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Oral NLRP3 Inhibitor BGE-102 Preserves Retinal Vascular Integrity in a Preclinical Model of Diabetic Retinopathy

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Abstract

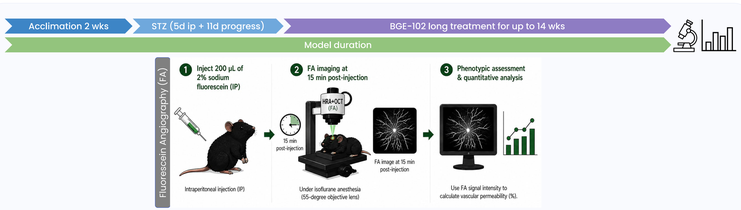
Introduction and Objective:
Diabetic retinopathy (DR) is a leading cause of vision loss, but treatment relies largely on intravitreal therapies, resulting in suboptimal real-world outcomes. Hyperglycemia-driven NLRP3 inflammasome activation contributes to retinal vascular leakage, suggesting that oral NLRP3 inhibition could address this unmet need. We evaluated whether BGE-102, an oral, brain-penetrant NLRP3 inhibitor with therapeutic retinal exposure, could preserve retinal vascular integrity in a streptozotocin (STZ)-induced DR model.

Methods:
Male C57BL/6 mice received STZ (65 mg/kg IP × 5 days). Eleven days later, mice were randomized to vehicle, BGE-102 20 mg/kg, or BGE-102 50 mg/kg (PO QD; n=16-20/group) for 96 days alongside healthy controls. Retinal vascular permeability was assessed by fluorescein angiography (FA). Blood-retinal barrier integrity was evaluated by Claudin-5 immunohistochemistry (IHC). Fasting glucose and A1c were monitored. Data were analyzed by one-way ANOVA with Dunnett's test.

Results:
All STZ groups developed sustained hyperglycemia (glucose ~300 mg/dL; A1c >8%) unaffected by BGE-102 at either dose. Despite persistent hyperglycemia, BGE-102 dose-dependently reduced retinal vascular permeability vs vehicle by 74% at 20 mg/kg and 98.7% at 50 mg/kg (both $p<0.0001$), with the higher dose restoring FA signal to healthy control levels. Claudin-5 IHC showed STZ reduced endothelial vascular content by 46% ($p<0.01$). BGE-102 restored tight junction integrity at both doses to 95% and 97% of healthy control levels (both $p<0.01$ vs vehicle).

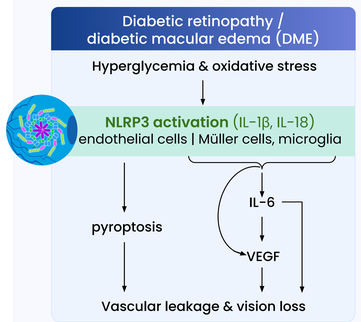
Conclusion:
Oral BGE-102 preserved retinal vascular integrity and restored endothelial tight junctions in a DR model, with efficacy independent of glycemic control. These findings support NLRP3 inhibition as a novel approach to DR and the planned Phase 1b/2a trial in diabetic macular edema.

Study Timeline



Background

NLRP3 activation is a key driver in retinal diseases, such as DR/DME, which have high unmet medical need.



Description	• Vision loss due to vascular leakage • Leading cause of vision loss in adults <65
Prevalence (US)	• 1M
Key risk factors	• Hyperglycemia, inflammation
Approved therapies	• Intravitreal anti-VEGFs, intravitreal steroids, laser
Key unmet needs	• Reduced injection burden: real world treatment outcomes are suboptimal given poor compliance • New MOAs: significant anti-VEGF refractory population

Source: Zheng 2023

Sources: Al Sakini 2024, Varma 2014, CDC, Mayo Clinic, Broker estimates

BGE-102 reduces retinal vascular permeability via fluorescein angiography (FA) signal analysis

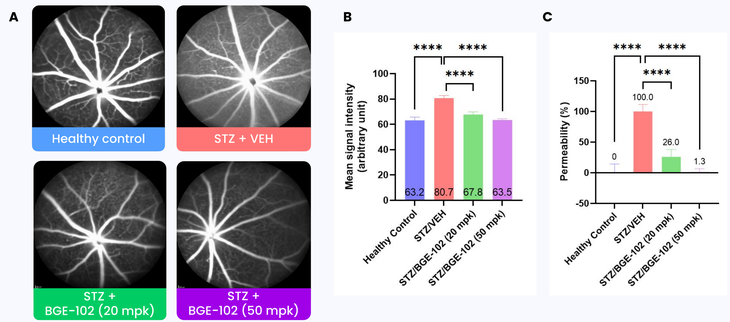


Figure 1. Representative fluorescein angiography (FA) images (**A**), mean FA signal intensity (**B**) and calculated vascular permeability (%) (**C**) after 3 months of treatment. Data are means ± s.e.m (One-way ANOVA).

BGE-102 improves retinal endothelial cell tight junction integrity

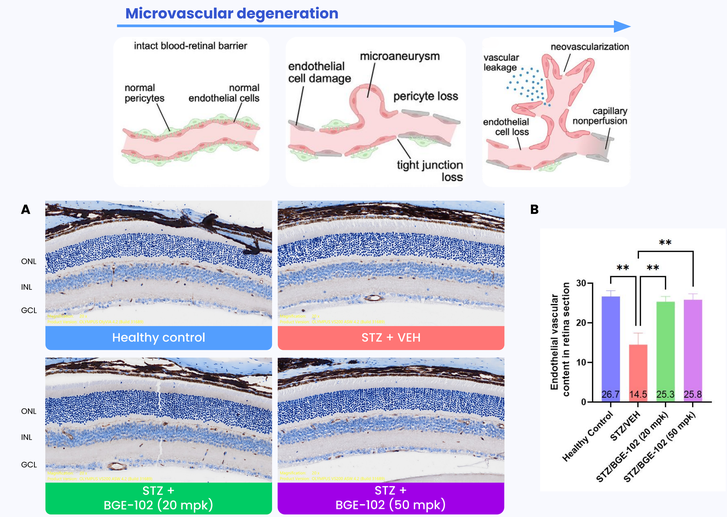


Figure 2. Immunohistochemistry (**A**) and quantification (**B**) of retinal endothelial vascular content with anti-mouse Claudin-5 antibody using paraffin embedded eye sections. Data are means ± s.e.m. One-way ANOVA.

Summary

- STZ-induced diabetic mice developed hyperglycemia-driven retinal vascular dysfunction, including increased fluorescein leakage and reduced Claudin-5 expression.
- Once-daily oral BGE-102 (20 and 50 mg/kg) dose-dependently reduced key features of diabetic retinopathy. These improvements in retinal vascular function and structural integrity support the therapeutic potential of BGE-102 as a next-generation treatment for diabetic retinal disease.

Disclosures: All authors are employees and/or shareholders of BioAge Labs.