Several etiologic factors for glaucoma have emerged from recent research: oxidative stress, altered optic nerve blood flow, effects of microenvironment on retinal ganglion cells (RGC), early structural changes in the optic nerve head (ONH) and the molecular biology of imbalances that contribute to changes in the trabecular meshwork (TM). With so many contributing aspects unsurprisingly most patients will need to use a combination of therapies to control their disease. To address this, researchers are addressing multiple fronts; developing formulation changes for existing therapies to enhance bioavailability (e.g. by increasing corneal permeability and ocular contact time), designing/developing novel delivery strategies (sustained release, implants, punctal plugs, gene therapy) and investigating new classes of compounds with novel and complementary mechanisms of action.

Several novel compounds in the pipeline target the TM to increase outflow through the conventional pathway, which accounts for 50% to 75% of aqueous humor outflow. The greatest resistance to outflow is thought to reside in the juxta-canicular (JCT) region and inner wall of Schlemm’s canal (SC). (Figure 1) Cytoskeletal agents interfere with the actin cytoskeleton, altering cell shape, contractility and adhesions. These actions affect the structural and functional biology of the TM, reducing resistance through relaxation and expansion. These agents also provide valuable information on the complex dynamics of ciliary muscle (CM)- and TM-centered control of TM contraction/relaxation, and how they may respond in synchrony to various physical and chemical stimuli to regulate hydraulic conductivity, and consequently IOP. Compounds that have shown promise in their ability to modify the architecture of the TM include myosin light-chain kinase inhibitors, rho kinase inhibitors, caldesmon, and derivatives of...
marine macrolides (e.g. latrunculins). Rho kinase inhibitors and marine compounds are being developed by a number of companies, with several already in early clinical trials.

Commercially available Prostaglandins (PGs) increase uveoscleral outflow by remodeling the extracellular matrix of the ciliary muscle and sclera, increasing the production of matrix metalloproteinases (MMPs) and decreasing levels of collagen in the interbundle spaces of the CM and the sclera, with relaxation of the CM playing a secondary role. There are several new PG derivatives, with novel mechanisms of action, in development. The selective prostanoid EP4 receptor agonist (3,7-dithia PGE1) lowered IOP and increased total outflow by 40% in monkeys. As there was no effect on uveoscleral outflow or aqueous flow, increased trabecular outflow facility appeared to account for a considerable proportion of the ocular hypotensive activity. A PG derivative in phase II clinical trials (BOL-303259-X) is thought to contain a NO donating element that increases its IOP lowering efficacy compared with commercially available FP receptor agonists.

Delivering drugs to target tissues can be achieved through novel methods such as encapsulated cell technology, nanoparticles, microspheres, gels, sustained release technologies and coated microneedles. The success of clinical trials using viral vector mediated gene therapy for Leber’s congenital amaurosis (LCA) is an encouraging development of gene therapy strategies for other ocular diseases (Figure 1) including glaucoma, where targets include cytoskeletal modulating proteins that can enhance outflow through the TM as well as the PG pathway elements that can increase uveoscleral outflow. Viral vectors encoding genes for green fluorescent protein (GFP) show long term (2+ years) expression in the outflow pathways of non-human primate eyes. (Figure 2) Ocular gene transfer may be accomplished through physical, non-viral, and viral based methods. Gene therapy has also been used in laboratory studies of neuroprotection. Vectors have been constructed to deliver neurotrophic factors (brain-derived neurotrophic factor, ciliary neurotrophic factor, glial cell-derived neurotrophic factor) that have positive effects on RGC survival in rodent models. Anti-inflammatory and immunological strategies are being pursued as well, such as T cells specific to antigens residing in the site of damage, immunomodulatory compound glatiram acetate.

The mechanisms of cell death in glaucoma are similar to other neurode-

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**Figure 1.** Diagram showing different ocular target tissues and strategies for glaucoma. Adapted from NEI/NIH image. From Gene therapy targeting glaucoma: where are we? Liu X, Rasmussen CA, Gabelt BT, Brandt CR, Kaufman PL. Surv Ophthalmol. 2009 Jul-Aug;54(4):472–86. Review.


A: Fluorescence, localized in the TM (arrows), is seen 5 days post-injection in an eye that received $1.0 \times 10^8$ YUs of an eGFP-expressing FIV vector.

B: The control eye, injected with equivalent volume of saline, shows no fluorescence.
generative diseases such as Alzheimer’s disease (AD), and amyotrophic lateral sclerosis (ALS). Commonalities include a primary injury resulting in cell death followed by a secondary injury with degeneration of surrounding neurons. Potential contributing mechanisms to neuronal death in general, and RGC apoptosis in particular, have been identified: excitotoxicity, abnormal accumulation of proteins and protein misfolding, mitochondrial dysfunction, oxidative stress, inflammation, immune disorders and neurotrophin deprivation. Amyloid deposits, consisting of aggregates of amyloid beta (Aβ), have been implicated in the pathogenesis of age-related macular degeneration (AMD) and glaucoma. Transgenic mouse models of AD show increased levels of Aβ deposition in the retina, which is associated with RGC apoptosis and visual functional impairment. In a rat ocular hypertension model, animals treated with a therapy targeting three different stages of the Aβ pathway (using BSI, Anti-Aβ antibodies and Congo red) showed significantly less RGC apoptosis compared with singular treatments (Figure 3). Drugs used for other neurodegenerative diseases (e.g. targeting alpha-synuclein in Parkinson’s disease and NMDA receptors in AD) are being investigated as therapies for glaucoma.

The only drug to reach Phase III clinical trials for glaucoma neuroprotection is memantine, a low to moderate affinity, noncompetitive NMDA receptor antagonist. Memantine protects cells from toxic levels of calcium by preventing glutamate from attaching to the cell. Without glutamate, calcium cannot enter the nerve cells. This process does not interfere with the normal function of the cell, making memantine an attractive compound. Unfortunately, memantine did not meet the primary endpoint of visual field progression by full threshold examinations performed every 6 months. This has raised questions about neuroprotection clinical trial design (e.g. enrolling more homogenous patient populations) and endpoints (the need to develop biologically and clinically relevant endpoints that can be used in both animal and human trials). In another long-term, randomized clinical trial, patients with low-pressure glaucoma who were treated with brimonidine tartrate 0.2% were less likely to have visual field progression than those treated with timolol maleate 0.5%. IOP levels were comparable between groups suggesting a non-IOP-related mechanism of action.

The glaucoma community is actively engaged in discussions with the FDA about surrogate endpoints, which could include structural measures from clinical imaging instruments such as scanning laser polarimetry (GDxVCC and GDxECC), confocal scanning laser ophthalmoscopy (HRT) and optical coherence tomography (OCT). Recently, examples of structural change preceding visual field change have been reported using all three of these instrument platforms. All three can be used with experimental glaucoma models, allowing continuity in imaging techniques throughout basic research, pre-clinical testing, clinical trials and post marketing surveillance. Other novel methods of determining efficacy of neuroprotective compounds include DARC (Detection of Apoptotic Retinal Cells) (Figure 3), which allows in vivo imaging of RGC apoptosis and magnetic resonance imaging (MRI), which allows measurements of visualization of LGN atrophy.

Given the incidence of disease progression in normal tension glaucoma and in patients with seemingly well-controlled IOP, research is rapidly expanding into treatments targeting the cellular basis of glaucoma and neuroprotection. Treatment strategies offering increased efficacy, duration of action, and specificity for the individual patient (genetic make up and co-morbidities) are moving forward. Not surprisingly, a disease with multifactorial mechanisms will most likely benefit from a multifactorial treatment approach.

References

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Clinical Issues: Adherence, Perseverance, Dyscompliance: Clinical Applications of Latest Findings

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Core Concepts
- A major obstacle in the treatment of patients with glaucoma is their poor adherence to topical treatment.
- Electronic monitoring studies show that physicians are unable to gauge patient adherence accurately. Patients seem to be even worse at judging their own compliance situation.
- Risk factors for poor adherence may include being of non-white race, age younger than 50 or older than 80 years, self-reported less than excellent health, receiving all disease related information only from the physician and a lack of concern about potential vision loss from glaucoma.
- Measures to raise awareness and ultimately compliance include educational videos, discussions on barriers to using medications and phone reminders by the treating physician or his/her staff.
- Medications with fewer side effects, simpler regimens and less costs enhance medication adherence.

A major obstacle in the treatment of patients with glaucoma is the poor adherence to topical hypotensive medications. The Travatan Dosing Aid Study, which used electronic monitoring in patients on travaprost, found that nearly 50% of patients used less than 75% of their once-daily doses¹. Pharmacy claims databases indicate that up to 90% of patients fail to renew their eye drops² continuously. Given ample evidence that lowering intraocular pressure slows the rate of glaucoma progression, it is likely that patients with poor drop adherence will have a worse outcomes (although this has never been formally tested in glaucoma). Thus, there is considerable interest in being able to identify those patients with poor adherence in order to intervene in such a way that improves medication usage.

Unfortunately, electronic monitoring studies have shown that physicians are unable to gauge adherence of individual patients accurately. Physicians’ estimates of adherence rates correlate poorly with actual recorded drop taking. Patients are even worse, and have an extremely “optimistic” view of their own drop usage. That is, despite knowing that they were being electronically monitored (and only taking around 80% of their doses), the median patient still self-reported 100% use³. Finally, these monitoring studies have shown that patients with poorer adherence are more likely to use drops just before and after a clinic visit, limiting our ability to use eye pressure as a surrogate for adherence. If a patient uses more medication just before coming to the office his/her eye pressure will seem controlled even though drop usage was low over time.

What then, can physicians use to identify patients that may be poorly adherent? A follow-up to the electronic monitoring study mentioned above, identified three risk factors which predicted poorer adherence: African-American race (even after adjusting for education and income), age less than 50 or greater than 80, and self-reported less-than-excellent health⁴. Similarly, the Glaucoma Adherence and Persistency Study (GAPS), based on pharmacy claims, interviewed patients and found that, in addition to nonwhite race, other independent risk factors for refilling drops less frequently than prescribed included learning everything about glaucoma from the doctor and a lack of concern about the potential for vision loss from glaucoma⁵.

These data suggest that patient education may be a modifiable risk factor for poor compliance. This was tested in the second phase of the Travatan Dosing Aid Study, which randomized poorly com-