



PRECLINICAL MODEL: OXYGEN-INDUCED RETINOPATHY IN MICE

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COMPARATIVE BIOSCIENCES, INC.
A TRANSLATIONAL APPROACH TO PRECLINICAL RESEARCH

COMPARATIVE BIOSCIENCES, INC.

Premier Preclinical Contract Research Organization

- **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**



Scientific Overview

We specialize in developing a custom study plan in order to best meet your pre-clinical research needs and prepare for regulatory submission.

- GLP and Non-GLP
- Toxicology
- Efficacy
- Pharmacokinetics
- Pharmacology
- Oncology Studies
- In-house histopathology, immunohistochemistry & TCR



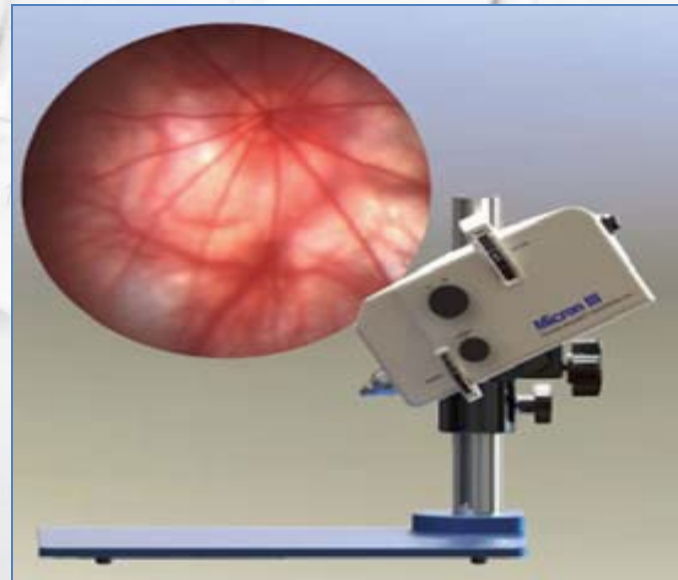
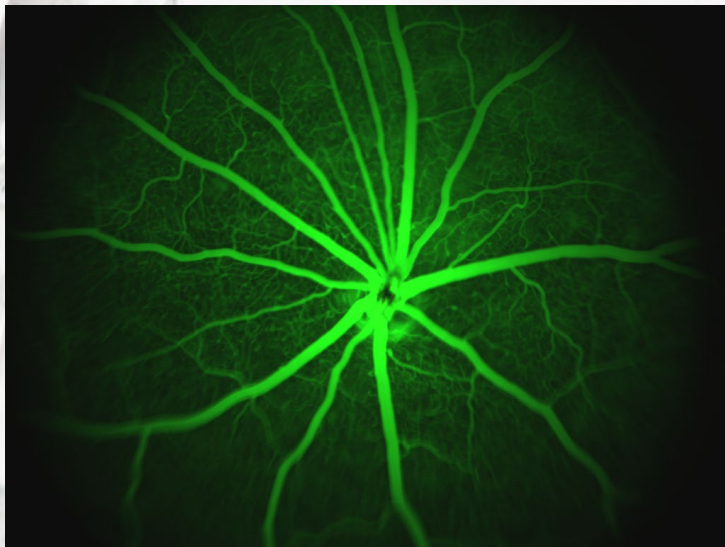
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- OIR in mouse or rat pups validated model assessing new vessel formation.
 - Pups placed in a high/low oxygen chamber for species appropriate duration and oxygen concentration
 - Treatment administered at appropriate time intervals.
 - OCT may be conducted during in life to assess in vivo retinal changes
 - Eyes collected for pathologic examination or FITC whole mount preparation.
 - Routine staining, special staining, immunohistochemistry
 - Retinal proliferative plaques identified and measured by any of several methods.
 - Dimensions of neovascular plaque proliferation compared between control and treatment groups.

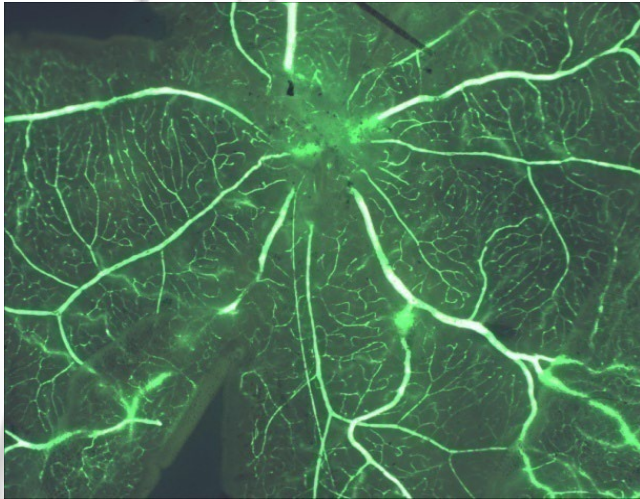


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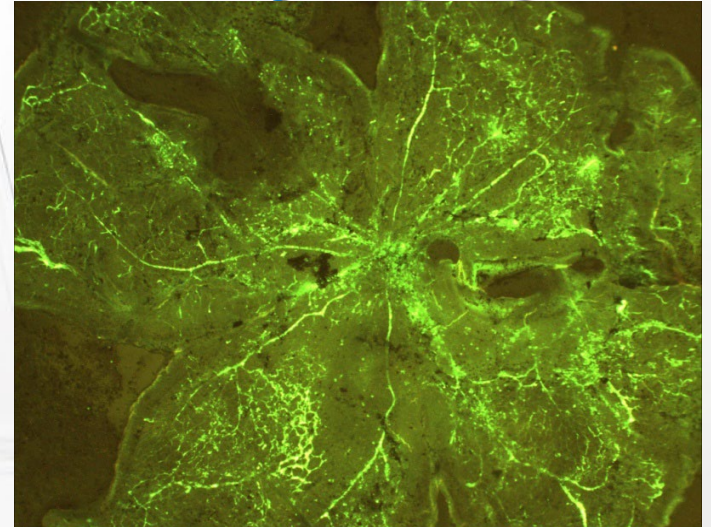
The OIR model in hyper-oxygenated neonatal mouse or rat pups is a robust and established model to investigate new vessel proliferation in the retina. This is a model for several important ocular disorders such as age-related macular degeneration, retinopathy of prematurity, and various spontaneous retinal disorders in which retinal vascular disorders are prominent.



Retinal Flat Mounts from Hyper-oxygenated Mouse Pups



Top Left: Normal retina from age-matched normo-air rat pup.



Hyper-oxygenated retina demonstrating vascular proliferation and leakage.



Triamcinolone-treated hyper-oxygenated retina showing a reduction in the amount of leakage and vascular leakage.



Optical Coherence Tomography

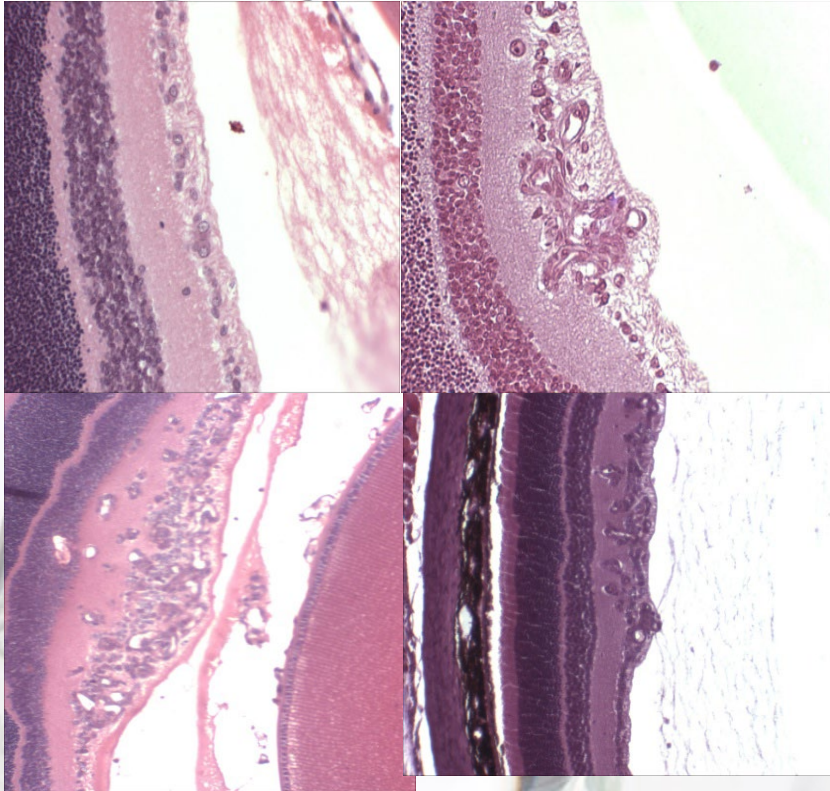
Bioptigen Envisu R-Class System (for preclinical studies)

OCT has several benefits and its inclusion in ocular toxicology, pharmacokinetic and pharmacology studies should be considered:

- Noninvasive - only requires brief immobilization
- Facilitates longitudinal, real time and repetitive tracking of ocular changes, in particular **retinal neovascular proliferations**, sub retinal injections, stem cell implants, intraocular implants, retinal changes, and tumors.
- Reveals or detects subtle retinal or ocular changes that are not visible with slit lamp biomicroscopy or funduscopy
- Retinal tufts and proliferation visible with OCT
- Contributes to improved clinical trial design



Retinal Histopathology in Hyperoxygenated Mouse Pups



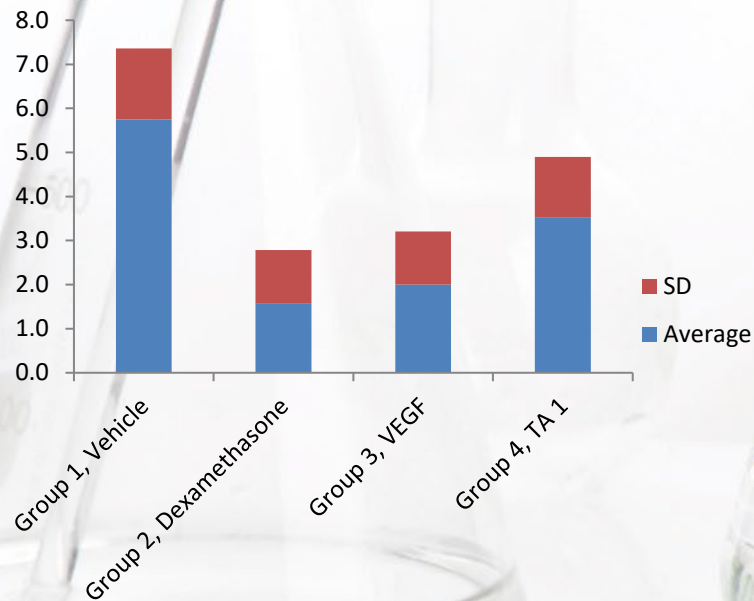
Top left: Normal retina from age matched mouse pup in normal air

Top right and bottom left: Hyper-oxygenated with vehicle treatment: There are large numbers of new vessel cross-sections proliferating on the surface of the retina and extending into the vitreous

Bottom right: Hyper-oxygenated with dexamethasone treatment: There are reduced numbers of vessel cross sections.



Neovascular cell counts in hyperoxygenated retinas



Mice were treated with vehicle, dexamethasone, and a test article

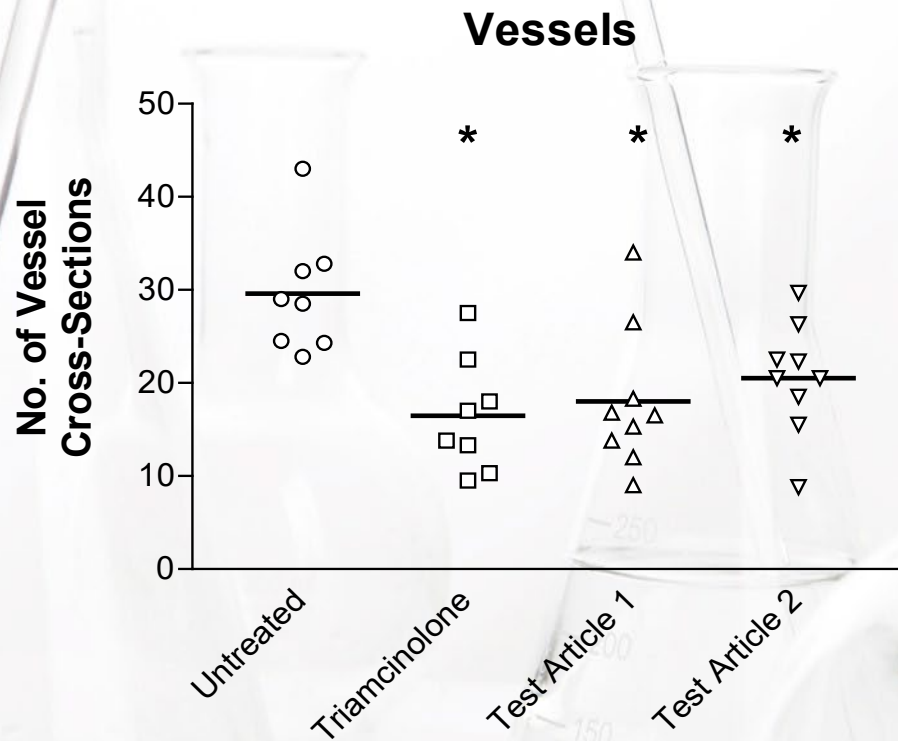
New vessel cross sections on the surface of the retina and within the vitreous were counted

Four eye sections for each mouse and 8 mice per group were examined for a total of 32 eyes per group

Dexamethasone and VEGF AB markedly and statistically reduce the number of new vessels in the eye in comparison to the vehicle control

The test article also demonstrated activity

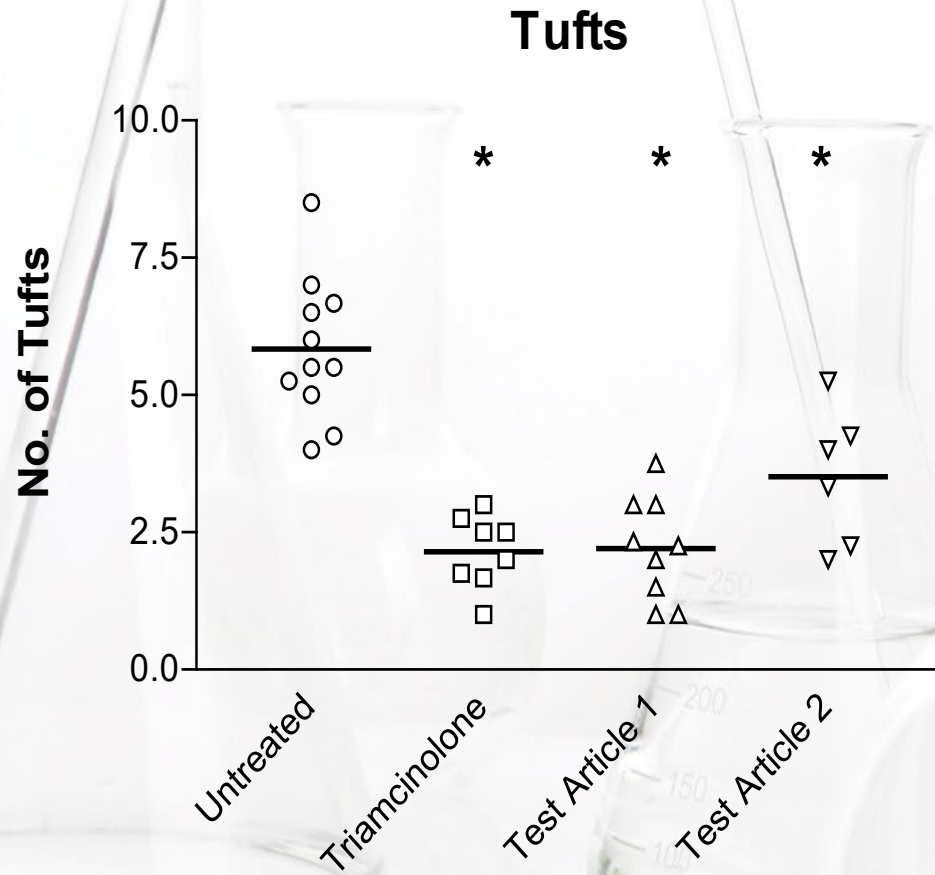




Assessment of retinal new vessel formation in hyperoxygenated mice showing number of vessel cross-sections. Horizontal bars show group means.

*** Statistically significant compared to hyperoxygenated untreated control group.**





Assessment of retinal new vessel tuft formation in hyperoxygenated mice showing number of vessel cross-sections. Horizontal bars show group means. * Statistically significant compared to hyperoxygenated untreated control group.



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**

