

CBI

STZ Induced Retinopathy in Rats

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STZ-Induced Retinopathy in Rats

- STZ administration induces a Type I diabetes with hyperglycemia, weight loss and ocular changes over a period of months.
- CBI has established this as a short or long term model in Brown Norway Rats to evaluation both systemic and ocular changes.
- In the retina, hypervascularity and thickening of the mid retinal layers occurs and is similar to changes in patients.
- OCT is a powerful, sensitive and sophisticated tool for assessment of changes in in the retinal mid layer thickness, an important determinant in diabetic retinopathy
- Fluorescein angiography is also an important assessment demonstrating retinal leakage and vascularity
- Histopathology and immunohistochemistry-important tools



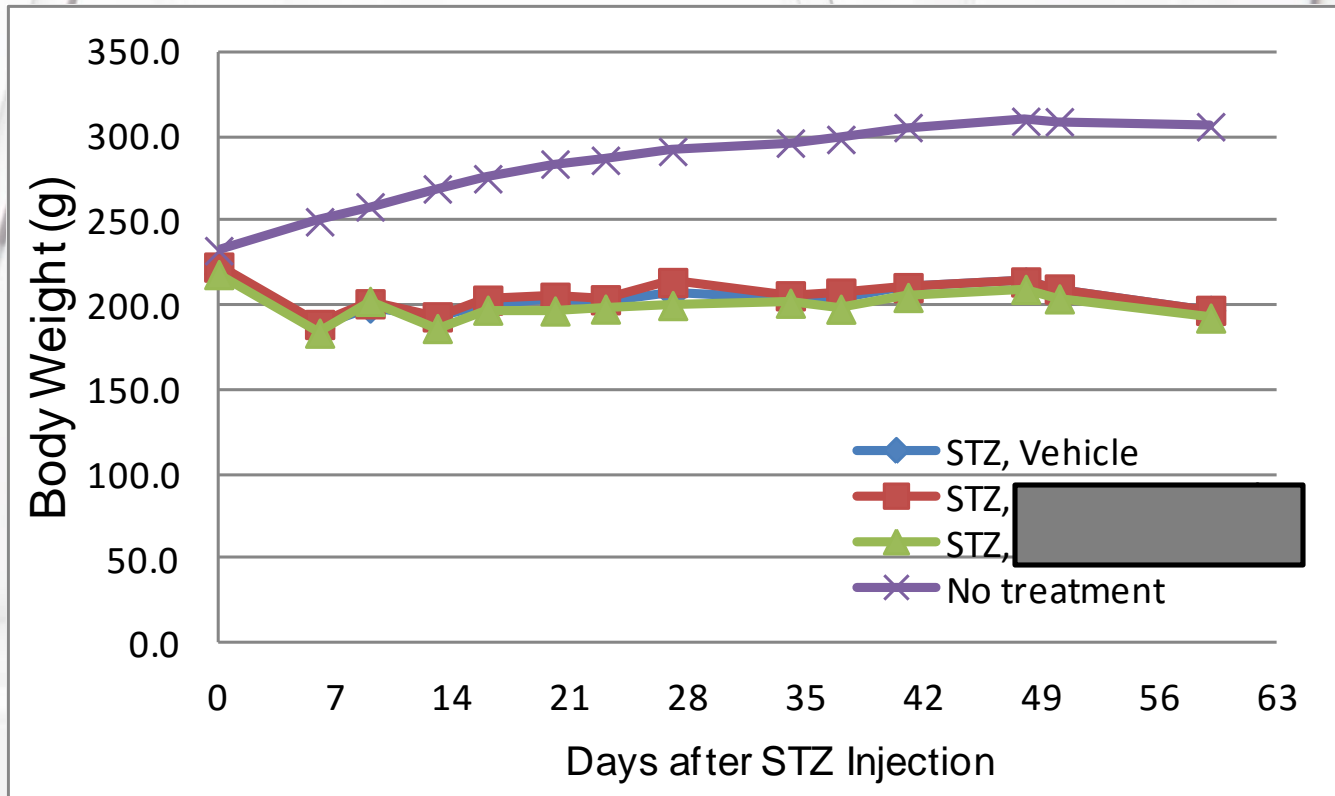
STZ-Induced Retinopathy in Rats

- STZ is glucosamine–nitroso-urea compound derived from *Streptomyces achromogenes* that is used clinically as a chemotherapeutic agent in the treatment of pancreatic β cell carcinoma. **STZ** damages pancreatic β cells, resulting in hypoinsulinemia
- There is severe hyperglycemia (>400 mg/dl) with weight loss, anorexia and dehydration. Long term management of these animals requires specialized skills.
- Blood glucose, body weights and clinical signs are important observations
- OCT, fluorescein angiography, histopathology and immunohistochemistry are important assessments

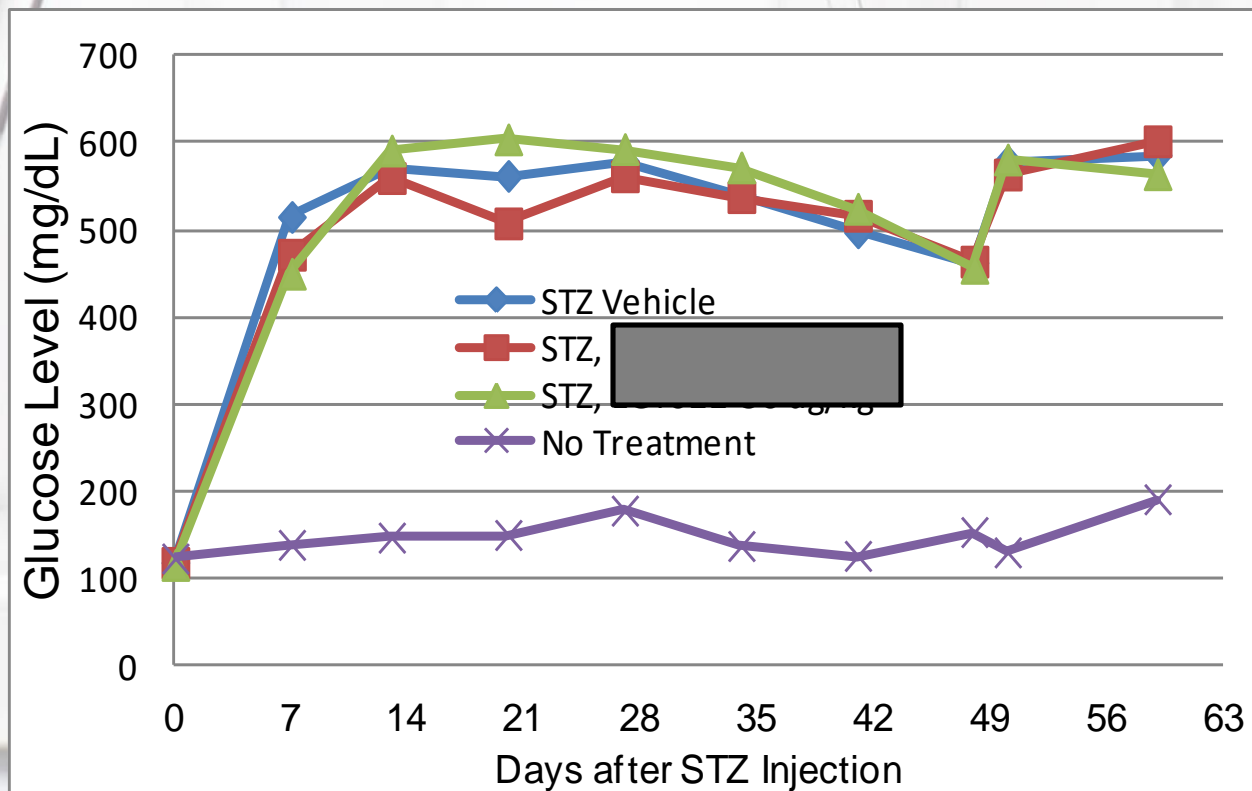


Body Weights After STZ Initiation.

Over a period of weeks weight can be stabilized



Blood Glucose After STZ Initiation. Blood glucose may be maintained below 600 mg/kg and the animals stabilized.



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:

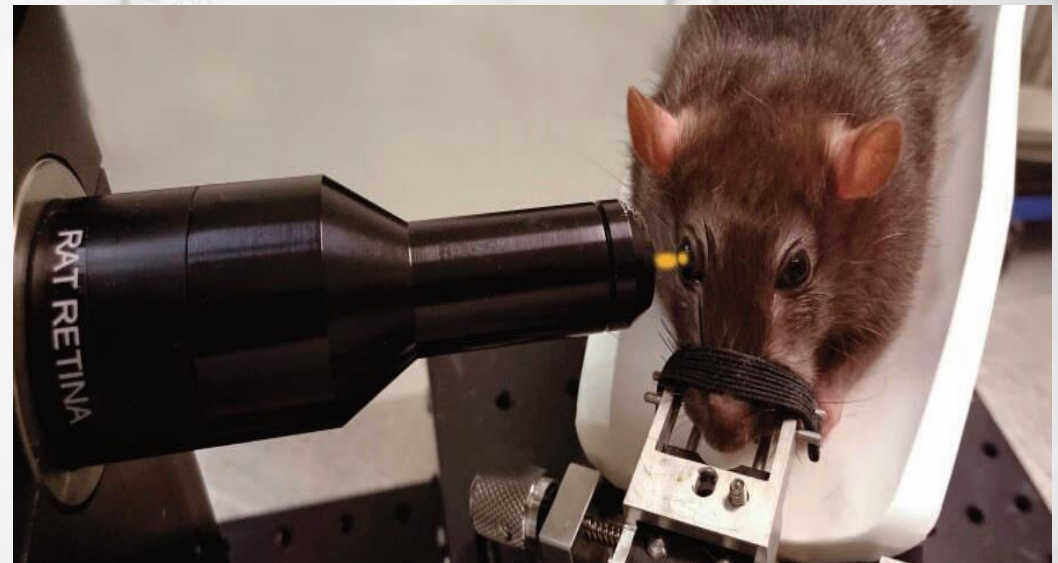
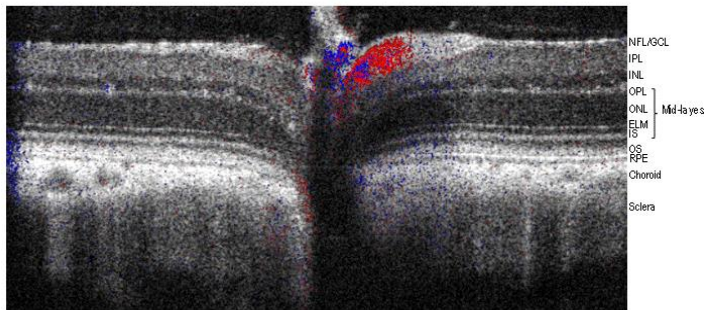
- Noninvasive - only requires brief immobilization
- Facilitates longitudinal, real time and repetitive tracking of ocular changes, in particular sub retinal injections, stem cell implants, intraocular implants, retinal changes, and tumors.
- Reveals or detects subtle retinal or ocular changes that are not visible with slit lamp biomicroscopy or funduscopy
- OCT changes are visible by 4-6 weeks post STZ-initiation
- Contributes to improved clinical trial design



OCT and STZ

Through the use of OCT, we have confirmed that there is thickening of the retinal mid layers in STZ-induced hyperglycemic rats in comparison to normal rats.

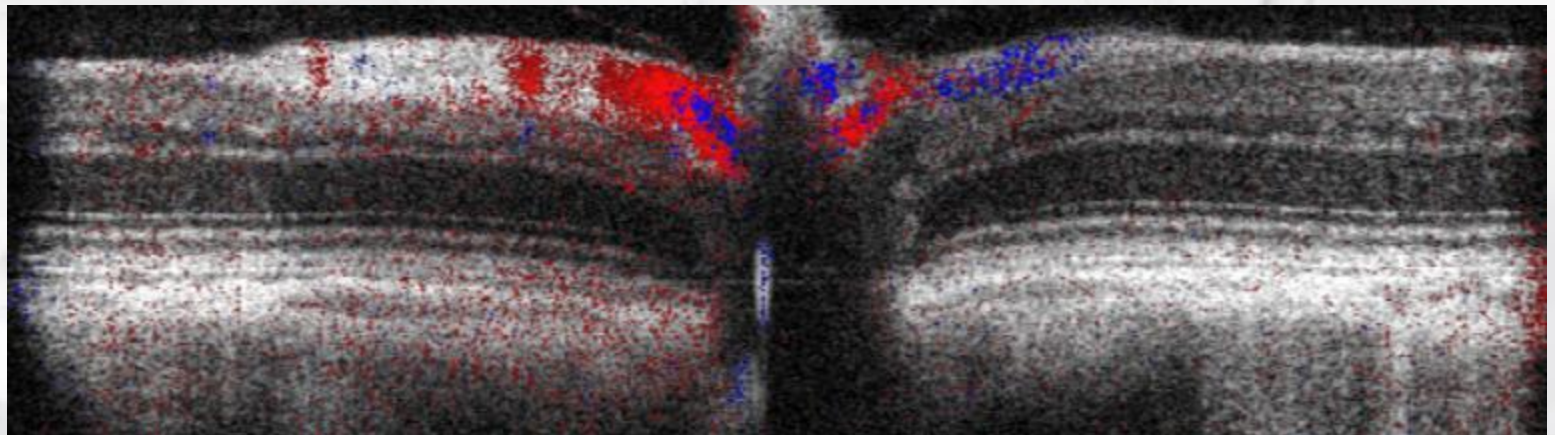
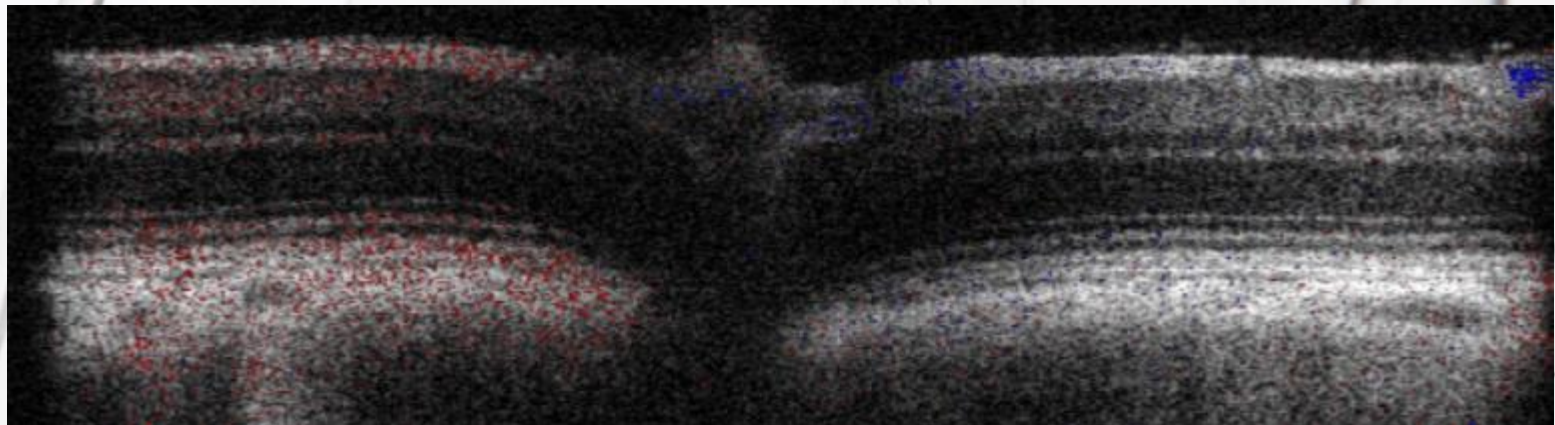
A series of confirmatory data has been obtained comparing the mid retinal thickness of STZ-initiated vs normal rats. There is a statistically significant increase in thickness in STZ-initiated rats.



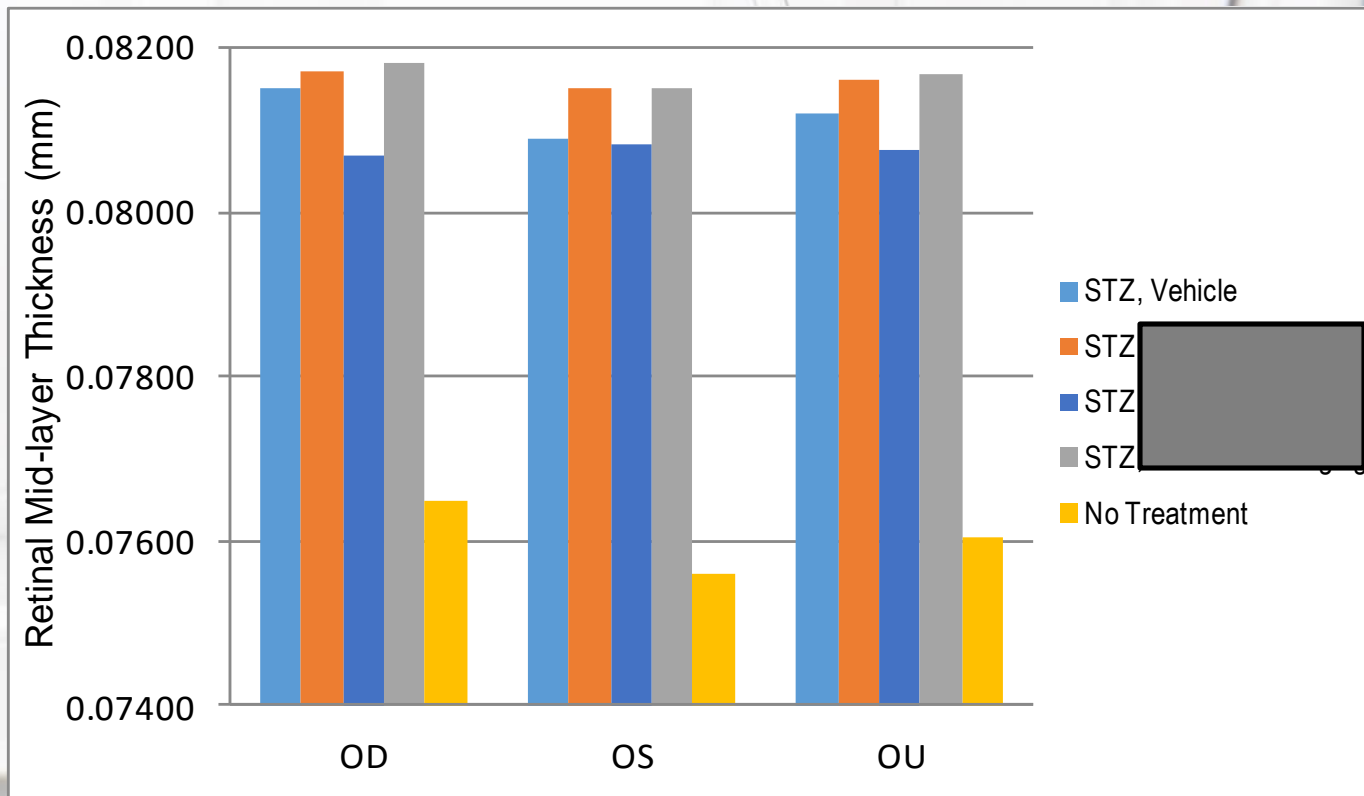
OCT Retinal Scan

Top: Normal animal

Bottom: 7 week post STZ-initiation demonstrating increased midretinal thickness and increased vascularity (red and blue)

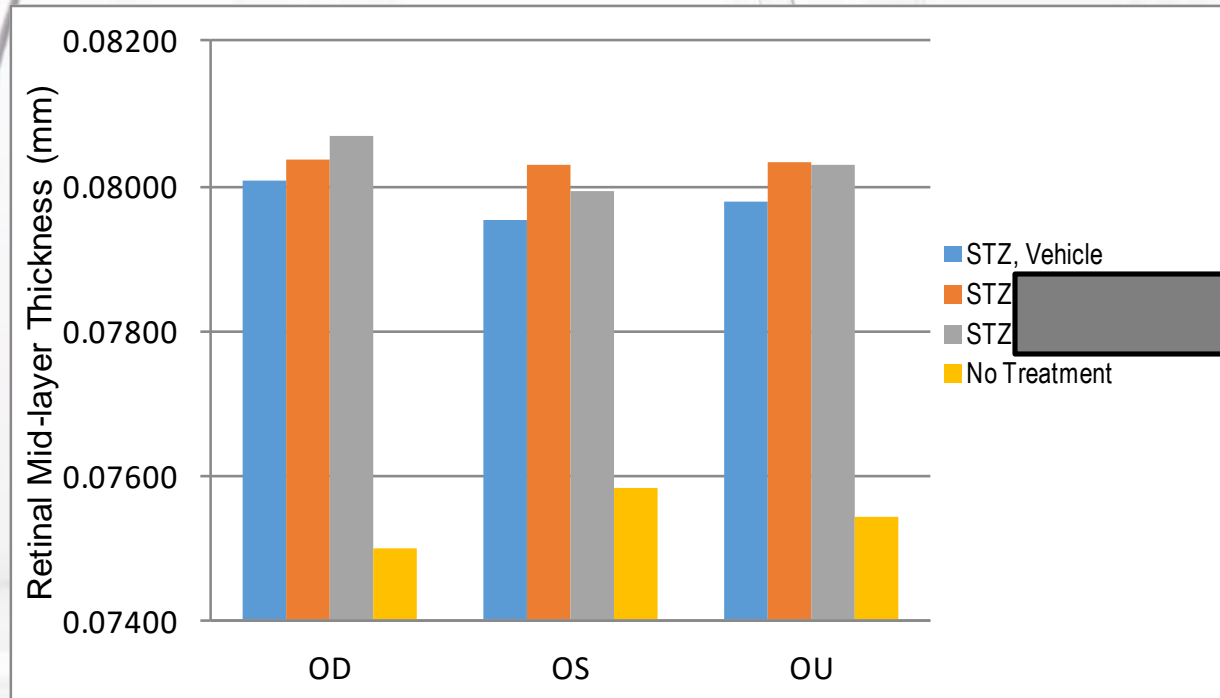


7 weeks post STZ initiation demonstrating consistent increases in midretinal thickness. There is no difference between the left and right eye.



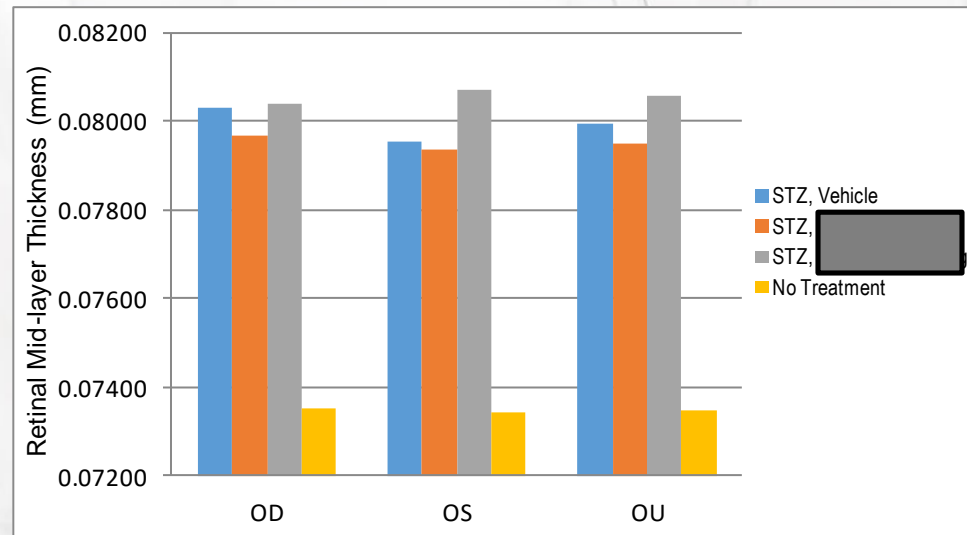
Four different vehicles are used
 No treatment=normal animal with no STZ
 initiation

11 Weeks Post STZ initiation demonstrating consistent increases in mid retinal thickness



Three different vehicles are used
No treatment=normal animal with no STZ
initiation

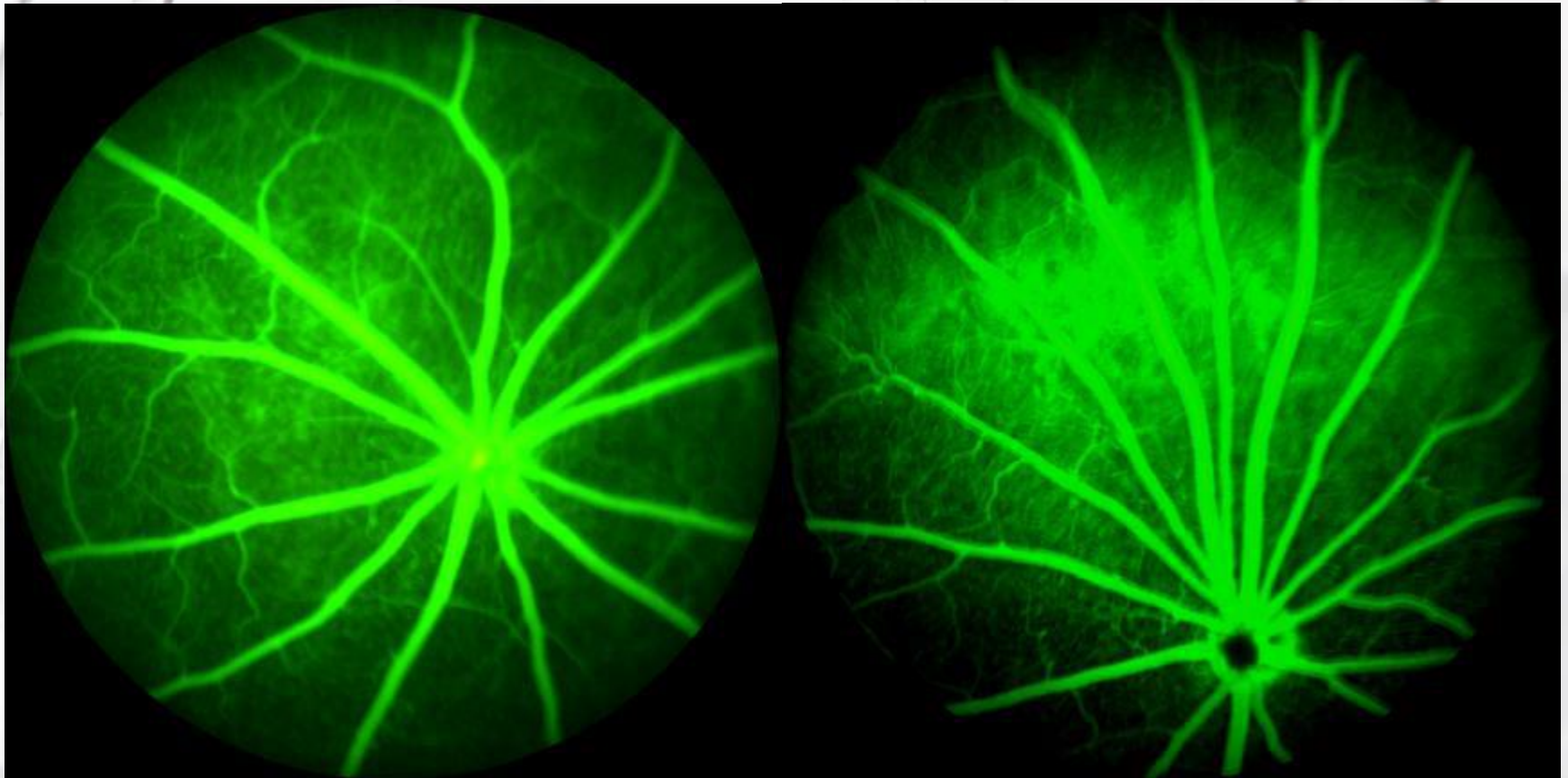
16 Weeks Post STZ initiation demonstrating consistent increases in mid retinal thickness



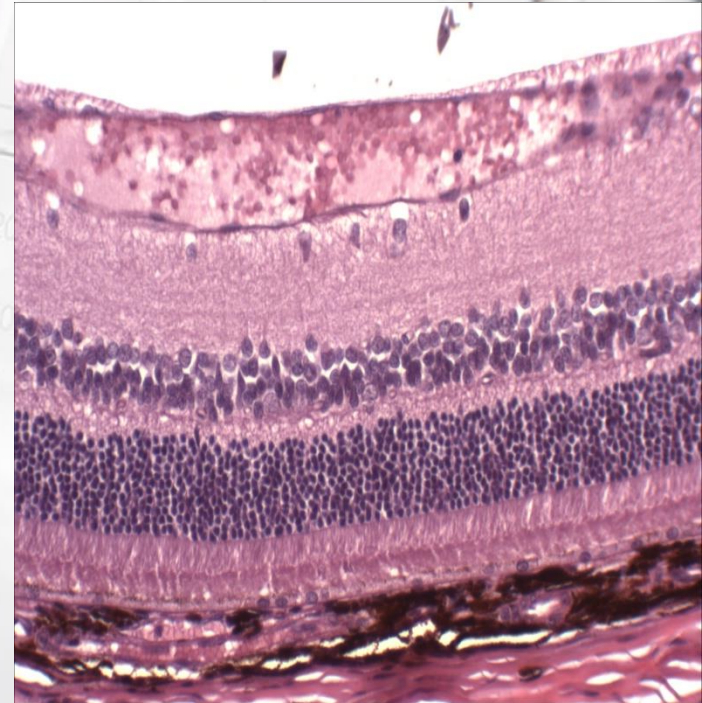
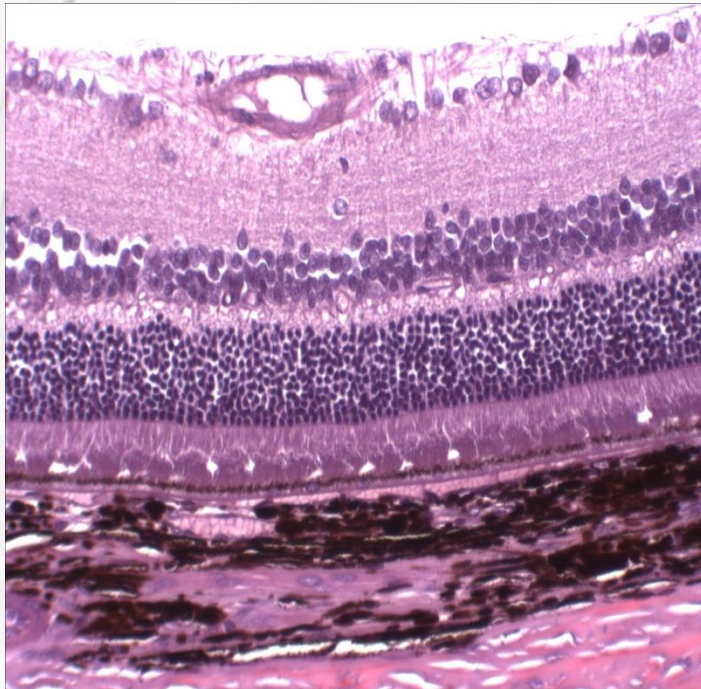
Three different vehicles are used
No treatment=normal animal with no STZ initiation

Fluorescein Angiography

Demonstrating increased vascularity of retina in post-7 weeks STZ-initiated animals. Left: normal; right-STZ-initiated, note increased vascularity and leakage.

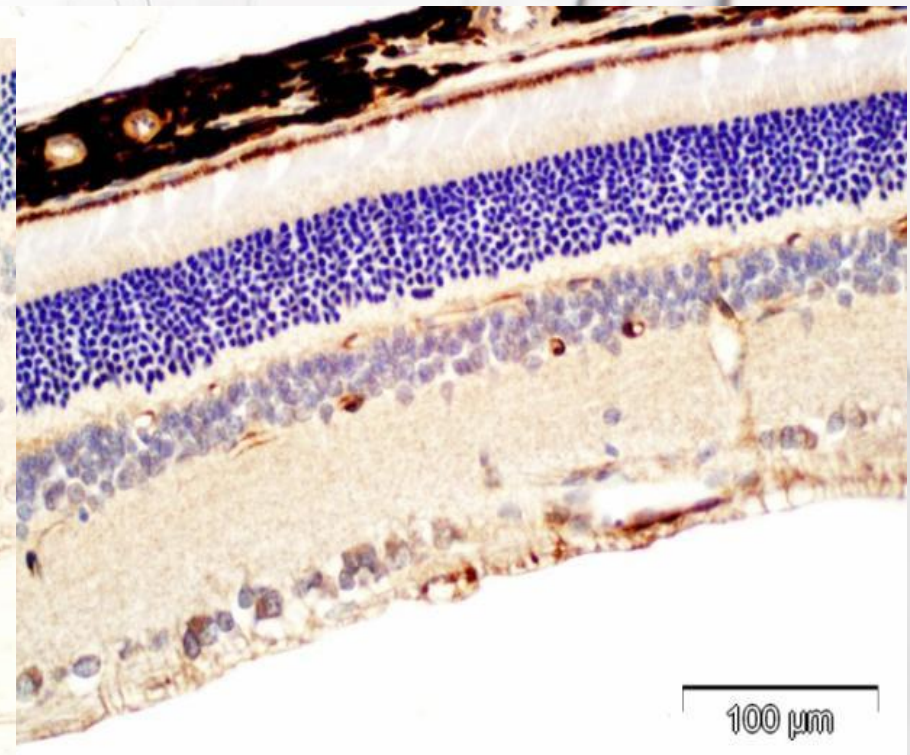
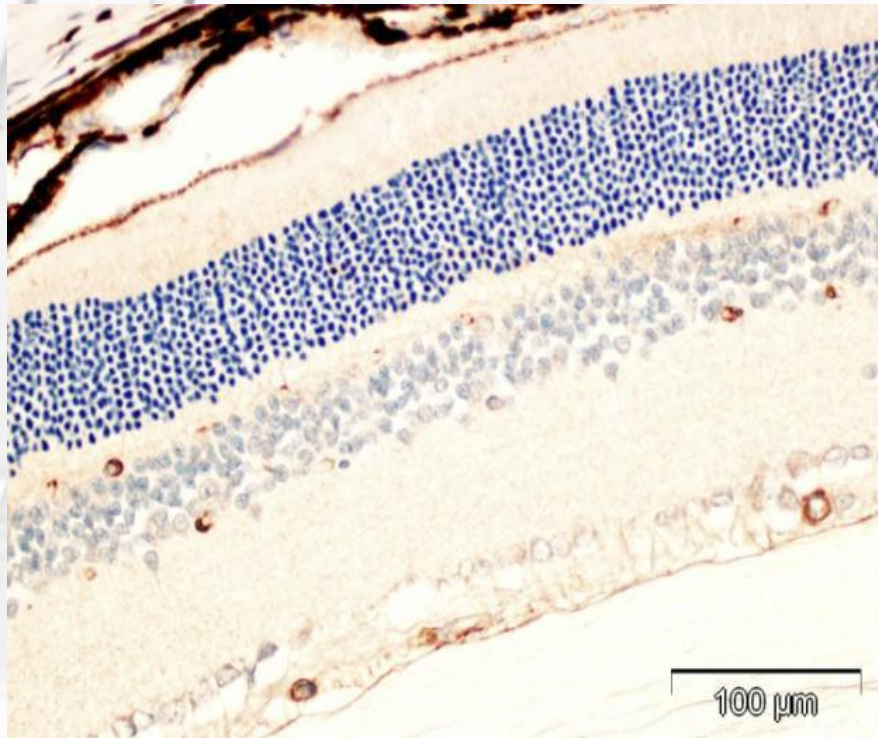


Histopathology demonstrating increased thickness of mid-retinal layer and increased vascularity of retina. post-7 weeks STZ-initiated animals. Left: normal; right-STZ-initiated.



Immunohistochemistry

NG for pericytes demonstrating up regulation of pericyte expression in post-7 weeks STZ-initiated animals. Left: normal; right-STZ-initiated.



Summary of STZ Model

- CBI has established a validated model in Brown Norway rats to assess systemic and ocular changes associated with STZ-induced Type I Diabetes
- STZ glucosamine–nitroso-urea compound derived from *Streptomyces achromogenes* administration induces a Type I diabetes with hyperglycemia (>400 mg/dl) , weight loss and ocular changes over a period of months. STZ damages pancreatic β cells, resulting in hypoinsulinemia
- In the retina, pericyte upregulation, hypervascularity and thickening of the mid retinal layers occurs and is similar to changes in patients.
- Blood glucose, body weights and clinical signs are important parameters
- OCT, fluorescein angiography, histopathology and immunohistochemistry are important assessments



Service and Quality

- ***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.
- ***We believe in sound science.*** Our ratio of scientists to non-scientists is one of the highest in the industry. Every study director is a PhD-level scientist.
- ***We believe in communication.*** Timely responses to your inquiries and frequent updates on your study are mandatory.
- ***We welcome visitors.*** You are always welcome at CBI to meet the staff, tour the laboratory and discuss the progress and results of your study.

