# Soluble Guanylate Cyclase a1–Deficient Mice: a novel murine model for Primary Open Angle Glaucoma

**Emmanuel S. Buys[1]*, Yu-Chieh Ko[2,3], Clemens Alt[4], Sarah R. Hayton[1], Alexander Jones[2], Laurel T. Tainsh[1], Ruiyi Ren[5], Andrea Giani[6], Maeva Clerte'[7], Emma Abernathy[2], Robert E. T. Tainsh[1], Dong-Jin Oh[6], Rajeev Malhotra[7], Pankaj Arora[7], Nadine de Waard[2], Binglan Yu[1], Raphael Turcotte[4,8], Daniel Nathan[1], Marielle Scherrer-Crosbie[7], Stephanie J. Loomis[6], Jae H. Kang[9], Charles P. Lin[4], Haiyan Gong[5], Douglas J. Rhee[6], Peter Brouckaert[10], Janey L. Wiggs[6], Meredith S. Gregory[2,6], Louis R. Pasquale[2,6,9], Kenneth D. Bloch[1,7], Bruce R. Ksander[2,6]**

[1]Anesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America; [2]Department of Ophthalmology, Schepens Eye Research Institute, Harvard Medical School, Boston, Massachusetts, United States of America; [3]Department of Ophthalmology, School of Medicine, National Yang-Ming University, Taipei, Taiwan; [4]Wellman Center for Photomedicine and Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America; [5]Department of Ophthalmology, Boston University School of Medicine, Boston, Massachusetts, United States of America; [6]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts, United States of America; [7]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America; [8]Department of Biomedical Engineering, Boston University, Boston, Massachusetts, United States of America; [9]Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America; [10]VIB Department of Molecular Biomedical Research, Ghent University, Ghent, Belgium

**Shweta Modgil**

Department of Zoology, Panjab University, Chandigarh, INDIA

### Background

Glaucoma is an optic neuropathy characterized by retinal ganglion cell degeneration leading to vision loss. Primary open angle glaucoma is a subtype of glaucoma that results in visual field loss due to optic nerve damage caused by increase in intraocular pressure. Events in primary open angle glaucoma (POAG) pathogenesis has been associated with nitric oxide (NO) which activates the soluble guanylate cyclase (sGC), a heterodimeric enzyme consisting of $\alpha$ and $\beta$ subunits by c GMP signaling.[1,2] In POAG patients NO metabolites and level of c GMP has been found to be decreased in aqueous humor. Impaired signaling can be a contributing risk factor to the etiology of the POAG.[3] However whether signal impairment can result in POAG and mechanism underlying is yet to be elucidated.

In the present work authors have identified a novel murine model to study the pathogenesis of age related optic neuropathy in POAG. Further study was extended to human subjects to explore the role of sGC in POAG pathophysiology in case of humans by performing gene association studies.

### Study Design

1 to 17 months old mice deficient in sGC $\alpha_1^{-/-}$ and age matched wild type mice were studied for POAG disease development. Female mice were studied to rule out the systemic hypertension that may give confounding effects. To determine the localization of sGC $\alpha_1^{-/-}$ and $\beta_1$ subunits immunohistochemical studies were carried in mice retinal sections as well as sections of human eyes obtained from New England Eye Bank. sGC $\alpha_1$ and sGC $\beta_1$ were found to be expressed abundantly at three major site ciliary muscles, smooth muscles of retinal vessels and retinal ganglion cells. The expression in these sites suggested that sGC might change contractibility of ciliary muscles, regulates blood flow or viability of RGC that ultimately lead to the disease. Retinal damage in young and old sGC $\alpha_1^{-/-}$ mice as compared to age matched wild type was assessed by measuring retinal nerve fibre layer (RFNL) and retinal thickness using non invasive technique of Spectral domain-optical coherence tomography. Retinal thinning was observed in old sGC $\alpha_1^{-/-}$ mice when compared with age matched WT mice but not in age matched young sGC and WT mice. Longitudinal studies were performed to investigate the impact of deficiency of sGC $\alpha_1^{-/-}$ on intraocular pressure. Central Corneal thickness (CCT) and depth of anterior chamber (DAC) were other parameters analyzed. DAC was measured using in-vivo ultrasound biomicroscopy. No significant difference was found in CCT. When intraocular pressure (IOP) was measured which is one of the major risk factor of POAG again elevated pressure was observed in sGC $\beta_1$ old mice comparable to age matched WT.

Fluorometric technique was utilized to assess the outflow rate of aqueous humor which revealed that 57 week old sGC $\alpha_1^{-/-}$ mice has less aqueous humor clearance than the same aged WT. Vascular dysfunction in retina was analyzed by measuring retinal arterial diameter by *in-vivo* laser opthalmoscopy. Further to explore the role of sGC in human POAG, association between POAG and genes encoding $\alpha$ and $\beta$ subunits of sGC was studied by single nucleotide polymorphism analysis in individuals with the disease.

### Implications

The present study has demonstrated that deficiency of sGC $\alpha_1$ leads to primary open angle glaucoma in old mice and thus sGC $\alpha_1^{-/-}$ mice provide a valuable tool for translational studies for POAG. This novel animal model may further be explored to deduce the mechanism or signal transduction leading to POAG. Genetic analysis studies revealed the relevance of this mouse model in case of humans. It can also be concluded from the present study that sGC is a potential target enzyme to be exploited for POAG therapeutics.

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## References

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