HHS Public Access

Author manuscript

*Exp Eye Res*. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

*Exp Eye Res*. 2015 December ; 141: 1–2. doi:10.1016/j.exer.2015.07.017.

# Introduction to Special Issue on glaucomatous optic neuropathy: in vivo models and techniques

**C. Ross Ethier***,

Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology & Emory University School of Medicine 315 Ferst Drive, Room 2306, Atlanta, Georgia 30332-0363

**John C. Morrison**, and

Casey Eye Institute, Oregon Health and Science University 3181 SW Sam Jackson Park Rd, BRB L467 ADM, Rm 215, Portland, OR 97239, USA. morrisoj@ohsu.edu

**Abbot F. Clark**

Cell Biology & Immunology, and North Texas Eye Research Institute CBH-441, U. North Texas Health Science Center, 3500 Camp Bowie Blvd., Ft. Worth, TX 76107 abe.clark@unthsc.edu

Glaucoma is a heterogeneous group of eye diseases that share common clinical phenotypes involving characteristic changes to the optic nerve and loss of visual function; together the glaucomas are a leading cause of blindness (Heijl et al., 2002; Tham et al., 2014). All manifestations of glaucoma have a characteristic type of optic nerve damage, or appearance, termed glaucomatous optic neuropathy (GON). Although GON can occur at any level of intraocular pressure (IOP), elevated IOP is a causal risk factor (Bengtsson and Heijl, 2005; Heijl et al., 2002; Leske et al., 2003; Weinreb and Khaw, 2004), and significant, sustained IOP reduction benefits patients with all forms of this disease (Anderson et al., 2001; Epstein et al., 1989; Heijl et al., 2002; Investigators, 2000; Kass et al., 2002; Leske et al., 2003). In addition to elevated IOP, there are a number of other risk factors for glaucoma, such as central corneal thickness, axial length, race, age, cup-to-disc ratio, and responsiveness to glucocorticoids. Clearly, GON is complex; further, clinical management tools are inadequate. Thus, animal models are essential to understand the basic pathophysiology of the condition and to develop improved treatments.

Many labs now use animal models to study the pathophysiology and pathobiology of GON, but there is significant variation in approaches, details and outcomes. We thus reasoned that there would be value in collecting together, in a reasonably comprehensive manner, a single issue that describes existing models and techniques. Towards this end, an expert group of authors was invited to provide articles that:

1. Describe the rationale for, and use of, models and techniques for studying GON.

* Corresponding author. ross.ethier@bme.gatech.edu.

2. Explicitly identify the pros and cons of these models and techniques, and thus place them in the broader context of glaucoma research.
3. Identify open questions/needs for the further development of models and techniques.
4. Provide some perspective on the relevance of each topic to the human disease.

In order to maintain focus, this special issue concentrates explicitly on animal models in which IOP is elevated, because of the prominent role that IOP and its management plays in the human disease. Thus, we do not include techniques such as cell culture and clinical studies. Nor does this issue include surrogate models of GON, such as optic nerve transection/crush, glutamate toxicity, ischemia, etc. Future special issues should consider these important topics.

Thematically, this special issue can be subdivided into two main areas. First we consider techniques to elevate IOP, and then go on to present techniques to assess elevated IOP and its effects. In the first category, we include articles on the various animal models of glaucoma. Burgoyne describes the primate model of ocular hypertension, which despite challenges of cost and regulatory complexity, most closely replicates the disease in humans. In addition to primates, multiple rodent models have emerged as important tools in the study of glaucoma. These models are not trivial to use, and each has their pros and cons. Pang et al. describe how IOP can be increased in rodents by using viral vectors that target the trabecular meshwork. Morgan and Tribble consider techniques for elevating IOP In rodents by using microbeads injected into the anterior chamber. Morrison et al. describe a technique for sclerosing the trabecular meshwork and other elements of the aqueous outflow pathway, and present information about the resulting elevation of IOP. Overby and Clark review emerging techniques to elevate IOP by chronic steroid delivery in mice and other species. We would be remiss if we did not include information on the important genetic models of elevated IOP, a field that is reviewed by Fernandes and coworkers. Finally, we consider the intriguing models that acutely elevate IOP: Crowston et al. have described this approach, and how it replicates certain features of the chronic models described above.

Of course, it is not enough to simply elevate IOP. One must be able to monitor IOP once elevated, and to have the ability to assess structural, functional, biomechanical and biochemical changes to the cells and tissues of the optic nerve head. There are many subtleties in the measurement of IOP in animal models, an area that is reviewed by Millar and Pang. The current state-of-the-art in IOP monitoring is based on intermittent use of tonometry, which by necessity gives an incomplete view of the entire range of IOPs to which the optic nerve is exposed. An emerging technique that has the potential to overcome these limitations is continuous telemetric monitoring, which is described by Downs.

It remains to evaluate changes to the ONH in models of glaucoma. As would be expected based on the complexity of the disease, investigators use multiple techniques towards this end. Fortune describes in vivo imaging-based methods to assess GON, an approach that has many similarities to clinical glaucoma management. Of course, part of the power of animal models is the ability to make measurements that cannot be considered in human patients. In this vein, Nickells and Pelzel describe gene expression changes in the retina and optic nerve

head that are secondary to elevated IOP, and how such changes are assessed. Nguyen and Ethier describe how one may assess the biomechanical environment in the optic nerve head and posterior eye in models of glaucoma. Nuschke and colleagues describe techniques for the morphologic assessment of optic nerve damage, focusing on axonal injury, axon transport, and RGC loss and injury. Porciatti reviews the electrophysiological assessment of retinal ganglion cell function, an important topic in the functional assessment of animals. In a similar vein, Grillo and Koulen describe techniques for carrying out psychophysical testing in rodent models of glaucoma. Finally, since changes in glaucoma are not confined to the eye, Yucel and colleagues describe what is known of changes occurring in the brain in models of this disease.

This is an exciting time to be doing glaucoma research, as the development and use of new models are (slowly) shedding light on this enigmatic disease. We anticipate that these articles, by providing insights into the current state-of-the-art, will be of interest to established researchers as well as to those new to this field, and prove to be a valuable resource as these labs work to better understand the molecular pathogenesis of pressure-induced optic nerve damage and to develop novel treatments for glaucoma.

## References


Anderson DR, Drance SM, Schulzer M. Natural history of normal-tension glaucoma. Ophthalmology. 2001; 108:247–253. doi:S0161642000005182 [pii]. [PubMed: 11158794]

Bengtsson B, Heijl A. A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. J Glaucoma. 2005; 14:135–138. doi: 00061198-200504000-00009 [pii]. [PubMed: 15741815]

Epstein DL, Krug JH Jr. Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects [see comments]. Ophthalmology. 1989; 96:1460. [PubMed: 2685707]

Heijl A, Leske MC, Bengtsson B, Hyman L, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002; 120:1268–1279. doi:ecs20122 [pii]. [PubMed: 12365904]

Investigators A. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000; 130:429–440. doi:S0002939400005389 [pii]. [PubMed: 11024415]

Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, Wilson MR, Gordon MO. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch. Ophthalmol. 2002; 120:701. [PubMed: 12049574]

Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003; 121:48–56. doi:ecs20139 [pii]. [PubMed: 12523884]

Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014; 121:2081–90. doi:10.1016/j.ophtha.2014.05.013. [PubMed: 24974815]

Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004; 363:1711–1720. doi:10.1016/S0140-6736(04)16257-0 S0140-6736(04)16257-0 [pii]. [PubMed: 15158634]

## Highlights

- Animal models are essential to understand the basic pathophysiology of glaucoma and to develop improved treatments

- There is significant variation in approaches, details and outcomes between labs and animal models

- An expert group of authors was invited to provide articles that describe animal models of glaucoma, and their pros and cons