteroids and cyclosporin. Ocular parameters include slit lamp biomicroscopy, intraocular pressure, OCT, histology and immunohistochemistry. This model recapitulates the human disorder of anterior uveitis, a disease of unmet need in man.

### **Introduction**

Anterior uveitis is a disorder of unmet need in man. Although somewhat responsive to corticosteroids, in many cases, conventional therapies are not successful. The melanin-associated antigen-induced model of

anterior uveitis in Lewis rats reasonably recapitulates the human disorder and is responsive to both corticosteroids and cyclosporine. CBI has developed and validated a robust MAA-induced model of anterior uveitis in Lewis rats. This model was initially based upon the model published by Bora, et al, but has been substantially improved and modified to make it a high caliber model for the assessment of ocular anti-inflammatories and immune inhibitors as well as determinations of disease mechanisms.

All in vivo experiments were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the guidelines established by the Animal Care Committee at Comparative Biosciences, Inc, an AAALAC accredited facility.

### **Model Induction**

Anterior uveitis is induced by administration of a melanin-associated antigen proprietary developed by CBI, which produces a uniform, consistent, and robust ocular inflammation in 100% of animals.



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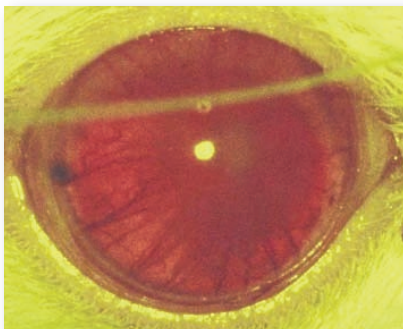
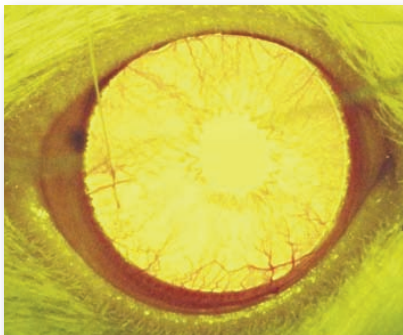
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### Clinical Ocular Findings

Beginning about Day 12 and extending for an additional 2 weeks there is a brisk inflammatory reaction composed of increased vascularity and swelling of the iris, exudate in the anterior chamber, miosis, and corneal opacity. Below are presented a normal eye and a severe Grade 4 eye.



### Drug treatment

Drug therapy may be topical or systemic and may begin about Day 10 or at other times requested by sponsor. Topical or systemic corticosteroids and/or cyclosporin serve as good positive controls.

### Clinical Scoring

Eyes are generally examined by slit lamp biomicroscopy, scored and photographed three times weekly for 2-3 weeks to follow the progression and response to treatment. The scoring system is presented in Table 1.

### Necropsy

For each animal, both eyes (with optic nerve attached) are collected and fixed overnight in modified Davidson's solution and then transferred to 10% neutral buffered formalin. Following processing, tissues are dehydrated, embedded sagittally in paraffin and serially sectioned (at 3-5  $\mu$ m) through the center portion of the eye, in particular, the cornea, iris, and limbal areas.



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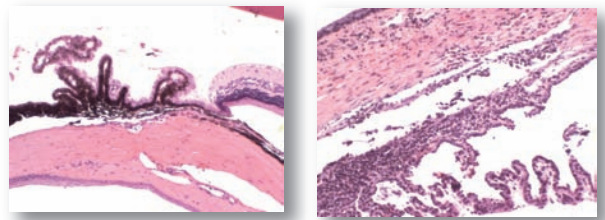
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### **Histopathologic Findings**

Lesions from both eyes for each animal are evaluated via light microscopy by an ACVP board-certified veterinary pathologist. Eyes are graded as per the grading scale (Table 2)

Histologically, the primary lesion re is a marked subacute inflammation of the iris, ciliary process, and limbus with an admixture of lymphocytes, plasma cells and neutrophils, with edema, congestion and hemorrhage. There is also inflammation and edema of the cornea, often with extension of inflammation into the cornea. The posterior segment has little change. The photomicrographs present a normal eye and a Grade 4 eye.



### **Conclusion**

At CBI, our MAA-induced model of anterior uveitis in Lewis rats is associated with consistent, reproducible nonsuppurative inflammation of the anterior segment. The inflammation may be modulated and reduced following administration of the positive control drug, such as a corticosteroid or cyclosporin. This model as developed by CBI and our assessment parameters are ideal for the evaluation of new drug entities for the treatment of this important disorder for which there is no treatment.



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**Scoring Systems Used**

**Clinical Ocular Grading for MAA-Induced Inflammation by slit lamp biomicroscopy**

<b>Grade</b>	<b>Criteria</b>
0	Normal, eye, translucent and reflects light (red reflex)
0.5 (Trace)	Dilated vessels in iris
1	Engorged blood vessels in iris; abnormal pupil contraction
2	Hazy anterior chamber, decreased red reflex
3	Moderately opaque anterior chamber by pupil still visible; dull red reflex
4	Opaque anterior chamber and obscured pupil, red reflex absent, proptosis

**Histopathology Grading for MAA-Induced Inflammation**

<b>Grade</b>	<b>Criteria</b>
0	Normal, no histopathologic lesions seen.
0.5 (Trace)	Trace multifocal infiltration of the iris and/or ciliary area with neutrophils and/or mononuclear cells. No to trace congestion.
1	Mild multifocal infiltration of the iris and/or ciliary area with neutrophils and/or mononuclear cells. Trace to mild congestion. No to trace extension of inflammation into cornea, anterior chamber and posterior chamber.
2	Mild to multifocal infiltration of the iris and/or ciliary area with neutrophils and/or mononuclear cells. Congestion and edema. No to mild extension of inflammation into cornea, anterior chamber and posterior chamber.
3	Moderate multifocal to diffuse, often expansile, infiltration of the iris and/or ciliary area with neutrophils and/or mononuclear cells. Hemorrhage, congestion and edema. No to moderate extension of inflammation into cornea, anterior chamber and posterior chamber.
4	Severe, expansile infiltration of the iris and/or ciliary area with neutrophils and/or mononuclear cells. Hemorrhage, congestion and edema. Inflammation may extend into cornea, anterior chamber and posterior chamber.