### Citation


### Published Version

doi:10.5214/ans.0972.7531.200207

### Accessed

June 16, 2017 7:13:45 AM EDT

### Citable Link

http://nrs.harvard.edu/urn-3:HUL.InstRepos:12987373

### Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)
Soluble Guanylate Cyclase α1–Deficient Mice: a novel murine model for Primary Open Angle Glaucoma

Emmanuel S. Buys¹*, Yu-Chieh Ko²,³, Clemens Alt⁴, Sarah R. Hayton¹, Alexander Jones⁵, Laurel T. Tainsh¹, Ruiyi Ren⁵, Andrea Gian³⁶, Maeva Clerête⁷, Emma Abernathy², Robert E. T. Tainsh¹, Dong-Jin Oh⁵, Rajeev Malhotra³, Pankaj Arora³, Nadine de Waard², Binglan Yu¹, Raphael Turcotte⁴,⁸, Daniel Nathan¹, Marielle Scherrer-Crosbie⁷, Stephanie J. Loomis⁸, Jae H. Kang⁹, Charles P. Lin⁴, Haiyan Gong⁵, Douglas J. Rhee⁶, Peter Brouckaert¹⁰, Janey L. Wiggs⁶, Meredith S. Gregory²,⁶, Louis R. Pasquale²,⁶,⁹, Kenneth D. Bloch¹,⁷, Bruce R. Ksander²,⁶

¹Anesthesia 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; ²Department of Ophthalmology, Schepens Eye Research Institute, Harvard Medical School, Boston, Massachusetts, United States of America; ³Department of Ophthalmology, School of Medicine, National Yang-Ming University, Taipei, Taiwan; ⁴Wellman Center for Photomedicine and Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America; ⁵Department of Ophthalmology, Boston University School of Medicine, Boston, Massachusetts, United States of America; ⁶Department of Ophthalmology, Boston Medical Center, Boston, Massachusetts, United States of America; ⁷Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America; ⁸Department of Biomedical Engineering, Boston University, Boston, Massachusetts, United States of America; ⁹Channing Division of Network Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, United States of America; ¹⁰VIB 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 increased intraocular pressure. Events in primary open angle glaucoma (POAG) pathogenesis have been associated with nitric oxide (NO) which activates the soluble guanylate cyclase (sGC), a heterodimeric enzyme consisting of α and β subunits by c GMP signaling³. In POAG patients NO metabolites and level of c GMP have been found to be decreased in aqueous humor. Impaired signaling can be a contributing risk factor to the etiology of the POAG.¹ 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 α₁⁻ mice 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 α₁⁻ and β₁ subunits immunohistochemical studies were carried in mice retinal sections as well as sections of human eyes obtained from New England Eye Bank. sGC α₁ and sGC β₁ 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 α₁⁻ mice as compared to age matched wild type was assessed by measuring retinal nerve fibre layer (RNFL) and retinal thickness using non invasive technique of Spectral domain-optical coherence tomography. Retinal thinning was observed in old sGC α₁⁻ 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 α₁⁻ 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 β₁ 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 α₁⁻ 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 ophthalmoscopy. Further to explore the role of sGC in human POAG, association between POAG and genes encoding α and β 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 α₁ leads to primary open angle glaucoma in old mice and thus sGC α₁⁻ 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.

doi : 10.5214/ans.0972.7531.200207

www.annalsofneurosciences.org
References

