Preclinical Models of Glaucoma at CBI

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COMPARATIVE BIOSCIENCES, INC.
A TRANSLATIONAL APPROACH TO PRECLINICAL RESEARCH

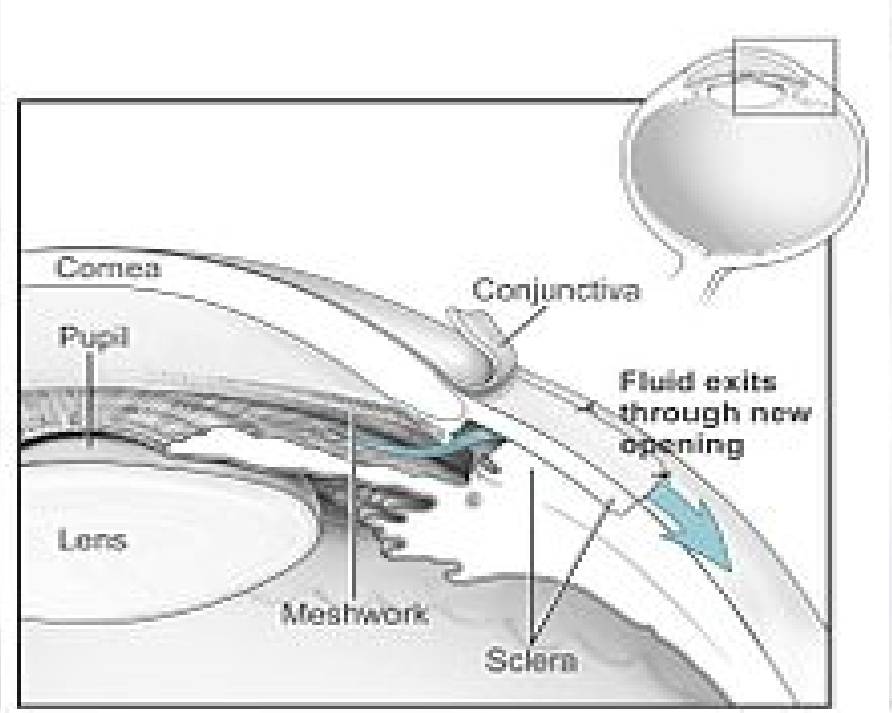
COMPARATIVE BIOSCIENCES, INC.

Premier Preclinical Contract Research Organization

- **Focus on Eyes**
- Over 20 years of experience
- Conveniently located in the heart of Silicon Valley, amidst many biotech companies
- State of the art, purpose-built facility
- Approximately 30 employees
- Highly experienced staff
- GLP, OECD, FDA, USDA, OLAW
- AAALAC Accreditation

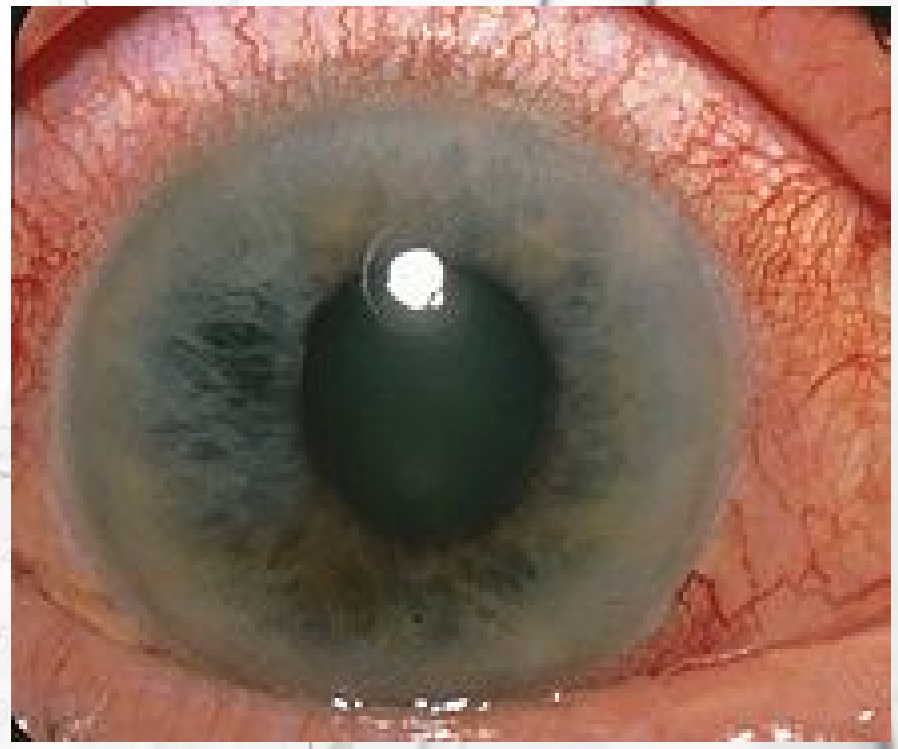
Glaucoma in Humans

- Common group of diseases resulting in increased intraocular pressure and damage to the retina and optic nerve
  - Most common: Wide or open angle slow exit of aqueous humor through trabecular meshwork
  - Narrow Angle-acute, iris blocks the trabecular meshwork
    - Normal Angle glaucoma-not common



Causes in Patients

- Heredity
- Age
- Ocular trauma
- Ocular inflammation
- Cataracts



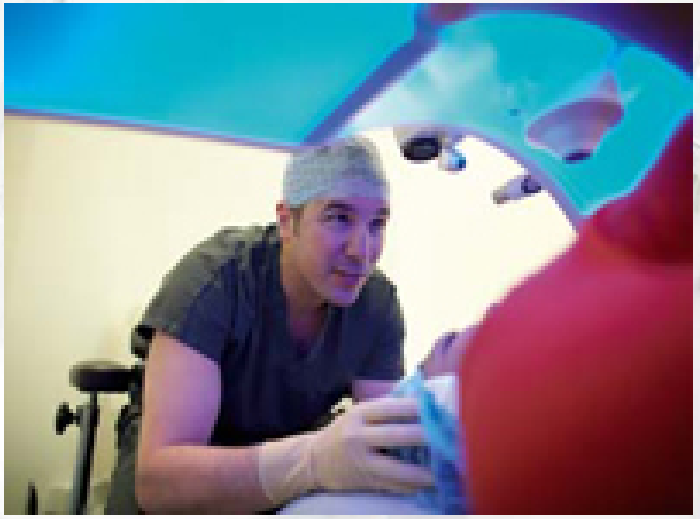
Clinical presentation of untreated glaucoma

Current Clinical Medical Treatments

- Drugs
  - Prostaglandin analogs (lanoprost)
  - Parasympathomimetic or mitotic agents
  - Carbonic anhydrase inhibitors
  - Adenergics – Beta 1 antagonists
  - Alpha 2 agonists
  - Hyperosmotic agents

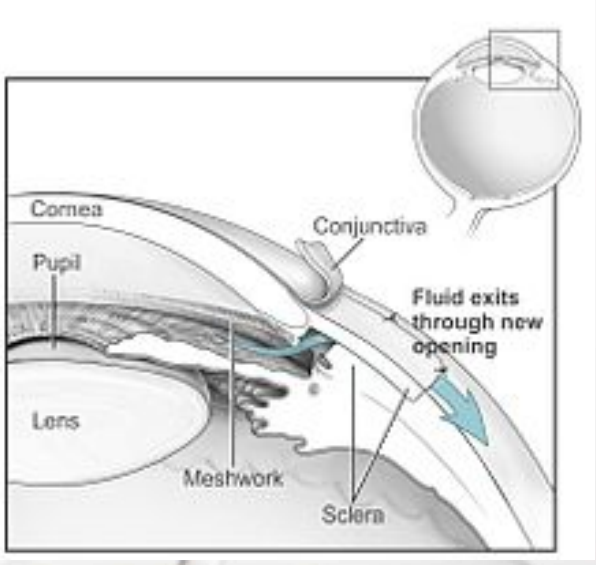
Clinical Surgery Treatments

- Trabeculectomy
- Canalplasty
- Glaucoma drainage implants
- Laser assisted non-penetrating deep sclerectomy



Preclinical Glaucoma Models at CBI

- Numerous models available:
  - Transgenic models in rodents
  - Episcleral vein cauterization in rodents
  - Surgical and device models
  - Steroid-induced in rabbits
  - Chymotrypsin-induced in rabbits
  - IOP reduction in normal rabbits and dogs
  - Other models or custom models upon request



Murine/Transgenic Models

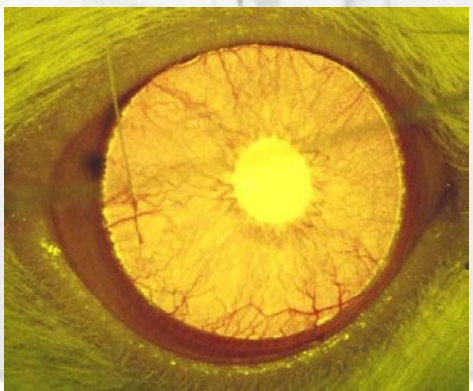
- DBA/2J inbred mice (aged) spontaneously develop glaucoma
- Tg-MYOC^{Y437H} mice - Mouse model of primary open angle glaucoma (POAG)-express human transgene, at >40 weeks (Zode, Sheffield, 2015)
- Mutations in the myocilin (MYOC) gene, which encodes a protein expressed abundantly in the trabecular meshwork, are the most common genetically defined cause of glaucoma
- CBI working with transgenic provider to be first non-academic CRO with this model

Episcleral vein cauterization rat glaucoma model

- **Assess IOP changes following unilateral laser cauterization of episcleral veins in rats**

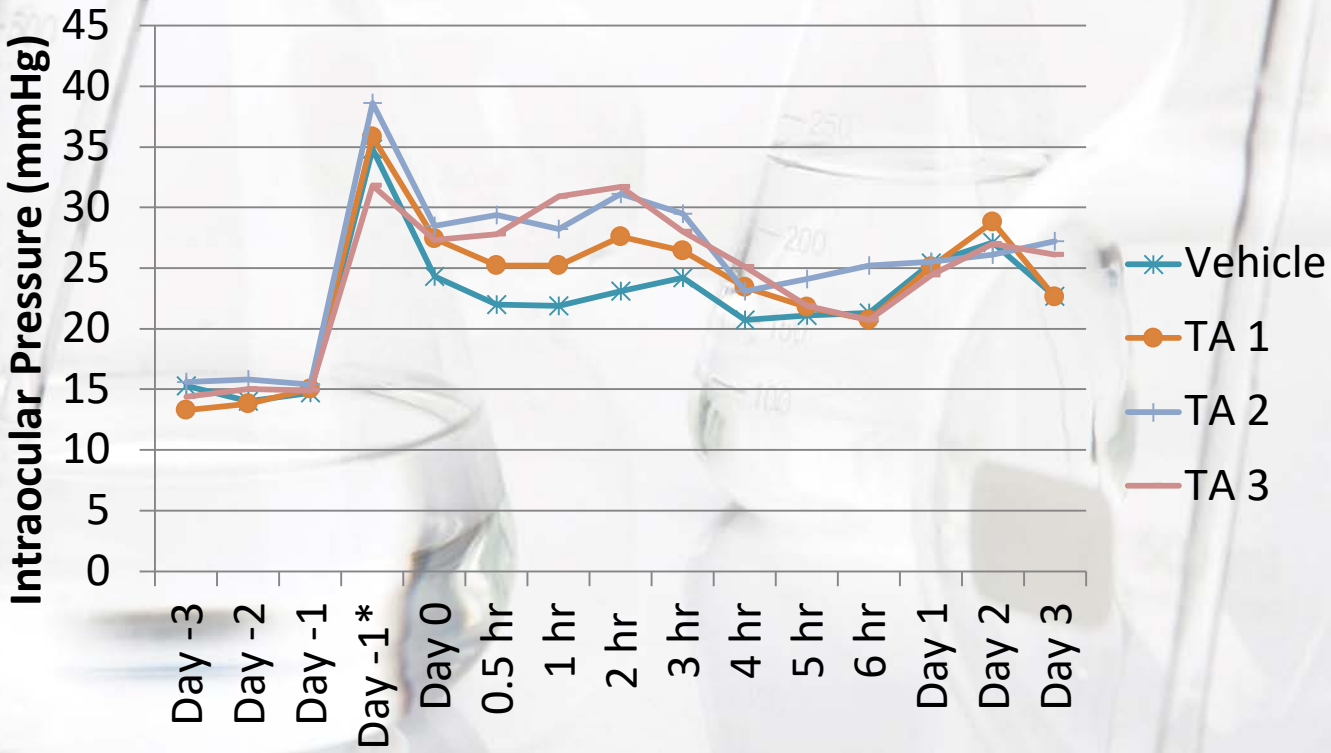
- Sprague Dawley or Brown Norway rats
- Laser photocoagulation of limbus on Day 0 on right eye, left eye untreated
- IOP measurements at prescribed intervals

- **Intraocular pressure in the operated eyes clearly increased dramatically within 15 minutes of cautery and remained fairly stable, and statistically significantly increased for days to weeks.**



Episcleral vein cauterization rat glaucoma model

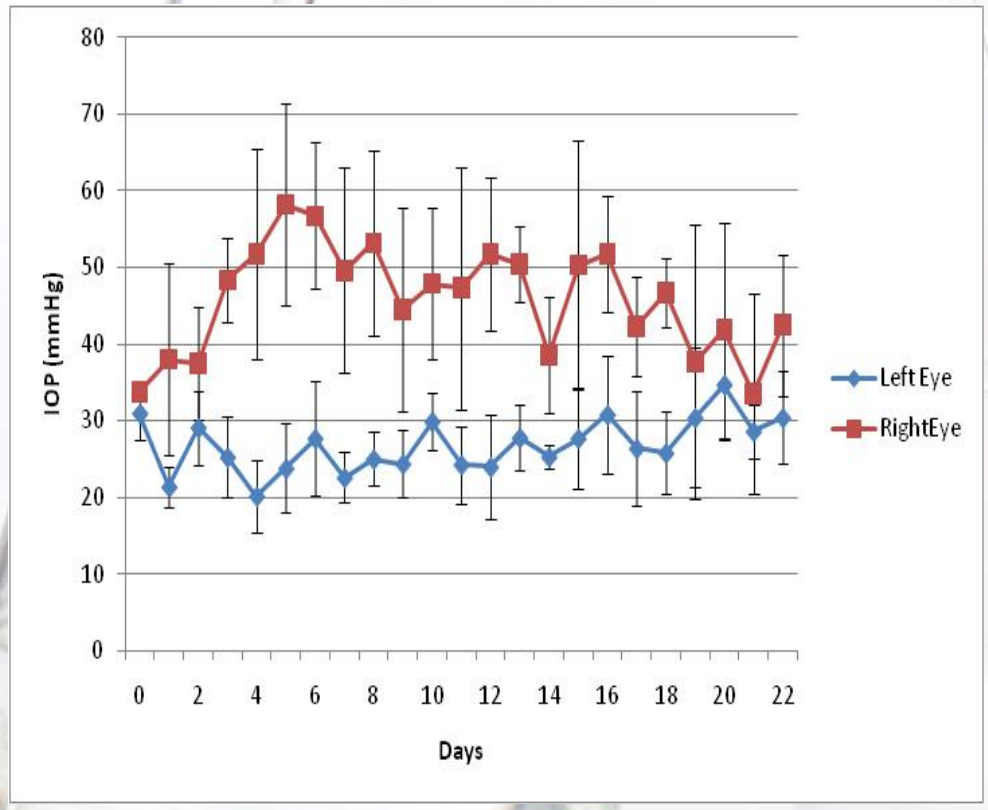
IOP is consistently increased over time



Rabbit Models of Glaucoma

- Chymotrypsin-induced glaucoma in rabbits-longest and most reliable IOP elevation
- Steroid-induced-3-5 week administration of cortico steroid will increase IOP
- Laser-induced-short term, not very reliable, structure of the iridocorneal angle, which is different from that of humans.

IOP in Chymotrypsin versus test article treated eyes

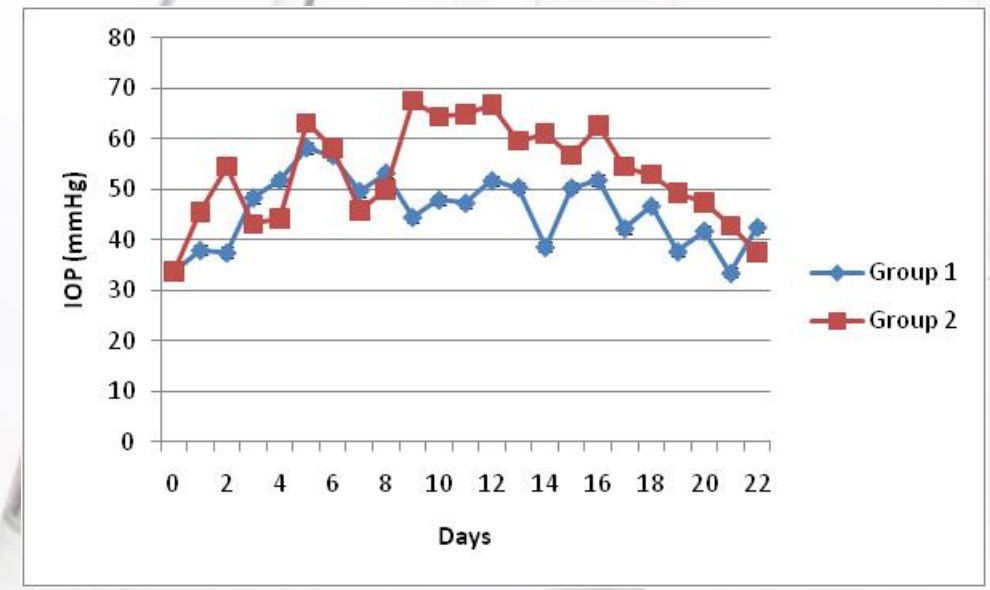


- Chymotrypsin injected unilaterally resulting in obstruction of the outflow and increases in the IOP.

- Right eyes-Chymotrysin treated. There is a significant increase in IOP over a 3 week period'

- Left eyes: Normal
- N=8

IOP in Chymotrypsin versus untreated eyes



Group 1-Chymotrysin-treated and vehicle-treated. There is a significant increase in IOP over a 3 week period.

Group 2: Chymotrypsin-treated and test article-treated. There is a positive response to test article treatment.
N=8

Steroid Induction

- Rat model induced by topical application of dexamethasone
  - Rats share similar anatomical and developmental characteristics of the anterior chamber, especially in aqueous outflow pathway with humans
  - Reasonable IOP elevation as retinal and ON changes are similar to humans
- Rabbit model induced via betamethasone subconjunctival injection
- Mimics human chronic open-angle glaucoma

Custom Surgical and Device Models

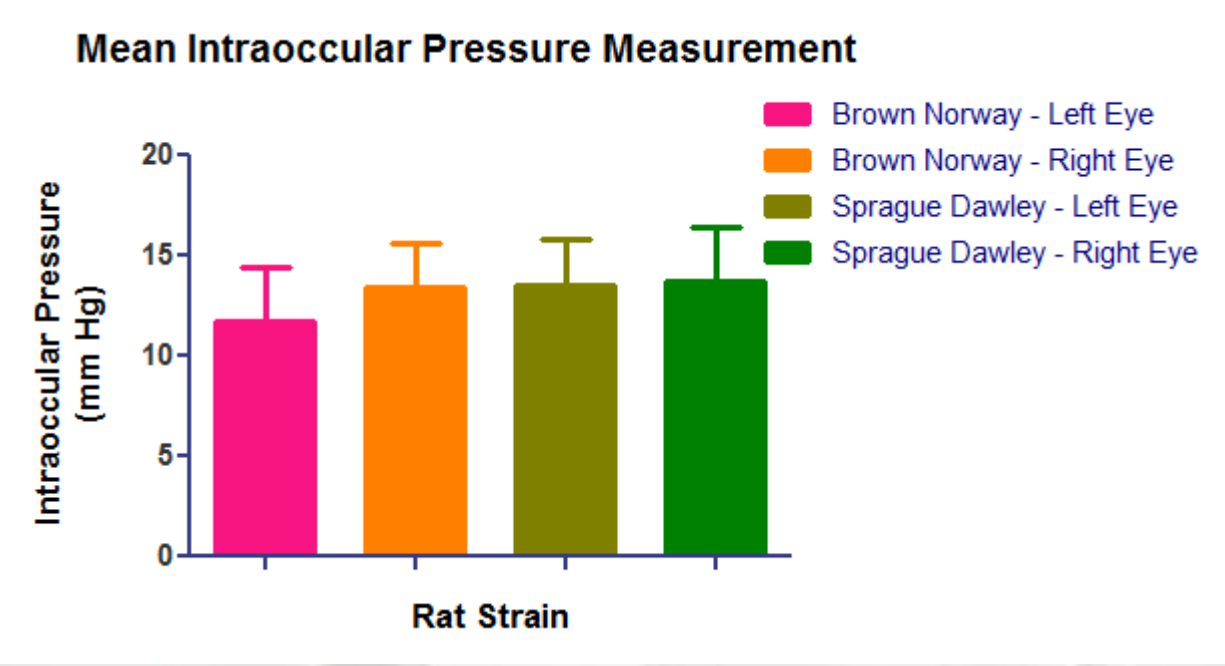
- Glaucoma filtration devices and drainage implant surgery-custom surgery
- Rabbits preferred species
- Study duration-days to months
- Parameters-local tolerability, IOP, funduscopy, histopathology,

IOP effects in normal animals

- The IOP lowering effects as well as local tolerability of test compounds may be assessed in normal animals effective
- Dogs, rabbits, rodents are suitable, particularly dogs
- Cost effective and large numbers of compounds are easily screened for days to weeks
- Lanoprost, Timolol are suitable positive controls

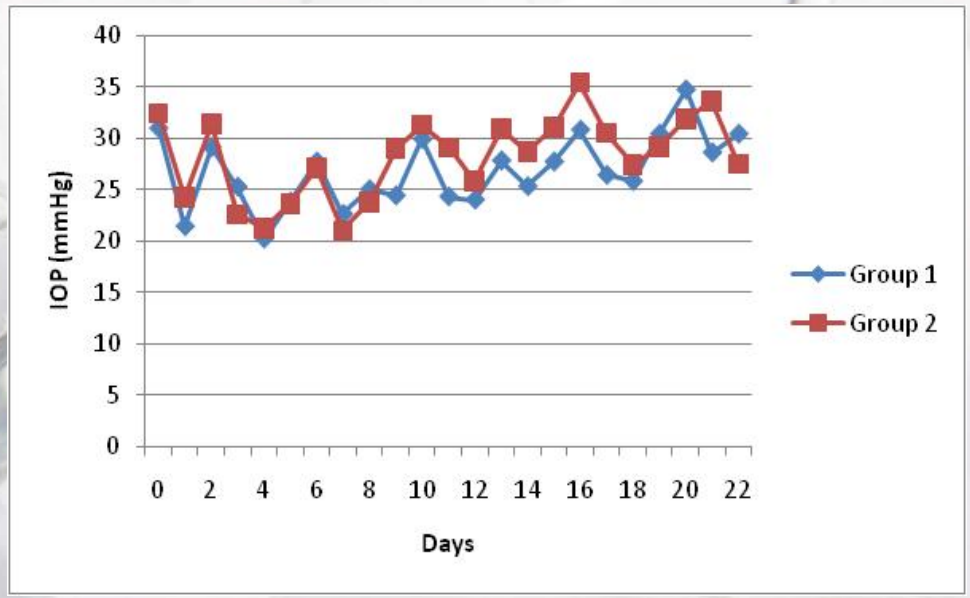
Normal Eye IOP in Rats

- Albino and Brown Norway - typical
- IOP consistent in normal animals
- No meaningful differences between left and right eyes, between sexes or between strains



Normal Eye IOP Reduction in Rabbits

- Dutch belted and Albino rabbits-No meaningful differences between left and right eyes, between sexes or between strains
- Below-comparison of normal values in Dutch belted vs Albino rabbits

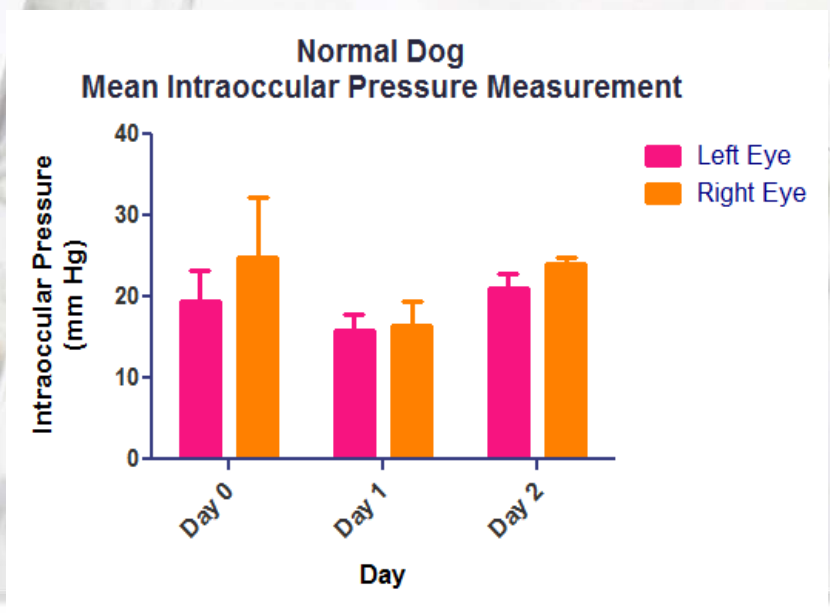


Normal Eye IOP Reduction in Dogs

- Beagle Dogs

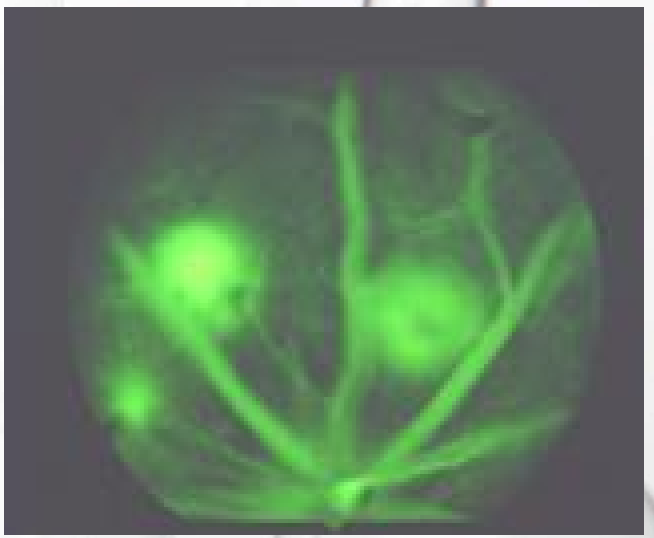
- No meaningful differences between left and right eyes, between sexes
- Below Left -IOP values in normal dogs.

- Below Right- left eye of patient dog with unilateral spontaneous glaucoma.



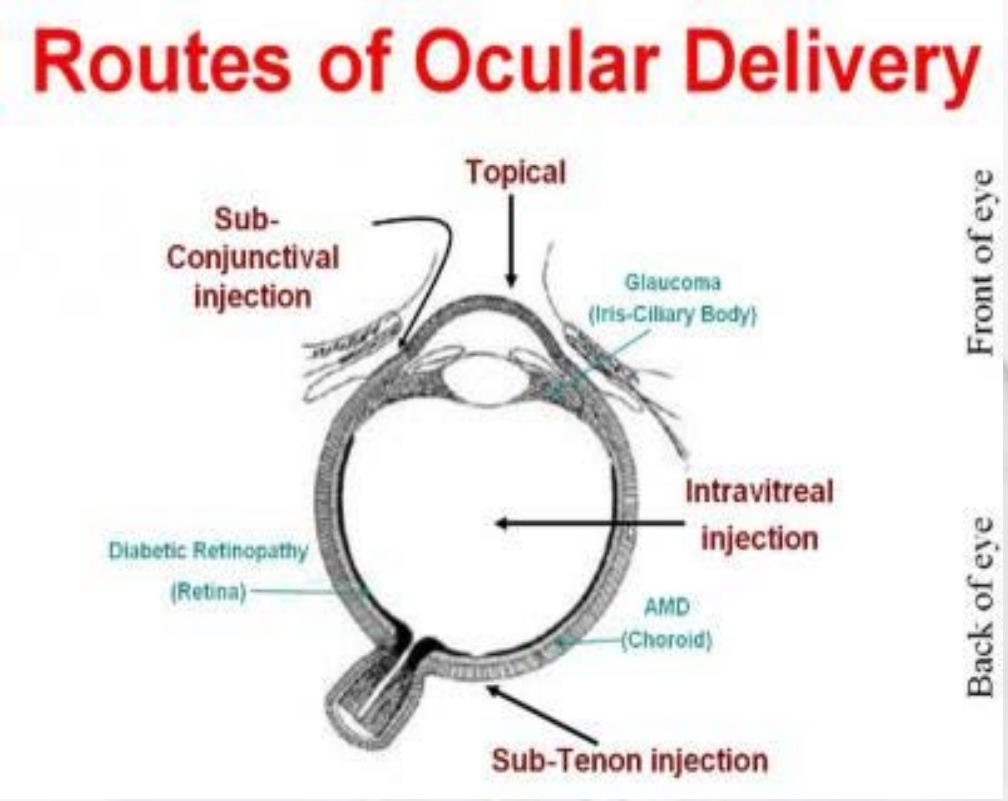
Typical Endpoint Assessments for Ocular Studies at CBI

- Slit lamp biomicroscopy
- Tonometry
- Pachymetry
- ERG
- OCT
- Goniscopy
- Funduscopy
- Angiography
- Histopathology and Immunohistochemistry
- Pathology
- Photomicroscopy and Histomorphometry



Typical Routes of Administration for Ocular Studies at CBI

- Topical
- Intra vitreal
- Subretinal
- Subconjunctival
- Intracameral
- Subtenon
- Transcleral
- Device implantation



Ocular Toxicology

CBI offers ocular toxicology, pharmacokinetic and pharmacology capabilities

- Acute, subacute and chronic toxicology studies
- Discovery and investigative toxicology studies
- Ocular and other routes of delivery
- Special ocular assessments
- Complete, prompt reports

Ocular Pharmacokinetics

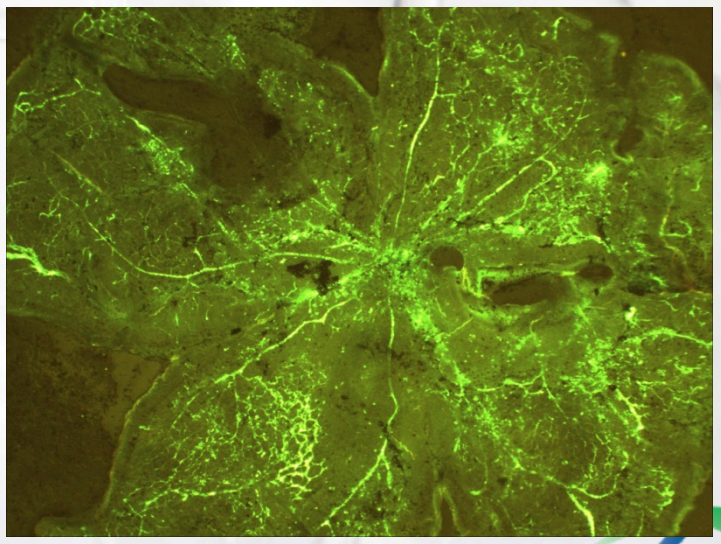
CBI offers ocular toxicology, pharmacokinetic and pharmacology capabilities

- Ocular and other routes of delivery
- Special ocular assessments
- Tissue and fluid collection from different subparts of the eye
- Ex. aqueous, vitreous, anterior segment, retina, sclera
- Complete, prompt reports

Ocular Pharmacology

CBI offers ocular toxicology, pharmacokinetic and pharmacology capabilities

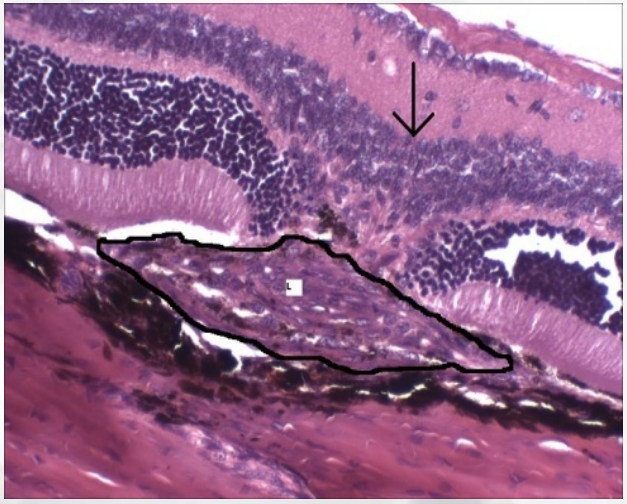
- Wide range of ocular pharmacology and efficacy studies
- Inflammation
- Oxygen-induced retinopathy
- Choroidal neovascularization
- Glaucoma
- Diabetes-induced retinopathy
- Cataract and lens
- Ocular surgery
- Corneal injury and transplant
- Ocular implants
- Dry Eye
- Custom studies

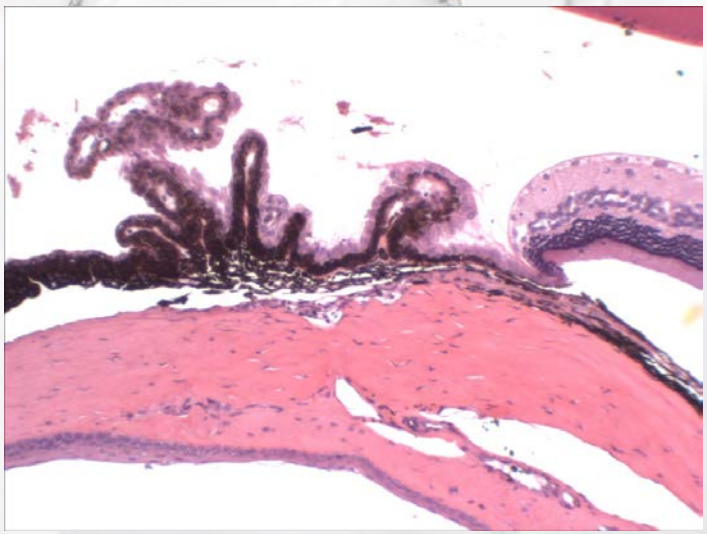


Ocular Histopathology

CBI offers ocular histopathology, immunohistochemistry and histomorphometry

- Routine ocular histopathology in all species
- Immunohistochemistry
- Ocular histomorphometry
- Complete, prompt reports, GLP, nonGLP





Service and Quality

- **The people at CBI**—from the executive team to the study directors to the research associates expect to have to earn your trust and business.
- **Our ratio of scientists to non-scientists** is one of the highest in the industry. We believe in sound science and every study director is a PhD-level scientist
- **Thoroughness in planning and execution** is key to a successful study. All protocols are vetted and approved by multiple personnel. Our QAU has a rigorous training program. All non-GLP studies are conducted in the spirit of GLP with the same SOPs.
- **We believe in communication**: timely responses to your inquiries and frequent updates on your study are mandatory.
- **Rapid initiation and adjustments**; with the collective expertise of must larger organizations but the flexibility of a smaller more nimble group.
- **You are always welcome** at CBI to meet the staff, tour the laboratory and discuss the progress and results of your study.

Our Staff

- **Study Directors**
  - PhD level scientists
  - Appointed by management for each job
  - Serves as single point of control and is responsible and accountable for study conduct and scientific interpretation
  - Experienced attentive and communicative
  - Rapid study initiation and report preparation
- **Research Associates**
  - Bachelor Level Scientists
  - Extensive technical training
- **Quality Assurance**
  - Full time, dedicated
  - Rigorous training program
- **CBI Management**
  - Experienced senior scientific management-with large and small pharma experience

Summary

- **With a focus on quality, CBI provides state of the art:**
  - Toxicology
  - Pharmacokinetics
  - Efficacy
  - Pharmacology
  - In house histopathology
- **Experienced attentive and communicative study directors**
- **Rapid study initiation and report preparation**
- **Established, stable business**
- **Regulatory compliance**
- **Favorable pricing structure**
- **LAST SLIDE**