



COMPARATIVE BIOSCIENCES, INC.
A TRANSLATIONAL APPROACH TO PRECLINICAL RESEARCH



Technical Bulletin: OCULAR STUDIES



Overview

CBI has demonstrated expertise in all phases of the drug development process in preclinical contract ocular studies. Our highly specialized staff is experienced in providing exploratory/proof-of-concept, GLP toxicology, pharmacokinetics, in vivo animal models, pharmacology, and histopathology/immunohistochemistry studies related to the eye. Due to CBI's unique and extensive experience in preclinical ocular studies and state-of-the-art facilities, we have the skill and expertise to accelerate new ocular drugs from discovery through the drug development process to regulatory submission.

CBI is committed and dedicated to providing ophthalmology research and offers a complete range of services to pharmaceutical, biotech, and medical device companies in the following areas:

- . Ocular Toxicology Studies
- . Ocular Pharmacokinetics Studies
- . Ocular Modeling and Pharmacology
- . Optical Coherence Tomography (OCT)



All laboratory animals are cared for and treated humanely in all CBI studies. These research animals are used to provide us with new science and new treatments for human and veterinary diseases.



Validated Efficacy Ophthalmic Models Available at CBI Include:

Models of Angiogenesis and Macular Degeneration

- Choroidal neovascularization in mice, rats, rabbits and pigs (laser-induced)
- Oxygen-induced retinopathy in mice and rats
- VEGF-induced choroidal neovascularization in rabbits
- Streptozotocin-induced retinopathy
- Senescent knockout mouse model of macular degeneration

Device Implantation

- Intraocular stents for glaucoma or drug delivery
- Corneal rings
- Punctal plugs
- Artificial lens insertion or removal
- Corneal surgery
- Corneal debridement
- Intraocular implants
- Endothelial damage or disease indications

Models of Corneal Injury, Inflammation and Healing

- Heptanol-induced corneal erosion in rabbits
- Suture-induced inflammation in rodents
- Corneal incision
- Bacterial or infectious models of ocular inflammation

Models of Ocular Degeneration

- MNU-induced retinitis pigmentosa
- Vitreal detachment





Ophthalmic Pharmacology

CBI Offers a wide variety of validated ocular efficacy and pharmacology models related to retinal neovascularization, dry eye, inflammation, glaucoma, and pain.

Models of Inflammation

- Melanin-antigen associated anterior auto-immune uveitis in Lewis rats
- IRBP-antigen associated posterior inflammation in rodents
- LPS-induced acute inflammation in rabbits and rodents
- Ovalbumin-induced immune mediated inflammation in rabbits
- F48/80-induced acute inflammation in rabbits (We used MRI to follow the consequences of non-immunological mast cell activation induced by compound 48/80 in the rabbits lungs in vivo.
- Corneal infection

Neovascular and Vascular Models

- Laser induced macular degeneration induction in mice, rats and rabbits
- Oxygen induced retinopathy in neonatal mice and rats
- STZ induced retinopathy in diabetic rats
- Angiotensin II induced retinal vascular leakage
- Corneal pocket or suture model
- VEGF-induced retinal vascular leakage

Models of Dry Eye

- Scopolamine-induced dry eye in mice
- Botulinum-induced dry eye in mice
- ConA-induced model in rabbits
- Glycopyrrolate-induced model in rabbits
- Benzalkonium chloride-induced model in rabbits.





Immune-mediated Inflammation

- Melanin associated antigen induced anterior uveitis in rats
- IRBP or S-antigen induced posterior uveitis in mice and rats

Glaucoma and Ocular Hypertension

- Laser induced glaucoma in rodents
- Corticosteroid-induced
- Water loading
- Chymotrypsin

Ocular Pain

- Capsaicin-induced
- Formalin-induced

Ocular Toxicology and Safety Assessment

CBI offers both exploratory proof-of-concept ocular toxicology and tolerability studies, and complete preclinical GLP toxicology and safety assessment studies suitable for regulatory submission for ophthalmic drugs, biologics, antibodies and proteins, and devices. CBI is versed in ocular toxicology studies employing stem cells, contact lens and punctal plugs as well as other surgically implanted ocular and intra-ocular devices. We have specialized techniques including OCT, ERG, tonometry, pachymetry and fundus angiography available for toxicology and pharmacology assessments.

Our GLP facility can conduct complete preclinical evaluations of your therapeutic. CBI can support any phase of your preclinical development program with in vivo studies and complete histopathological assessment for your therapeutic. All slides are read by a board-certified veterinary pathologist with years of experience evaluating ocular tissue. **Contact us today to learn more!**



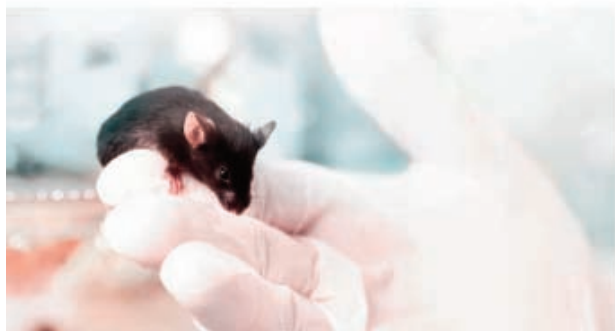
Eye Shapes Of The Animal World Hint At Differences In Our Lifestyles

In Vivo Ocular Studies

In vivo assessments may include clinical signs, Draize scoring, McDonald-Shadduck scoring, biomarkers, body weights, phenol red thread test, TBUT test, Schirmer test, slit lamp biomicroscopy, funduscopy, IOP, pachymetry, retinal scanning with our retinal scanner, ERG, OCT, ultrasound and ocular photography

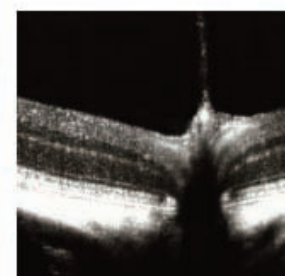
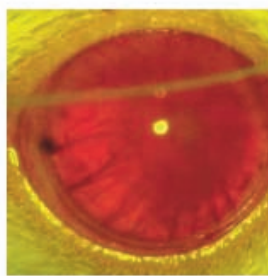
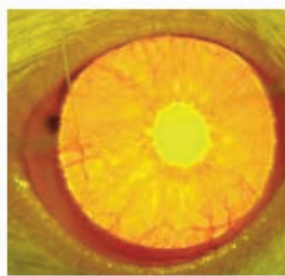
STZ Studies

CBI offers a robust and validated model of STZ-induced hyperglycemia and retinopathy in rats. Streptozotocin-induced hyperglycemia results in changes in the retinal pigmented layer consisting of increased thickness of the middle retinal layers, increased new vessel formation, reactive endothelium, dilated capillaries distended with either blood or edema fluid, acute inflammation composed of intravascular neutrophils, and neutrophils adhered to vessel walls and extravascularly by 4 weeks or longer post-STZ treatment. These changes were clearly evident histologically and were supported by Optical Coherence Tomography and retinal angiography. OCT provides a real-time, in vivo measure of the development of diabetic retinopathy, which previously had to be evaluate post-mortem by histopath. Examination of the retina via fluorescein angiographs reveals increases in retinal vascularity in streptozotocin-treated rats with areas of leakage particularly surrounding the optic nerve. These changes were compatible with and correlated with the histopathologic findings of increased vascularity of the retinal pigmented layer. OCT assessments clearly demonstrating thickening of the retina, primarily the middle layers following STZ induction. Treatment with triamcinolone significantly reduced STZ-induced retinal thickness as well as other ocular changes. Streptozotocin (STZ) is an antibiotic that can cause pancreatic β -cell destruction, so it is widely used experimentally as an agent capable of inducing insulin-dependent diabetes mellitus (IDDM), also known as type 1 diabetes mellitus (T1DM).



STZ Assessments Include:

- Clinical observations
- Body weights
- Blood glucose
- Blood insulin
- Angiography
- OCT
- Histopathology
- Immunohistochemistry



Normal rat eye, Grade 4 inflammation following MAA treatment

Brightfield

Optical Coherence Tomography (OCT)