SECTION I: EXECUTIVE SUMMARY

Key Needs and Opportunities for Treating Glaucoma

Gerald J. Chader

Every year, millions of Americans and countless more around the globe lose significant vision or go blind. This number is expanding dramatically as life spans increase, along with changes in lifestyles that run counter to good ocular health. Along with losing what Americans perceive as their most important sense, there is a high cost to pay in loss of an individual’s quality of life and independent living. In addition, the increased financial burden on the individual and on society is enormous.

Basic research on the causes of specific eye diseases has been especially productive in recent years, as the bases of many of these diseases are now understood. Some, such as retinitis pigmentosa, are now known to be genetic in nature, with the underlying causes being mutations in a variety of genes that regulate the synthesis of important proteins needed for proper functioning of the neural retina. The past two decades have taken us from virtually no knowledge of these faulty genes to knowing the identity of a substantial number of them, along with now having the gene therapy tools to replace these genes with normal copies and restore partial visual function. Other diseases, such as glaucoma and age-related macular degeneration (AMD), are now known to be “complex diseases,” with both genetics and the environment playing roles in the disease process. Biologically, many of the cellular pathways leading to ocular cell dysfunction and death also have been explored. In glaucoma, for example, it is now clear that the affected ganglion cells in the retina die by a well-defined process known as apoptosis (programmed cell death). The situation is similar for photoreceptor cell death in retinitis pigmentosa and AMD. Understanding these pathways allows the use of specific agents and drugs that block retinal cell death and prolong—and even improve—vision. This course of action should be viable, not only for young patients with limited damage, but also for older patients who may have already lost a substantial amount of their eyesight.

In general, scientists and clinicians believe that some of the greatest unmet needs in eye diseases involve problems of the neural retina and specific conditions of the cornea such as dry eye. In particular, the neuropathology of the retina has been difficult to understand and, therefore, to treat. Successful treatment of blinding retinal diseases lags far behind conditions such as cataract, which can, through surgery, generally be quickly remedied. However, new information on retinal diseases such as glaucoma, AMD, retinitis pigmentosa, and diabetic retinopathy now makes successful treatment a practical reality.

A recent review article in the scientific literature reports that “1 in 40 adults older than 40 have glaucoma with vision loss, equating to 60 million people worldwide.” Glaucoma affects more than 2.7 million Americans, approximately half of them undiagnosed, with an additional 5 to 10 million at risk of developing glaucoma. Direct costs in the United States total about $3 billion annually; indirect costs, due to loss of productivity and loss of independent living, are still greater. It is now recognized that glaucoma is actually a group of diseases with the common endpoint of death of the ganglion cells in the neural retina. Glaucoma is a complex disease in that many factors increase a person’s risk, increased intraocular pressure within the eye being just one of them. Genetics has also been shown to play an important role in the disease process. In preclinical experiments, our new knowledge now allows us to go well beyond simply trying to maintain normal intraocular pressure through drugs and surgical interventions to directly treat the ganglion cells and their extended processes, the optic nerve. For example, drugs called “neuron-survival agents” are being tested to determine whether they can block ganglion cell death and maintain a healthy optic nerve, thus prolonging functional vision. Preclinical testing of these agents, delivered to the eye through sophisticated gene therapy techniques, is now well advanced.

The result of this accumulated knowledge is a recent upsurge in our capability to move from the laboratory bench to the clinic, testing new therapies in preclinical and clinical trials. Moreover, preclinical studies have shown that blindness can be staved off and vision partially restored in specific animal models of glaucoma and other ocular diseases. Even though more basic research is needed on chronic ocular problems such as glaucoma, scientific barriers to our understanding of many of the causes of ocular diseases and the theoretical approaches that can be taken for their treatment are falling. Now is the time to capitalize on these opportunities. What remains is finding the will and the financial resources to use this knowledge to move through clinical testing and provide treatments to all in need.

THE ORSF GLAUCOMA SYMPOSIUM

The participants in the ORSF Glaucoma Symposium identified key needs—areas where more work is needed in addressing the problems of glaucoma—and exciting opportunities for moving laboratory work through clinical trials to bone fide treatments. Following is a synopsis of these key needs and opportunities.

Framing the Issue

1. Where Are the Opportunities for Glaucoma Treatment?

The time is right for a concerted effort to pursue new treatments for glaucoma. Advances in basic research in the anterior segment (i.e., reducing intraocular pressure) and in the retina of the eye as well as in the brain point to fruitful opportunities in controlling, reversing, and possibly prevent-
ing glaucoma-related vision loss. Both new drugs and new drug delivery systems are now available. If applied, new early diagnosis and imaging techniques could lead to a dramatic decrease in glaucoma pathology.

2. Glaucoma Prevalence and Worldwide Impact. Glaucoma is common, is on the rise, and affects millions around the world. Some groups (e.g., African Americans) are at substantially higher risk than the general population. It is poorly diagnosed, with detection and treatment often only at relatively late stages of the disease process. Given its end product (marked vision loss or blindness), glaucoma is a disabling disease, severely degrading the patient’s quality of life, and often reducing employment opportunities and capacity for independent living. Early and accurate diagnosis is needed with rapid and effective treatment to prolong vision or even stop the course of the disease.

Key Needs and Opportunities. Scientifically, we need to understand the role that aging plays in the development of primary open-angle glaucoma (POAG). We must increase awareness of the high POAG burden among women, especially elderly non-Hispanic white women, and to investigate the roles of sex and racial disparity in the prevention and treatment of POAG in women and Hispanics. We must implement screening and intervention programs targeting non-Hispanic white women and Hispanic men, especially in states with the highest density of POAG (New Mexico, Texas, and Florida). We should support continued periodic population-based studies in the United States to better assess the impact of screening and treatment on the burden of POAG. To limit the financial cost of glaucoma and the impact on a patient’s quality of life, an early diagnosis of the disease is essential. To achieve early diagnosis, education must be improved so that persons at risk recognize the potential of glaucoma and an early diagnosis can be made. Both standard and new techniques being developed for diagnosis must be implemented and made available to larger patient populations. For those known to have glaucoma, better and more affordable treatment regimens have to be devised.

Understanding the Cell and Molecular Biology of Glaucoma

The bases of treatment for any disease lie in laboratory research. Determining the cause(s) of a disease and how it affects a cell, resulting in dysfunction, degeneration, and possibly cell death, is usually a prerequisite for effective treatment. Much is now known about the disease process in glaucoma. For example, ganglion cell death is effected by apoptosis. Also, similarities with other neurologic diseases are now apparent based on general accumulated knowledge, such that common therapies can be applied. Significant progress in understanding glaucoma has been made recently in several research areas.

3. Insights from Genetics, Epigenetics, and the Environment. As a complex disease, glaucoma is now known to have several factors that increase risk of its development. Several gene mutations have been identified that lead to increased risk. Among them are the well-known mutation in the myocilin gene and the recently identified CDKN2BAS gene. Epigenetic factors are those that influence gene expression. These factors may be developmental or related to aging or the environment. Several such factors are now being investigated for their possible influence on glaucoma—notably, aging, which is a significant risk factor in glaucoma, as it is in AMD. Similarly, environmental factors are being investigated for their possible impact on glaucoma. For example, latitude of residence (i.e., north versus south) may be related to glaucoma risk.

Key Needs and Opportunities. We need to continue to search for gene mutations associated with glaucoma. For this, we must have larger numbers of well-phenotyped (i.e., characterized) patients. To enable larger scale genetic studies, we should attempt to establish better collaborations and consortia of clinical investigators who agree on specific diagnostic criteria. Whole-genome genotypes should be established with appropriate DNA sequencing in glaucoma patients. We now can do secondary analyses with methods for understanding gene × gene interactions and gene × environment interactions, and we can do pathway analyses and functional mutation assessments. Finally, we have the knowledge now to proceed with gene-based treatment. Promising possibilities would be neuro-protection against CDKN2BAS, the transforming growth factor-β pathway, and the tumor necrosis factor-α pathway.

4. Molecular and Cellular Mechanisms in the Conventional Outflow Pathway. Controlling intraocular pressure is a principal mechanism for reducing damage from glaucoma in many patients. In the anterior segment of the eye, natural channels in the trabecular meshwork (TM) are present for outflow of aqueous humor, thus helping maintain normal pressure in the eye. Understanding the nature of these channels, how they are normally controlled, and how they can become blocked is critical in reducing the risk of glaucoma.

Key Needs. There is a need to better understand the pharmacology of outflow resistance. How do substances within the eye (endogenous mediators) orchestrate regulation of outflow resistance? What are more specific ways to control contractility (contraction) of the TM? What controls the preferential pathways for flow? For this, there is a need to understand the fundamental basis of increased ocular pressure (hypertension). For example, how do mutations in the myocilin gene affect outflow resistance? What are the critical molecular pathways and mediators that contribute to elevated intraocular pressure? We need better conventional outflow medications to clear debris from the outflow channels, decrease outflow resistance, and restore capacitive function.

Key Opportunities. We have an opportunity to restore drainage function to the conventional pathways in the eyes of glaucoma patients and to significantly lower pressure beyond the levels currently possible. We have an opportunity to slow or stop vision loss in all glaucoma patients through manipulations of outflow channels (TM) alone or in combination with other therapies.

5. Cellular and Molecular Biomechanical Factors in Glaucoma. The biomechanical integrity of ocular tissues such as the sclera, the TM, and the optic nerve head region of the retina plays a large role in glaucoma. Specifically, biochemical and biophysical factors determine whether fluid can efficiently leave the eye through the TM outflow channels and whether the structure of the optic nerve head remains normal. In particular, various stresses—namely oxidative stress—can cause changes in the biomechanical properties of these tissues, leading to pathology and loss of vision.

Key Needs and Opportunities. We need to better understand how cells in the TM function, how the retina and optic nerve head sense biomechanical stress, and what signaling pathways are involved. We must be able to characterize the cellular and tissue “tensile” of the TM and optic nerve head in normal and glaucomatous eyes. We have to determine whether glaucoma-related cytoskeletal changes in the cells of the TM and optic nerve head are responsible for altered cell and tissue stiffness and whether these changes are directly involved in glaucoma’s pathogenesis. We also must find out whether the cross-linking of extracellular matrix is associated with glaucoma-causing changes in the TM and optic nerve head and whether the “stretch” channels in the TM, optic nerve head, and/or retinal ganglion cells are a cause of glaucoma.
6. Molecular and Cellular Mechanisms of Retinal Ganglion Cell Death. Ganglion cells of the retina and the optic nerve are the major sites of damage in glaucoma. The initial insult—perhaps a gene mutation, increased intraocular pressure, or oxidative insult—leads to ganglion cell apoptosis, a natural but usually quiescent pathway that, when activated, leads to cell death. The sick, injured, or stressed cell essentially “commits suicide.” Vision researchers have now worked out many of the steps in the apoptotic pathway in ganglion cells and can begin to test inhibitors that can block the pathway and thus at least slow ganglion cell dysfunction and death.

**Key Needs.** We need better strategies for protection of the ganglion cells of the retina and the optic nerve and must gain a better understanding of the different pathways that cause degeneration. We should evaluate the early molecular, preapoptotic changes leading to atrophy and loss of ganglion cell function, and we should investigate cell death pathways.

**Key Opportunities.** We should focus on epigenetic (genetic modifiers) changes, such as histone deacetylase activity and the use of inhibitors (e.g., histone deacetylases) to determine whether pathologic changes can be blocked or reversed. We now have many of the tools needed to define the different apoptotic pathways (e.g., Bim versus Bas versus BId versus PUMA, etc.) in glaucoma-induced cell death. Also, we can determine whether these pathways are active in the same cell (i.e., serial or simultaneous), or whether there are different activation pathways for different cells. Finally, advances now allow better definition of other related degenerative pathways, including the role of other retinal neurons, glial cells, and immune responses.

7. Axonopathy and the Brain in Glaucoma. Early glaucomatous changes in the optic nerve and the optic nerve head include impairment of transport of molecules in the fibers of the optic nerve that causes glaucomatous damage to accumulate as the patient gets older. Injury of specialized brain structures is also seen in the early stages of glaucoma. Understanding the mechanisms by which such injury occurs in these structures of the optic pathway is critical in designing strategies for maintaining vision in glaucoma. The potential is high to turn this knowledge into improved diagnoses and practicable therapies.

**Key Needs.** We need to identify the initiating event(s) in early disease changes of the ganglion cell and optic nerve (axonopathy). Clinically sensitive assays of the health of ganglion cells, optic nerve, and brain centers must be developed to identify early disease. We should seek to better understand the effects of both age and glaucoma on the whole visual system from retina to brain. We must identify intrinsic factors in the optic pathway that can act to protect ganglion cells in the retina (neuroprotection) and the pathways that are stressed by high pressure in the eye leading to axonopathy.

**Key Opportunities.** New biomarkers should be tested to predict loss of vision. For early clinical identification of glaucoma, new cation-based functional imaging tools must be tested. Advances in the understanding of age-related changes in other diseases ought to be applied to the visual system and glaucoma. For protection of the neurons of the optic tract, we need to leverage knowledge already gained in other diseases of the nervous system, such as Alzheimer’s disease and stroke. For identification of pathways involved in glaucoma, advances in rapid (high-throughput) screening methods can be applied to identify early and late destructive cellular events.

8. Common Neurodegenerative Pathways and Relevance to Glaucoma. Glaucoma is one of the many neurodegenerative diseases that strike tissues of the central nervous system; these diseases include Parkinson’s and Alzheimer’s as well as AMD. Although much work has been done, no adequate solutions have yet been found for any of these major debilitating conditions. Many of these diseases are strikingly similar in both physical and biochemical manifestations; most, for example, are age-related. Thus, pooling the information on these diseases that has been painstakingly gathered over the years should be helpful in studying glaucoma.

**Key Needs.** Glaucoma, an age-related, chronic degenerative disease of the optic nerve, retina, and brain, exhibits similarities to the molecular and cellular features of other chronic degenerations of the neurologic systems, including amyotrophic lateral sclerosis. Sharing approaches to understanding these diseases and their treatments should be productive. It is critical to continue studies of the immune system in relation to the development and progression of glaucoma. It is also critical to understand the role of micro-RNAs in the regulation of retinal and optic nerve gene expression in glaucoma.

**Key Opportunities.** Therapies directed at treating other chronic neurodegenerative diseases should be tested in glaucoma models. Conversely, therapies that have been successful in treating glaucoma could be used to treat other chronic neurodegenerations. The molecular and cellular abnormalities evident in other chronic neurodegenerations may be detectable in the eye; testing could lead to earlier diagnosis.

**Detection and Diagnosis**

Imaging creates a faithful representation or image of a cell or tissue. For example, imaging bones through tissues such as skin and muscle is essential in conditions such as fractures and osteoporosis. With the eye, viewing the internal tissues such as the retina through the pupil is easy, as the cornea, lens, and vitreous body are transparent. Magnified and graphic representations of retinal areas including the optic disc are now available. Thus, diagnosis of glaucoma and its progression has become much better and more efficient—with even better imaging techniques to come.

9. Ocular Imaging for Glaucoma. The goal of ocular imaging in glaucoma is to provide a reproducible, quantitative assessment of the status of the ocular structure, for accurate diagnosis and detection of progression. Imaging can also be useful for identifying eyes at high risk for conversion to or progression of glaucoma. Ocular imaging reduces both uncertainty and repeated perimetric testing, especially in cases of structure–function correspondence.

**Key Needs.** We need to achieve the following: validation of imaging glaucoma progression algorithms; automated structure–function correspondence assessment; rapid, accurate, and reproducible image alignment and registration, with robust algorithms for quantitation of relevant features; standardized scan patterns and analysis methods and software; and integration of technology with electronic health records, allowing on-demand export of data from the imaging device to the electronic record.

**Key Opportunities.** Opportunities include the following: early, rapid, noncontact, noninvasive, accurate, rapid detection of glaucoma and glaucoma progression; mass-market evaluation of glaucoma globally; telemedicine for global glaucoma evaluation at an expert level; automated glaucoma detection and identification of glaucoma progression; and patient-centered electronic health records with all historical digital ocular structural data possessed by the patient at all times for easy evaluation and comparison for change by any clinician.

**Advances in the Treatment and Management of Glaucoma**

Because the tissues and cell types that can be damaged in glaucoma are diverse and risk factors are varied, current treatments are also diverse. In the anterior segment, they include drug therapy to decrease the production of aqueous humor or
increase its outflow and surgery to open outflow channels. In the posterior segment, research on neuroprotection—that is, the use of natural agents or drugs to prolong the life and function of ganglion cells—is progressing. Advances in gene therapy techniques allow for testing for both gene replacement therapies and the application of genes that produce neuroprotective agents to prolong and possibly even improve vision in glaucoma patients. In the future, stem cell therapy may be used to replenish the ganglion cell supply.

10. Advances in Surgery Treatment for Glaucoma. Surgical intervention in glaucoma is increasingly successful, particularly in opening drainage channels in the anterior segment of the eye to lower intraocular pressure. New surgical techniques may enable reduction of pressure through the back (posterior segment) of the eye as well.

Key Needs. It is important to identify new treatment methods besides our current surgical procedures. We need more scientifically sound trials on glaucoma patients, comparing new surgical procedures to those currently used, such as trabeculectomy. We must promote global standardization of definitions of success and outcomes for these trials.

Key Opportunities. New and better surgical techniques are available to insert or place drugs or drug delivery devices for best effect. We should consider the use of surgeries that are not reliant on the reduction of intraocular pressure, such as optic nerve fenestration, to preserve vision. We should determine whether it is time to begin thinking about optic nerve or even whole eye transplantation and should look at the possibilities of rejoining or regrowing ganglion cell axons.

11. Outflow Drugs in Glaucoma. One of the most successful treatments for glaucoma has been the use of drugs that lower intraocular pressure. Some of these drugs were first used for other purposes but were subsequently found to be safe and efficacious in treating glaucoma. As these drugs are drops applied to the surface of the eye, they are relatively low risk. Unfortunately, they are not effective in all cases of glaucoma and do not constitute a cure; rather, they prolong functional vision in treated patients. New types of outflow drugs are being devised that could lead to much better management of the disease, further reducing vision loss.

Key Needs. Biologically, there are specific factors that could lead to better control of intraocular pressure. These involve the development of “tunable” models for the study of outflow of fluid from the eye, the use of devices for continuous measurement of intraocular and outflow pressure, the use of methods for clinical measurement of outflow in the back (posterior, uveoscleral area) of the eye, and focused studies of genetic manipulation of the production of fluid within the eye (aqueous inflow). We need the involvement of large and small pharmaceutical companies to test risky but promising modalities for controlling intraocular pressure.

Key Opportunities. We now can use better drug delivery strategies, such as nanoparticulate systems for outflow modulation and better, targeted vectors for gene therapy. We can apply improved gene transfer systems for in vivo testing.

12. The Use of Neurotrophic Agents in Glaucoma. A promising emerging area of focus is the protection of retinal neurons such as photoreceptor cells against cell death (apoptosis). Many neuron-survival agents that slow photoreceptor cell degeneration have been identified, but only a handful have been tested in animal models of glaucoma. Current knowledge from preclinical and clinical testing on photoreceptor degenerative diseases allows us to take better advantage of this opportunity.

Key Needs. We need a better understanding of glaucoma animal models for the study of similarities with and differences from the human disease. We must take advantage of improved methods of drug delivery now being tested in the eye for other disease entities.
Key Needs and Opportunities. We need to determine whether there are differential susceptibilities of different types of retinal ganglion cells to increased intraocular pressure. If glaucoma is to be treated with stem cell-based replacement therapy, a more complete description of cell targets (e.g., TM cells) and plasticity of retinotectal projections must be obtained. We must better understand the relationship between microglia, inner retinal vessels, and retinal ganglion cells if we are to exploit paracrine rescue effects of targeted progenitor cells.

Harnessing Academia, Government, and Industry to Find New Glaucoma Treatments

Many steps beyond basic research are needed in treating patients. Although most treatment possibilities begin as small pilot projects in an academic setting, cooperation with the government is needed to identify and fund promising research and to move it through preclinical testing. Cooperation with industry is also needed in finishing preclinical safety and efficacy testing and in moving the treatment through the clinical trial pipeline. This cooperation is often difficult to achieve and is beset with many barriers and pitfalls. Success in harnessing these entities can lead to significant improvement in both the number and quality of treatments available to glaucoma patients.

Key Needs. Investigators should be familiar with the range of programs that the National Institutes of Health (NIH)/National Eye Institute provides in terms of funding, in addition to traditional grant mechanisms. These funding avenues include collaborative research and development agreements, clinical trial agreements, Small Business Innovation Research and Small Business Technology Transfer grants, the Public-Private Partnership Program, and the Foundation for the NIH. We need an assessment of the cost effectiveness and risk–benefit ratios of diagnostic tests such as imaging and visual field assessment in populations (such as African Americans) at high risk of developing glaucoma.

Key Opportunities. Researchers can take advantage of NIH initiatives, such as its Pipeline to Partnership program, which offers a virtual space for NIH licensees and a showcase for NIH Small Business Innovation Research and Small Business Technology Transfer technology and product development for an audience of potential strategic partners and investors. They can also take advantage of NIH’s Public-Private Partnership Program, in which the NIH in collaboration with a wide range of organizations such as patient advocacy groups, professional societies, charitable foundations, industry members, and academic institutions work together to improve public health. Investigators can take advantage of the Foundation for the NIH, a nongovernment charitable foundation that supports the mission of the NIH in advancing collaboration with biomedical researchers from universities, industry, and nonprofit organizations. Another potential partner is the National Center for Advancing Translational Sciences, which catalyzes the development of innovative methods and technologies that enhance the development, testing, and implementation of diagnostics and therapeutics in human diseases.

From Discovery to the Clinic: Lessons Learned

Glaucoma is a complex family of diseases of different origins but with similar endpoints that cause ganglion cell damage and death. New advances in understanding the causes of glaucoma as well as technical advances in the treatment arena (e.g., drug delivery, nanotechnology, gene therapy) put new treatments within reach.

Key Needs. We need a better drug that controls outflow from the eye and thus better manages intraocular pressure. We must gain a better understanding of pathogenic mechanisms and related pathways in glaucoma such that drugs are better targeted to specific biochemical outcomes.

Key Opportunities. We can develop “university incubators” that promote work on promising new therapies. We also have an opportunity to develop a new university-industry model that can rapidly integrate basic advances in glaucoma research into an industry framework for clinical testing. We must actively pursue therapeutic strategies that may have a neuroprotective effect on the optic nerve fibers and ganglion cell bodies and develop improved drug delivery methods/devices that effectively remove the patient from the drug delivery system for long periods.

References