

Ocular Hypertension and Glaucoma: A Review and Current Perspectives

Najam A. Sharif^{1, 2, 3}

¹Global Alliances and External Research, Global Research & Development, Santen Incorporated, Emeryville, USA

²Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Texas Southern University, Houston, USA

³Department of Pharmacology and Neuroscience, University of North Texas Health Sciences Center, Fort Worth, Texas, USA

Email address:

najam.sharif@santen.com

To cite this article:

Najam A. Sharif. Ocular Hypertension and Glaucoma: A Review and Current Perspectives. *International Journal of Ophthalmology & Visual Science*. Vol. 2, No. 2, 2017, pp. 22-36. doi: 10.11648/j.ijovs.20170202.11

Received: March 7, 2017; **Accepted:** March 27, 2017; **Published:** April 14, 2017

Abstract: Hypertension of the eye fundamentally results from an imbalance between the production and extrusion of aqueous humor (AQH) within the anterior segment of the eye. Vitreous humor (VH) (in the posterior segment of the eye) and AQH are responsible for maintaining the shape of the eye-ball in order that light is correctly focused on the retina for good vision. However, as we age, cells of the AQH drainage system (trabecular meshwork, TM) die and cellular debris accumulates within the TM and the canal of Schlemm thereby slowing, and in some cases, preventing AQH efflux. This results in increased resistance and elevation of hydrostatic pressure within the anterior segment, also termed as elevated intraocular pressure (IOP) or ocular hypertension (OHT). Sustained OHT exerts mechanical pressure on the retinal ganglion cells (RGCs) and the optic nerve fibers at the back of the eye leading to their progressive demise by apoptosis, thereby distorting and diminishing visual acuity over time, and eventually leading to irreversible blindness. In some patients even “normal” IOP is destructive because their RGCs and their axons projecting to the brain are genetically or chemically predisposed to early cell death. These pathologies are termed “glaucomatous optic neuropathy (GON)” and OHT is often associated with glaucoma, especially primary open-angle glaucoma (POAG). Today, there are several pharmacological and minimally invasive surgical interventions / devices that constitute therapeutic modalities to treat OHT and glaucoma. OHT etiology and treatments will be discussed in more detail in this review article.

Keywords: Glaucoma, Ocular Hypertension, Neuroprotection, Pharmacology, Aqueous Humor

1. Introduction

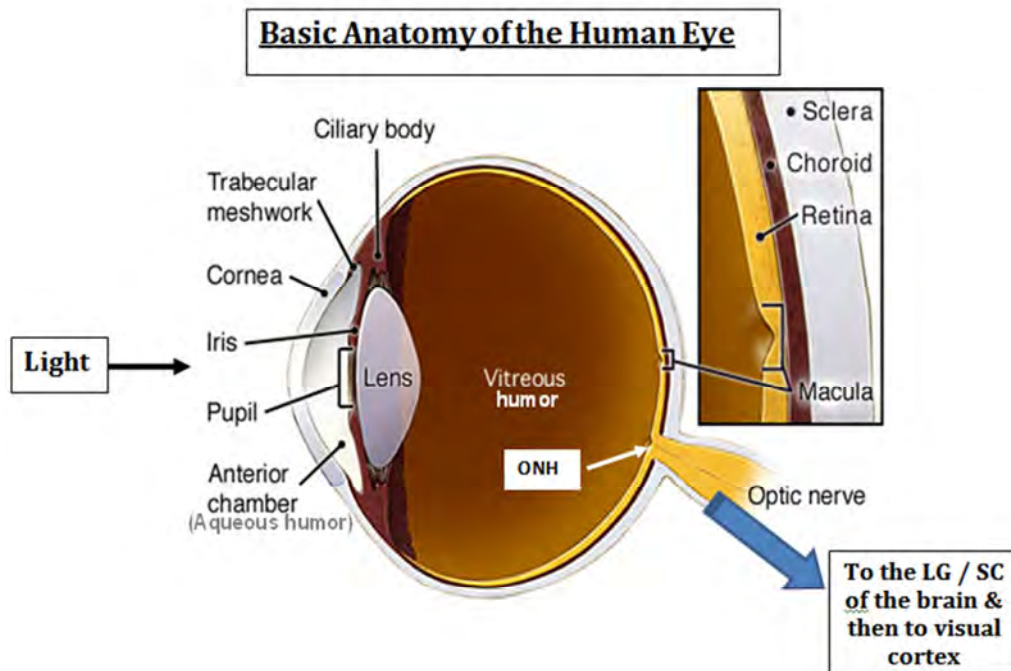
Aqueous humor (AQH) in the anterior segment and vitreous humor (VH) in the posterior segment of the eye, encased in a tough fibrous materials (the sclera), provide the necessary pressure to help maintain the shape of the human eye globe (Fig. 1A). Level of AQH is maintained by an equal rate of AQH production (2 μ l/hour by the ciliary body) and the rate of its efflux through the trabecular meshwork (TM) via the canal of Schlemm located at the corner of the iris-corneal junction [1] (see Figs. 1A/1B below).

As in the rest of the body, hypertension within the eye is caused by increased resistance, but in this case due to accumulation of cellular debris and various components of extracellular matrix (ECM) in the TM and Schlemm’s canal (SC) drainage system [2-5]. The latter dysfunction is age-

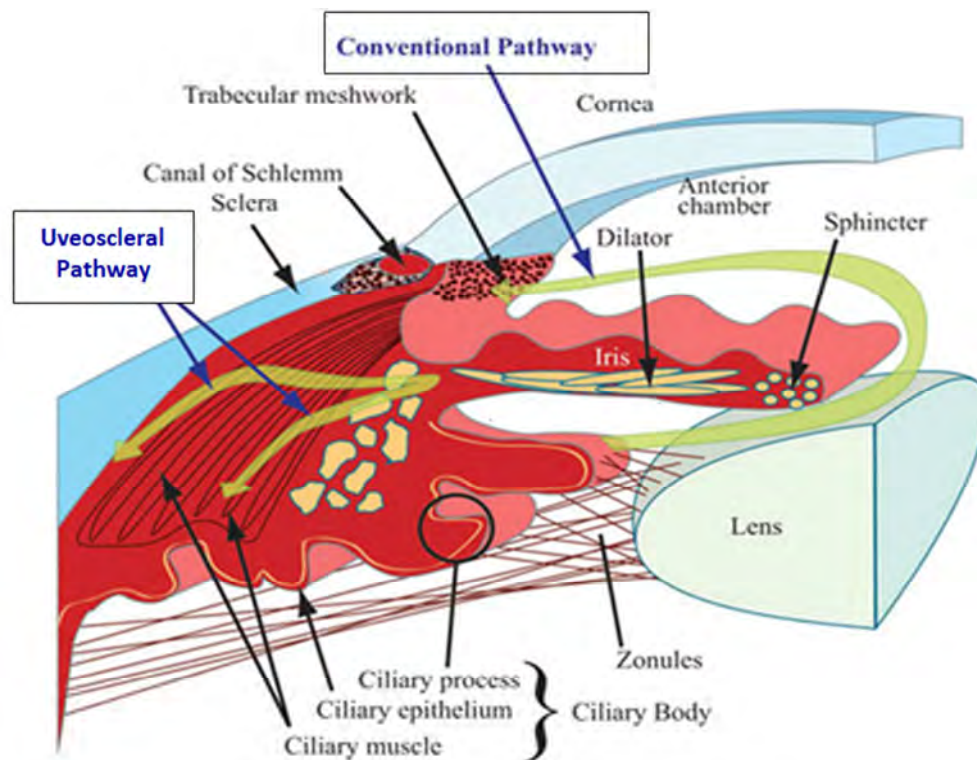
related but some patients are more predisposed to this than others [6, 7]. Indeed, such ocular hypertension (OHT), due to elevated intraocular pressure (IOP), is one of the major risk factors associated with the optic neuropathies known as “glaucoma” [2-7]. Whilst many forms of glaucoma exist [10-12], primary open-angle glaucoma (POAG) has the highest prevalence globally, and it causes irreversible blindness if left untreated [3-5]. In fact POAG ranks as the second leading cause of preventable blindness (after cataracts) afflicting millions of people, with projections ranging from ~80 million by 2020 to >112 million by 2040 [13, 14]. Associated with such global visual impairment is poor quality of life, lost revenue and a huge medicinal and/or surgical treatment burden on nations around the world [3-5; 13, 14]. As the search for genetic markers [15] and potential cures [16-18] for POAG and the related OHT continues, a number of

pharmacological agents [19-23], surgical procedures [24-26] and devices [27-31] have become available to at least treat the symptoms of POAG, vis-à-vis mitigation of OHT. Before

tackling the treatment modalities it is important to understand how elevated IOP is believed to cause visual impairment leading to blindness.



A



B

Figure 1. Outline of the basic overall anatomy of the human eye illustrating some of the key features discussed in the text. LG denotes lateral geniculate; ONH denotes optic nerve head; SC denotes superior colliculus (Fig. 1A). In Fig. 1B, the key elements of the AQH synthetic machinery (ciliary epithelium), and AQH outflow via the trabecular meshwork (conventional outflow) and via the uveoscleral pathway from the anterior chamber are shown. Note: none of the elements shown are to scale. Original figures were obtained from various on-line sources and then modified to fit the needs of the current article.

Pathophysiology of OHT and POAG Leading to Blindness

While the prominent and pervasive trigger in POAG is the elevated IOP [2-4], it is the down-stream events and associated factors that actually cause the damage to the visual system that culminates in blindness. The mechanical effects of too high a fluid pressure in the anterior segment of the eye is transmitted throughout globe and heavily impacts the retinal ganglion cells (RGCs), their axons and the optic nerve [32, 33] where it exists the rear of the eye. Elevated IOP is thought to excessively stretch the axons of the most peripheral RGCs (closest to the sclera) and cause them to break leading to the demise of their cell bodies, thereby adding stress to the next layer of axons. As this trauma progresses, the optic nerve begins to thin and to bow like heavy wires on an electric pylon, thereby bending and crimping the surrounding blood vessels [33-38]. Such mechanical stress at the lamina cribosa and ONH triggers local macrophages and/or glial cells to release matrix metalloproteases (MMPs) that begins to digest the ECM thereby thinning and excavating the area where the optic nerve exits the eye [39-43]. The resultant constriction of the ciliary and central arteries and their capillaries causes varying amounts of additional local hypoxia / ischemia and reperfusion [34-38]. This oxidative and neurochemical stress disturbs the metabolic profile of the various retinal cell types and reactive astroglial activation initiate release of various noxious chemicals. The latter includes reactive oxygen species, nitric oxide, glutamate and a variety of inflammatory cytokines (e.g. various interleukins) and chemokines ensues [39-46]. It is believed that retina with its high metabolic rate, begins to deplete its mitochondrial energy sources [47-52], and since RGCs are highly sensitive to hypoxia and to these damaging chemicals [52-57], which also include endothelin [49-54], they are unable to sustain cellular homeostasis. The ensuing ionic over-load leads to swelling and eventual RGC death. As the demise of some of the RGCs progresses they empty the contents of their cytoplasm and this leads to more damage of the RGCs in the immediate vicinity of the dying cells. This process continues unabated, albeit very slowly. The dead RGC axons undergo phagocytosis and pruning by macrophages [52-60], and the thinning of the retinal nerve fiber layer (RNFL) and the optic nerve continues [39-45]. Concomitantly, the fragile area where the RGC axons merge to form the optic-nerve-head (ONH; [lamina cribosa]) also feels the physical pressure and weakened RGC axons break, thereby killing their respective RGC neurons in a retrograde manner. As this process continues, the ONH of the optic nerve and the associated blood vessels bend even more [38, 46, 52] leading to further ischemia and retardation of anterograde and retrograde axonal transport of nutrients and growth factors. The combination of the resultant oxidative stress [47-52], neurotrophin deprivation [52, 61], neurotoxicity [48-50, 54] and local inflammation [43, 44, 48] lead to further demise of the RGCs and their axons. Such axonal atrophy thins the optic nerve causing it to buckle even more, that then kills even more RGCs. The end result of this

vicious cycle is a severe loss of retinal connections to the lateral geniculate and the visual cortex of the brain leading to visual impairment [63-66]. Even though these deleterious processes may take years, since there is no overt pain or other warning signal perceived by the patient, the insidious and progressive damage continues unabated. During early to mid-stages of POAG induced by OHT the first signs perceived by the patient are dark spots in the images of the outside world giving the impression of missing details within the images, loss of depth of perception and decreased contrast sensitivity. This is followed by a loss of overall peripheral vision giving a "tunnel vision" syndrome [3-8, 67-70]. As the damage and disease progress over several more years, vision continues to deteriorate and eventually total blindness results. Sadly, most patients only realize the visual deficits setting in after demise of about 40% of their original 1 million RGCs. Thus, OHT causes a slow but progressive loss of vision that develops over several decades. Due to lack of symptoms and suitable diagnostic tools, many people do not even know they have POAG until significant damage has already occurred in their visual system. Thankfully since other risk factors for POAG (apart from OHT) [3-8], including increasing age, race (especially African and Asian heritage), myopia, genetic factors, diabetes and vascular dysfunctions have become known, at least there is increasing public awareness of their risk for visual impairment. Accordingly, regular visual exams and consultation with ophthalmologists are leading to earlier diagnosis and treatment for POAG and associated OHT.

In recent years, it has also become clear that it is not just elevated IOP that causes the damage to the visual system in glaucoma. Since the retina and optic nerve are connected to the central nervous system (CNS) [68-70], and the optic nerve is bathed in cerebrospinal fluid (CSF) [71, 72] and surrounded by three layers of thin membranes, disturbances within this microenvironment also have grave effects on the health of the optic nerve and its components. Thus, the hydrostatic pressure gradient between the intraocular space (high pressure) and the retrobulbar space (low pressure) adversely affects the fragile lamina cribosa of the ONH causing it to undergo remodeling and breakage. Since a low CSF pressure [71, 72] is mirrored by a low systemic blood pressure, especially at night, this causes a high trans-lamina cribosa pressure differential and abnormal fluctuations ("spikes") in IOP [52, 64] that adversely impact RGCs and the ONH. Therefore, there is now an emerging link between systemic blood pressure and low ocular blood flow [33-39], CSF pressure [71, 72], and IOP [1-5, 20-31]. Vascular dysregulation [33-38] is thus, in part, responsible for the onset and/or progression of glaucomatous optic neuropathy leading to eventual loss of sight.

Ocular Hypotensive Therapies

Elevated IOP is intimately linked to glaucomatous damage [2-5] and thus ophthalmologists have targeted this readily measurable and treatable biomarker [17] in an effort to treat POAG [20-31, 73]. Due to the high correlation of high IOP with RGC death and glaucoma [32, 40, 44, 62-64] a number

of useful tools have been developed to reliably and reproducibly measure IOP in patients and laboratory animals in order to guide and provide appropriate treatment(s) [75]. The ultimate goal is to achieve an IOP < 12-13 mmHg in order to preserve RGC function and maintain good visual acuity even though the “normal range” of IOP is considered to be 12-22 mmHg [2-5, 75]. Very few drugs or devices actually achieve this level of sustained IOP reduction but

every mmHg decrease in IOP reduces the progression of POAG by 13% and is therefore considered beneficial as illustrated by multiple clinical trials [3-5, 76, 77]. Likewise, it's been shown that a 50% reduction in rate of visual field loss can be achieved by lowering of IOP by only 20-40% [3-5, 63, 64]. These desired levels of IOP reduction need to be considered when comparing relative efficacies of drugs and devices, along with their overall therapeutic indices.

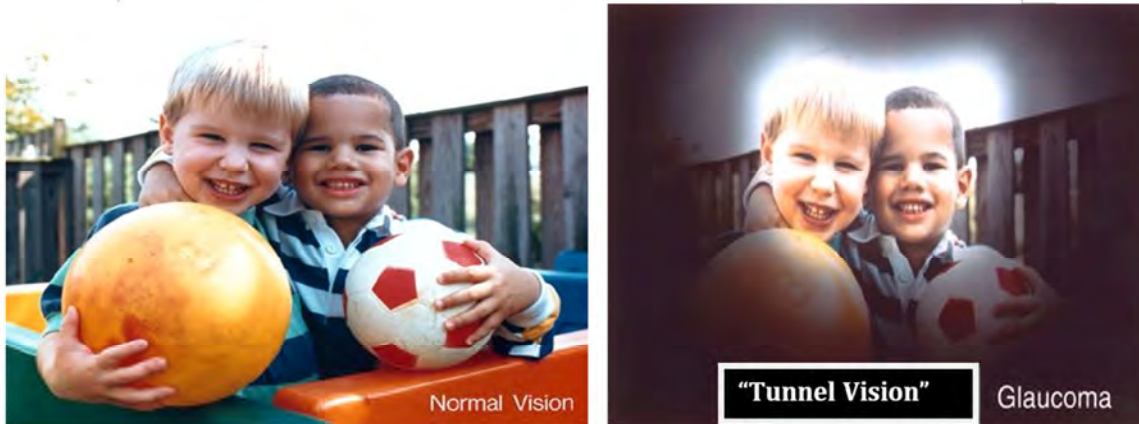


Figure 2. A pictorial view of the outside world seen through normal eyes without visual impairment, and then the same photo as seen through glaucomatous eyes where the peripheral vision is diminished, thus often resulting in “tunnel vision”. The original figures were obtained from the National Eye Institute (NEI) website online and modified to fit the needs of the current article.

Reduction of AQH production and/or acceleration of AQH drainage from the anterior chamber by pharmaceutical means are primarily used to reduce and control IOP [1-5, 24-31]. However, the inadequacies of these medicines either in terms of overall efficacy, duration of action, local and/or systemic side-effects necessitate the discovery and development of new drugs that lack these problems or where such liabilities are reduced. However, patients who are refractory to pharmacotherapy, or are on multiple drug treatment regimens, often require more invasive procedures such as surgical/laser-induced ablation of some of the TM and SC [25, 26]. Drainage of AQH can also be achieved using shunts, valves and micro-invasive-glaucoma-surgeries (MIGS) [27-31]. IOPs of glaucoma patients are routinely monitored and prescription medicines are applied topically to the cornea to either suppress AQH production using inflow inhibitors [1, 20-23], or to stimulate AQH outflow via the trabecular meshwork (TM) (“conventional outflow”) [73, 78, 79], and/or via the uveoscleral (UVSC) pathway (through spaces between CM fibers and the sclera) [20-23, 73, 78, 79]. The resultant IOP reduction has been demonstrated to diminish RGC death, thereby slowing the development and progression of POAG [3-5; 52; 60; 63-65; 68-70]. Pharmaceutical intervention to lower IOP further in ocular normotensive [76-78, 78-80] patients is still desirable since the trajectory of their visual impairment and declining peripheral visual acuity continues. This is one reason why the normotensive patients may require retinoprotectant regimens on top of ocular hypotensive medications [76, 77]. Various neuroprotective agents have been proposed and consist of anti-oxidants like α -lipoic acid [81, 82], Na^+ and Ca^{2+} -

channel blocker treatment [47, 83, 84], polyamines [85-87] and N-methyl-D-Aspartate receptor-coupled channel blockers [47-52].

2. OHT / POAG Pharmacotherapy Today

One of the earliest pharmacological agents to be used, back in 1875, to treat POAG and associated OHT was the miotic muscarinic agonist pilocarpine [19-23, 88]. However, the inadequate IOP-control by pilocarpine and its side-effects (pupillary constriction and brow-ache) prompted pharmaceutical research that culminated in discovery of carbonic anhydrase inhibitors (CAIs; acetazolamide; dorzolamide; brinzolamide; oral and topical ocular [t. o.]) [20-23, 89]. Whilst CAIs lower IOP they cause conjunctival allergy and hyperemia. The discovery and clinical use of beta-adrenergic antagonists (timolol; betaxolol) [20-23, 90, 91] in the seventies was followed by the introduction of alpha-adrenoceptor agonists (brimonidine; para-amino-clonidine) [20-23] in the nineties that primarily impact ciliary body/processes to cut down generation of AQH (Table 1). Unfortunately, even though beta-blockers are potent and efficacious ocular hypotensives, they cause local burning and stinging and worsening of pulmonary insufficiency, and reduce cardiac contractility and heart rate [20-23]. Likewise, alpha-2 agonists are prone to initiate conjunctival allergies, and cause arrhythmias, elevated blood pressure, headaches, fatigue, hyperemia, dry mouth and even drowsiness [20-23, 92] as they lower IOP. Furthermore and unfortunately,

reducing AQH production is insufficient, and despite twice- or three-times daily instillation of inflow inhibitors, IOP-lowering is achieved only for a few hours and only by a few mmHg. It is also not advisable to reduce the AQH production too much since the nutrients and oxygen within this fluid are essential for the healthy maintenance of corneal endothelial cells, lens and TM cells amongst other structures of the anterior segment.

A revolutionary paradigm shift in POAG/OHT treatment occurred in the 1990s and 2000s when FP-receptor-selective prostaglandin analog agonists (PGAs) (e.g. Latanoprost; Travoprost; Tafluprost) [93] (Table 1) were approved. This represented a novel class of pharmacological agents that promoted AQH outflow through the uveoscleral [UVS] pathway to lower IOP. The PGAs utilized an extracellular-matrix (ECM) remodeling mechanism of action by releasing matrix metalloproteinases (MMPs) that digested the ECM within the ciliary muscle bundles and the scleral tissue [20-23, 93]. Since the PG pro-drugs possess a longer duration of action than the inflow inhibitors, they are only dosed to the eye once daily [20-23; 93-95]. This reduced overall drug and preservative exposure to the ocular surface and ultimately enhanced patient adherence to therapy. Nevertheless, compliance remains a major challenge, and FP PGAs also have side-effects such as causing hyperemia, ocular surface irritation, darkening of the iris and periorbital tissues, lengthening of eyelashes and occasionally causing cystoid macular edema [93-95]. While pilocarpine represents the only approved drug that facilitate AQH outflow through the TM and down the canal of Schlemm (conventional outflow; CNV outflow), recent evidence suggests that FP-PGAs reduce IOP by activating AQH egress from the anterior chamber via both UVSC and CVN outflow pathways since FP receptors are present in both CM and TM [96]. Since enhancing AQH drainage via the TM is the preferred mode of treatment for OHT, another three classes of agents that specifically targets the TM, by relaxing this tissue, include rho kinase inhibitors [97-98], a bifunctional molecule that releases both a PGA and nitric oxide (NO) (latanoprostene bunod) [100, 101], and an adenosine A1 receptor agonist [102]. Some of these small molecules have reached late-stage clinical trials and look quite promising. However, the therapeutic index associated with these potential drug candidates remain to be described in more detail prior to approval by health authorities. Additionally, whether they deliver the same or superior efficacy, over a protracted period of time, to the current gold-standards (FP-PGAs) remains to be seen.

Unfortunately, patients whose IOP remains uncontrolled by one medicine, or those who are no longer responsive to a given medication, require adjunctive therapy. This involves beta-blocker or CAI eye-drop instillation during the day, and PGA eye-drops instilled at night. Some patients ultimately require three or more different classes of drugs to lower and control their IOP, and perhaps even surgery as a last resort. Various fixed-dose combination drug products [103, 104] in a single bottle have been approved by some world health

authorities for such ocular hypertensive patients. Some examples of combination formulations include Azarga (brinzolamide 1% + timolol 0.5%), Cosopt (dorzolamide 2% + timolol 0.5%), Combigan (brimonidine 0.2% + timolol (0.5%), Duotrav (travoprost 0.004% + timolol 0.5%), Simbrinza (brinzolamide 1% + brimonidine 0.2%) and tafluprost + timolol combination [103, 104]. A triple fixed-dose combination formulation consisting of dorzolamide + brimonidine + timolol has recently been shown to lower IOP to a significant extent beyond the efficacy provided by each of the drugs in the combination product and is approved in Mexico [104]. While other combination products are on the horizon, such a triple fixed-dose combination product has yet to be approved by any ministry of health where dual combinations are approved (β -blocker + CAI; CAI + α 2-agonist; β -blocker + α 2-agonist; PGA + β -blocker; etc.). Another novel approach has been to generate multifunctional molecules that possess dual activity by virtue of conjugation of a PGA with other IOP-lowering agents [105]. Whilst there is much hope pinned to these novel approaches, an older drug nipradolol that has intrinsic beta-blocker and NO-releasing properties has not gained much prominence in clinical practice [20-23;73]. This may be due to its rather low IOP-lowering efficacy.

The clinical management of IOP associated with POAG and OHT has clearly advanced in recent years. However, due to the side-effect profiles of many of the approved pharmaceutical agents described above, there still remains a need to find even better medications for OHT treatment. Some of the ocular and/or systemic side-effects that limit the utility of the current topical ocularly utilized medicines involve their overall effectiveness, duration of action, posology and/or significant side-effects (local irritation/stinging/redness and/or bradycardia and exacerbation of asthma). The duration of action is a key hurdle for some of the afore-mentioned non-PG drugs, since they only provide efficacy for ≤ 12 hours. Thus, CAIs (e.g. dorzolamide and brinzolamide) have to penetrate cornea/conjunctiva/ciliary epithelial cell membranes and then block almost 100% of the CA-enzyme activity within the NPE cells to reduce AQH generation. Additional hurdles include the prevalence of several isoforms of the CA with each having a different replenishing rate as the enzymes are synthesized from scratch. These aspects necessitate twice/thrice daily instillation regimen to achieve sufficient IOP reduction and control, and the burden of attendant local ocular irritation and redness (hyperemia). Sharp stinging and burning of the ocular surface is associated with topical ocular β -blockers such as betaxolol and timolol. Additionally, such β -adrenoceptor antagonists reach the systemic circulation from the ocular-nasal duct and produce pulmonary and cardiac side-effects that then limit their utility in asthmatic and hypertensive patients. While FP-receptor PG agonists (PGAs) potently and efficaciously reduce and control IOP for up to 24 hrs and represent first-line ocular hypotensives, they are responsible for local hyperemia, thickening and elongation of eye-lashes, and darkening of the iris and

periorbital area, plus cystoid macular edema in some cases. Even though the latter side-effects are apparently reversible upon PGA drug discontinuation, the long-term consequences of the latter side-effects remain unknown and due caution is

still required in the use of these agents. Therefore, the search for better tolerated and more effective ocular hypotensive drugs continues around the globe. These are discussed more fully in the section below.

Table 1. Selected IOP-lowering agents and their reported or potential mechanisms of actions.

Compound classes	Investigative agent or approved drug	Reported or potential mechanism(s) of action
Conventional Outflow (via TM pathway) Promotors		
Muscarinic receptor Agonists	Pilocarpine [88]; Aceclidine; Carbachol	Contract ciliary muscle /TM to promote outflow of AQH via the TM-SC pathway
Inhibitors of chloride transport	Ticrynafen, Ethacrynic acid; Indacrinone [172]	Inhibition of $\text{Na}^+ \text{--} \text{K}^+ \text{--} \text{Cl}^-$ -transporter activity in the TM changes cell shape & volume and thus AQH efflux is increased
Kinase inhibitors	ROCK inhibitors [97-99]: Y-27632; Y-39983; H-7; ML-9; Chelerythrine; Staurosporin; K-115; AR-12286; LIM-K inhibitor [165], Myosin-II ATPase inhibitor: Blebbistatin Sc kinase inhibitor [166]	Modification of actomyosin contractility that leads to changes in actin cytoskeleton of TM and this leads to AQH efflux; direct relaxation of the TM may also be involved.
Marine macrolids	Latrunculins A and B; Bumetanide; Swinholide [79]	Promote sequestration of actin monomers and dimers in TM; cause cell TM shape change and thus AH efflux
Guanylate cyclase activators NO Donors Soluble guanylate cyclase activators	Natriuretic peptides: ANP; CNP [167] sodium nitroprusside; Hydralazine; 3-morpholinolinosyndnonimine; (S)-nitrosoacetylpenicillamine; NCX-125 [100, 101] IWP-953 [119]	Type-A and type-B receptor activation leads to cGMP production, TM relaxation and AQH efflux via TM
κ -opioid receptor agonists	Bremazocine; dynorphin [168]	Release natriuretic peptides and thus raise cGMP in TM leading to its relaxation & thus AQH efflux
Cannabinoid receptor agonists	WIN55212-2; CP55940; SR141716A [169]	Receptor stimulation opens BKC-channels and relaxes TM which then causes AQH efflux via TM and SC.
FP-class PG-receptor agonists	Latanoprost; Travoprost; Bimatoprost; Tafluprost; Unoprostone isopropyl ester [93-96; 170]	Some clinical evidence of promoting conventional outflow in addition to UVS outflow
Serotonin-2 receptor antagonists	BVT-28949; ketanserin and its analogs [171]	Unknown and unverifiable mechanism(s) of action (may block beta-adrenergic receptors indirectly?)
Releasers of MMP & AP-1	FP-class PGs [93-96]; <i>t</i> -butylhydroquinone (t-BHQ); β -naphthoflavone;	Local production of MMPs; ECM degradation; stimulation of AQH efflux via TM
Uveoscleral Outflow promotors (via CM bundles and sclera)		
FP-class PG-receptor agonists	Latanoprost; Travoprost; Bimatoprost; Tafluprost; Unoprostone isopropyl ester [93-96;170]	FP receptor activation in CM causes release of MMPs that breakdown ECM ("clog") around CM bundles and within sclera thus causing UVS outflow of AQH
EP ₂ - and EP ₄ - PG-receptor agonists	AL-6598 [93, 121]; Butaprost; ONO-AE1-259-01; PF-04217329 [122]; DE-117 (Omidenedap Isopropyl) [110, 123]; PF-04475270 [120]	Receptor activation increases cAMP that relaxes CM & TM; EP ₂ agonists also cause release of MMPs that breakdown ECM ("clog") around CM bundles and within sclera thus causing UVS outflow of AQH
Serotonin-2 (5HT-2) receptor agonists	(R)-DOI; α -methyl-5HT; AL-34662 [124-126]	Contraction / relaxation of CM and TM by activation of 5HT ₂ receptors. May also release MMPs and/or PGs or other local mediators that promote CM remodeling and thus promote UVS outflow
Bradykinin B ₂ -receptor agonists	Bradykinin; FR-190997; BKA278 [135-146]	B ₂ -receptor activation causes PI hydrolysis production of IPs and DAG; cause PG release and release of MMPs that digest ECM and this promote UVS outflow in cynomolgus monkey; conventional outflow also stimulated in isolated bovine /porcine anterior eye segments [177, 178].
Dual pharmacophore PGs	FP/EP ₃ receptor agonist (ONO-954) [127, 128]	Promote UVSC outflow and TM outflow
Inflow inhibitors (reduce AQH production)		
β -adrenergic antagonists	Betaxolol; Levobetaxolol; Timolol; Levobunolol; Metipranolol [19-23]	Block β -adrenergic receptors in the ciliary process, decrease cAMP generation and thus decrease AQH formation
α 2-adrenergic agonists	Brimonidine; Clonidine; Apraclonidine [19-23]	Intracellular cAMP reduced in CP that decreases AQH generation; may also prevent NE release. Brimonidine also promotes TM outflow
Carbonic anhydrase inhibitors	Dorzolamide; Brinzolamide [89]	Inhibit ciliary process CA-II and CA-IV and thus reduce bicarbonate production that in turn reduces AQH generation
Chloride channels inhibitors	5-nitro-2-(3-phenylpropylamino)-benzoate [172]	Ion flux of CP NPE cells causes reduction of AQH formation
$\text{Na}^+ \text{--} \text{K}^+ \text{--} \text{ATPase}$ inhibitors	Ouabain; Digoxin analogs [173]	Ciliary process $\text{Na}^+ \text{--} \text{K}^+ \text{--} \text{ATPase}$ inhibited leading to inhibition of AQH production

Compound classes	Investigative agent or approved drug	Reported or potential mechanism(s) of action
Dopamine receptor agonists	PD128907; CHF1035; CHF1024; SDZ GLC-756; (S)-(-)-3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP) [174]	Inhibit release of NE & prevent AQH production; may also release natriuretic peptides
Na ⁺ -K ⁺ -ATPase inhibitors	Ouabain; Digoxin analogs [173]	Ciliary process Na ⁺ -K ⁺ -ATPase inhibited leading to inhibition of AQH production
Aquaporin Inhibitors	Various aromatic sulfonamides and dihydrobenzofurans [180]	Inhibit release of NE & prevent AQH production
Other IOP-lowering agents		
Mas receptor stimulator	DIZE via ACE-2 activation [131]	Prevent ECM (including TGFβ) accumulation (outflow stimulation ?)
Angiotensin-II receptor antagonists	CS-088 [129]	Various mechanisms of action; not robust IOP-lowering
Ca ²⁺ -channel inhibitors	Lomerazine; Nivaldipine; Nifedipine; Nimodipine; Verapamil; Brovincamine; Iganidipine [84]	Enhance retinal blood flow; some may lower IOP; work well in normal tension glaucoma patients
Alpha-adrenergic receptor antagonists	Oxymetazoline; 5-methylurapidil; Ketanserin [175]	Work mostly via outflow mechanism but this needs to be defined
Other prostaglandin receptor agonists	AL-6598 (DP/EP ₂ receptor agonist); AGN192093 (TP receptor agonist); BW245C (DP receptor agonist); Sulprostone (EP ₃ receptor agonist) [19-23; 121]	These work through multiple mechanisms of action involving cAMP production, Ca ²⁺ mobilization leading to relaxation / contraction of ciliary muscles/ TM
PG-conjugates [101, 105]	Latanoprostene Bunod (NO donor coupled to latanoprost) [101]	Combination of NO-cGMP production and FP-receptor activation
Combination products	Brinzolamide-brimonidine; Brinzolamide-brimonidine; Acetazolamide-Timolol-Brimonidine; Travoprost-brimonidine; Bimatoprost-brimonidine; Tafluprost-Timolol [103, 104]	Complementary mechanisms of action encompassing inflow-outflow inhibition, and inflow-uveoscleral outflow inhibition.

POAG / OHT Pharmacotherapy: Tomorrow and Beyond

The continued and concerted efforts of researchers in academia and industry is providing new targets and pathways for pursuit of new ocular hypotensive drugs and agents that could potentially protect the RGCs in a more direct manner. Development of more robust and translatable animal models of OHT/glaucoma involving numerous animal species [10-12, 23, 88, 93, 106-110], ex-vivo ocular models (e.g. perfused anterior eye segments [107]), and new screening assays and techniques [20, 40, 42, 46, 47, 62, 65, 74, 75], including biomarkers [17] are helping advance our knowledge of the etiologies of OHT and POAG. Similarly, development and use of methods to detect RGC death in real-time [111], ocular metabolomics [112], ocular proteomics [113], radiowave telemetric recording of IOP [114] and refined computer modelling of visual field progression [115] is proving of immense value in the diagnosis and prognosis of OHT and POAG. This in turn is helping discover new ways and novel agents to treat these diseases. Pharmacological agents that have shown promise in combating OHT in various assays and animal models include NO- and hydrogen sulfide- donors [116-118], soluble guanylate cyclase activators [119], rho-kinase inhibitors (e.g. Y-39983, K-115, AR-12286, AR-13324, and AMA0076) [79, 97-99], PG-NO donor conjugates (e.g. Latanoprostene bunod [BOL-303259-X]) [101], adenosine receptor agonists (e.g. OPA-6566; CF-101; Trabodendosone) [102], EP₄ PG-agonists (e.g. 7-dithia PGE1; PF-04475270) [120], EP₂ receptor PG-agonists (e.g. AL-6598; ONO-AE1-259-01; PF-04217329; DE-117 (Omidanepag Isopropyl™) [93, 121; 122-124], serotonin-2 (5-hydroxy-tryptamine-2 [5-HT₂]) receptor agonists (e.g. R-DOI; AL-34662) [125, 126], dual pharmacophoric PGs, having both FP- and EP₃-receptor agonist activities (e.g. ONO-9054) [127, 128], dopamine

receptor agonists, melatonin receptor agonists, cannabinoid agonists, receptor-coupled-guanylate cyclase activators, etc (Table 1).

An area of research that overlaps between the systemic hypertension and OHT relates to the renin-angiotensin and kallikrein-kinin systems. Local intrinsic location and production of various components and products of the renin-angiotensin system (RAS) that activate distinct receptor-effector pathways have now been delineated in anterior uveal ocular cells and tissues. Furthermore, angiotensin converting enzyme (ACE) inhibitors, angiotensin (AT) receptor antagonists [129], a novel angiotensin-derived peptide (Ang-1-7) [130] and a novel ACE-2-activator [131] have demonstrated ocular hypotensive [129-132] and neuroprotective [131] activity in various animal models [129-133]. However, at present less is known about translation of these findings to the human OHT patient population, but warrants further investigation.

Recent research has provided strong evidence for an endogenous local enzymatic system that generates various kinins in cells of tissues involved in IOP regulation [134-138]. Indeed, bradykinin (BK) and various BK-related peptides (and some BK-mimetic non-peptidic agents FR-190997; BK2A78) [139, 140] stimulate B₂-receptors in animal and human cells derived from ciliary body (both epithelial and smooth muscle) [141, 142] and TM [138, 144] to generate intracellular inositol phosphates, intracellular Ca²⁺ and promote secretion of PGs and MMPs [141-146]. Such cellular and molecular cascades are now believed to be responsible for causing profound lowering and controlling IOP with a long duration of action in ocular OHT cynomolgus monkey eyes [145, 146]. Again, whilst translation of these observations in OHT patients is eagerly awaited, the afore-mentioned lead compounds (FR-190997;

BK2A78 [145, 146]) represent new drug candidates and potential novel templates for further studies in this arena.

3. Microinvasive Glaucoma Surgeries (MIGS) and Devices

As mentioned earlier, it is the elevated IOP due to AQH accumulation in the anterior chamber of the eye that causes glaucomatous damage to the optic nerve. Obviously if the AQH can be drained in a controlled manner, and on a slow continuous basis, an homeostatic state would be achieved thereby normalizing IOP and preventing RGC death. To this end, laser-induced TM ablation and surgical procedures [24-26] have been enhanced by implantation of tiny devices (microshunts) [27-31] into the anterior chamber of the eye. The classic laser-treatment and surgery that pertains to removal of some of the TM tissue is quite an effective procedure because endogenous ocular hypotensive agents are

released into the AQH that promote AQH efflux from the anterior chamber [24-26]. However, the latter procedures are confounded by the rather short duration of IOP-lowering efficacy and robust ocular healing process that seals the opening and scars the sclera, thereby necessitating further lasering and surgery. Consequently, it was believed that once an orifice is created from the anterior chamber for AQH egress, that implantation of a device that remains in the anterior chamber and extrudes the AQH fluid out to the sclera, conjunctiva and sub-tenons space would be more effective than the surgery alone. Indeed several devices have been tested in animals and humans and one recently approved by the FDA, iStent [27-31]. Another very efficient device is the InnFocus MicroShunt™ that lowers the IOP in POAG/OHT patients down to 10-12 mmHg and maintains the IOP close at to this level for up to 3-years [29] (see Figs. 3-4 below).

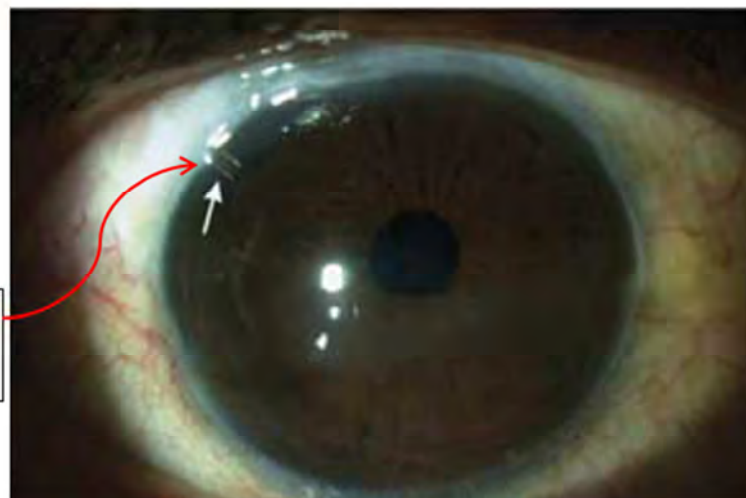
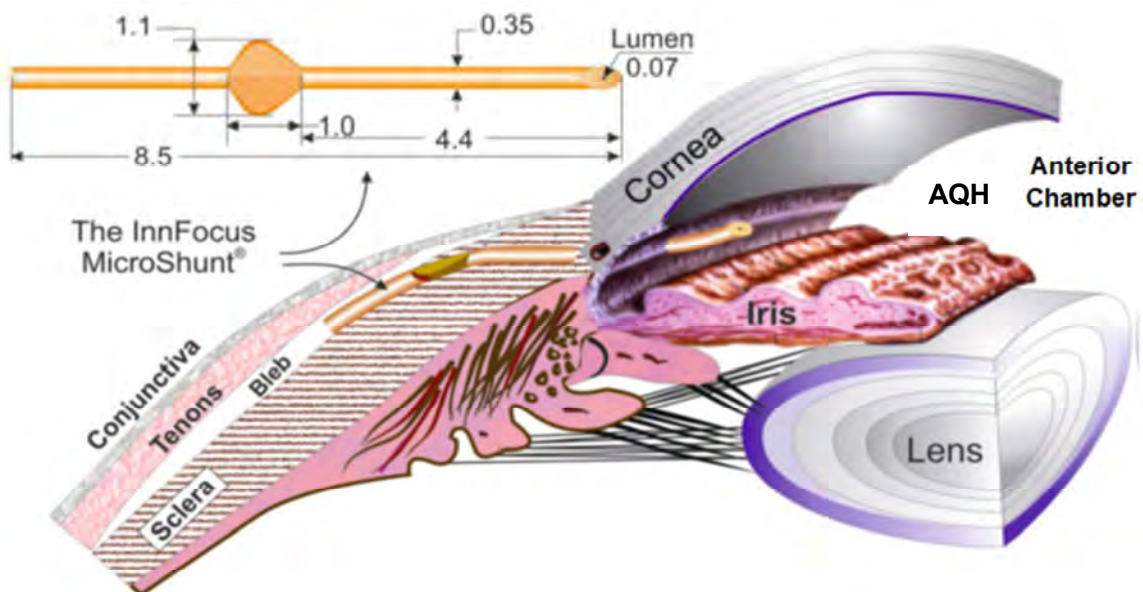


Figure 3. Top portion of the figure depicts an InnFocus Microshunt™ (IFMS; dimensions and its positioning inside the front of the eye to drain the AQH from the anterior chamber to the sub-tenons space). The lower portion of the Figure shows the location of an implanted IFMS in a human eye (front view). Modified from ref 29.

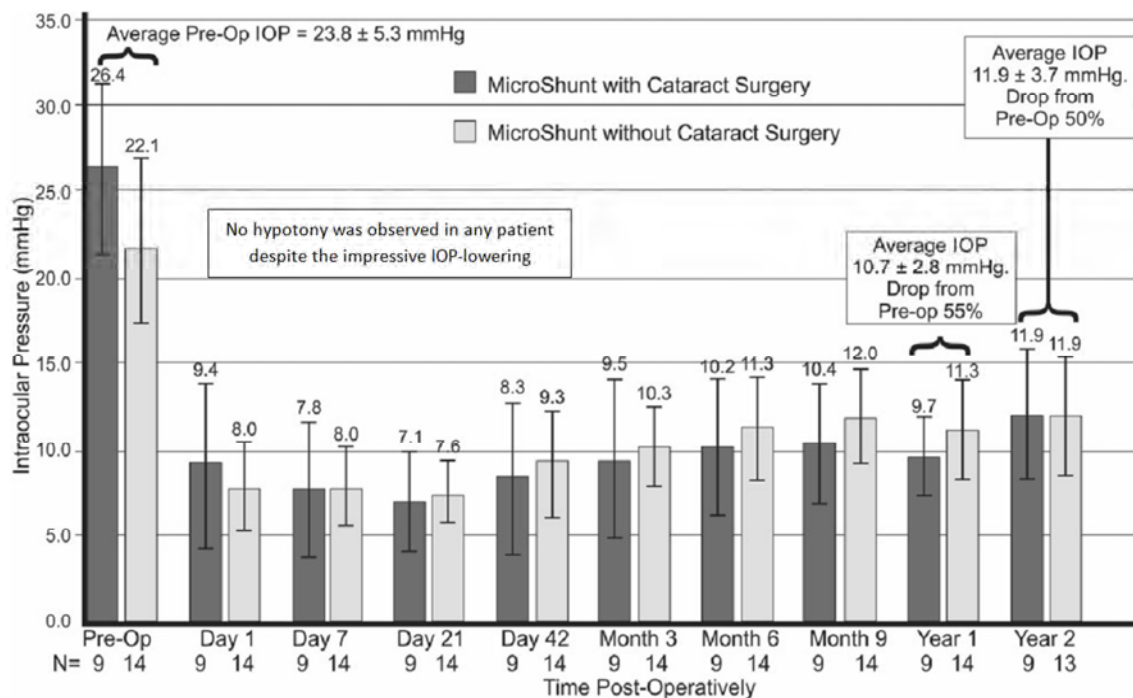


Figure 4. This figure depicts the lowering and controlling of IOP in numerous patients who had the InnFocus Microshunt™ (IFMS) implanted into their eyes in absence or in conjunction with cataract surgery. The IOPs were monitored and recorded over many months and years as shown to demonstrate the longevity of the ocular hypotension induced by this device. No hypotony was observed. Modified from ref 29.

Due to the extraordinary ocular hypotensive effect and the maintenance of low IOPs for years (Fig. 4), such micro-devices are going to revolutionize the treatment for ocular OHT, POAG and other forms of glaucoma. These MIGS-coupled devices have the potential for replacing some of the topical ocularly applied medications. This is indeed an exciting time for ophthalmology and the patients afflicted with OHT and glaucoma. Preservation of vision by any safe and effective means continues to be a goal for all ophthalmologists and researchers involved in cutting-edge research. We should be encouraged by these new findings and hope for more rapid progress in this arena of tackling the undesirable effects of old age and other ocular pathologies connected with POAG and OHT.

OHT and Neuroprotection

Since some patients continue to lose vision despite having their IOP under control, such as in ocular normotensive glaucoma [33, 39, 76, 77], there is a need to reduce or prevent the apoptotic death of RGCs. Consequently, direct protection of RGCs, independent of lowering IOP, has become an important avenue of glaucoma/OHT research. However, despite many drug candidates having demonstrated efficacy in isolated cells and in animal models of RGC demise, none have proven effective in human clinical trials thus far. Agents that have been investigated and shown positive results in animal studies include anti-oxidants (e.g. α -lipoic acid) [81, 82] glutamate / N-methyl-D-Aspartate receptor-channel antagonists (e.g. MK-801; memantine) [47, 50, 52, 55, 60, 147], caspase and NOS inhibitors [52, 55, 60, 67, 148], neurotrophic factors (e.g. nerve growth factor; brain-derived growth factor) [149-151], alpha-2 agonists (e.g.

brimonidine) [150, 152, 153], beta-blockers (e.g. betaxolol) [149, 154, 155], delta opioid agonists [156], etc. Continued research effort in this area to mitigate glaucomatous optic neuropathy would eventually be rewarded. Drugs that directly protect the RGCs and their axons and thereby preserve vision are thus eagerly awaited.

4. Conclusions

In conclusion, hypertension of the eye is intimately involved in causing serious and blinding visual impairment around the world. It is believed that physical and mechanical effects of the elevated IOP leads to apoptotic death of RGCs which in turn leads to loss of their axonal connections to the brain thereby negatively impacting vision. Since every mmHg of IOP reduction is important, many pharmaceutical small molecule drugs have become mainstay treatment modalities for combating OHT, with FP-class PGAs being the most preferred due to their extraordinary efficacy. Hopefully the new non-PG EP₂-receptor agonists such as omidenepag isopropyl (DE-117), and ROCK inhibitors such as Netarsudil [97] will continue to demonstrate long duration of IOP-lowering efficacy with reduced or minimal side-effects. Combination products have also been introduced into clinical management of OHT since some patients are refractory to certain medications and/or whose IOP is not controlled by one drug. Furthermore, fixed-dose ocular hypotensive combination products have alleviated some of the compliance issues associated with topical ocular drugs. In recent years implanted valves/shunts and MIGs to promote efflux of AQH from the anterior chamber have also become

important tools to overcome the destructive effects of elevated IOP. It is hoped that steady progress in the discovery, development and regulatory approvals of novel medications and devices will continue in order to help preserve vision of POAG patients. Clearly, advances in ocular genetics and metabolomics-wide association studies [157], a better understanding of AQH dynamics and lymphatics [158-160], refinement of clinical trials, both for OHT [161] and neuroprotection [55, 147], will also be very useful. Likewise, use of novel molecules such as vitamin B3 [18], micro-RNAs [162] and transplantation of stem cell [163, 164] could also prove of value in the fight against OHT/glaucoma, including glaucomatous optic neuropathy (GON).

References

- [1] Civan M, Macknight AD. The ins and outs of aqueous humor secretion. *Exp Eye Res.* 2004; 78: 625-631.
- [2] Sacca SC, Pulliero A, Izzotti A. The dysfunction of the trabecular meshwork during glaucoma course. *J Cell Physiol.* 2015; 230: 510-525.
- [3] Coleman AL. Glaucoma. *Lancet* 1999; 354: 1803-1810.
- [4] Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet* 2004; 363: 1711-1720.
- [5] Quigley HA. Glaucoma. 2011. *Lancet* 377: 1367-1377.
- [6] Sivak JM. The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease. *Invest Ophthalmol Vis Sci.* 2013; 54: 871-880.
- [7] McKinnon SJ. The cell and molecular biology of glaucoma: common neurodegenerative pathways and relevance to glaucoma. *Invest Ophthalmol Vis Sci.* 2012; 53: 2485-2487.
- [8] Peters JC, Bhattacharya S, Clark AF, Zode GS. Increased endoplasmic reticulum stress in human glaucomatous trabecular meshwork cells and tissues. *Invest Ophthalmol Vis Sci.* 2015; 56: 3860-3868.
- [9] Casson RJ, Chidlow G, Wood JPM, Crowston JG, Goldberg I. Definition of glaucoma: clinical and experimental concepts. *Clin Expt Ophthalmol.* 2012; 40: 341-349.
- [10] Overby DR, Clark AF. Animal models of glucocorticoid-induced glaucoma. *Exp Eye Res.* 2015; 141: 1126-1130.
- [11] Gerometta R, Podos SM, Candia OA, Wu B. et al. Steroid-induced ocular hypertension in normal cattle. *Arch Ophthalmol.* 2004; 122: 1492-1497.
- [12] Gelatt KN, Brooks DE, Samuelson DA. Comparative glaucomatology, II: the experimental glaucomas. *J Glaucoma* 1998; 7: 282-294.
- [13] Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol.* 2004; 122: 477-485.
- [14] 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. *Ophthalmol.* 2014; 121: 2081-2090.
- [15] Aung T, Khor CC. Glaucoma Genetics: recent advances and future directions. *Asia Pacific J Ophthalmol.* 2016 (in press).
- [16] Borrás T. Advances in glaucoma treatment and management: gene therapy. *Invest Ophthalmol Vis Sci.* 2012; 53: 2506-2510.
- [17] Bhattacharya SK, Lee RK, Grus FH et al. Molecular biomarkers in glaucoma. *Invest Ophthalmol Vis Sci.* 2013; 54: 121-131.
- [18] Williams PA, Harder JM, Foxworth NE, Cochran KE, Philip VM, Porciatti V, Smithies O, John SWM. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. *Science* 2017; 355: 756-760.
- [19] Clark AF, Yorio T. Ophthalmic drug discovery. *Nature Rev Drug Discov.* 2003; 2: 448-459.
- [20] Sharif NA, Klimko P. CNS: Ophthalmic Agents, in *Comprehensive Medicinal Chemistry II.*, 2007; Vol. 6, Chapter 12, p. 297-320 (Eds: J. B. Taylor & D. J. Triggle), Elsevier, Oxford.
- [21] Bucolo C, Salomone S, Drago F, Reibaldie M, Longo A, Uva MG. Pharmacological management of ocular hypertension: current approaches and future perspectives. *Curr Opin Pharmacol.* 2013; 13: 50-55.
- [22] Chen J, Runyan SA, Robinson MR. Novel ocular antihypertensive compounds in clinical trials. *Clin Ophthalmol.* 2011; 5: 667-677.
- [23] Toris CB. Pharmacotherapies for glaucoma. *Curr Mol Med.* 2010; 10: 824-840.
- [24] Coleman AL. Advances in glaucoma treatment and management: surgery. *Invest Ophthalmol Vis Sci.* 2012; 53: 2491-2494.
- [25] Francis BA, Singh K, Lin SC, Hodapp E, Jampel HD, Samples JR, Smith SD. Novel glaucoma procedures. A report by the American Academy of Ophthalmology. *Ophthalmol.* 2011; 118: 1466-1480.
- [26] Rekas M, Danielewska ME, Byszevska A, Petz K, Wierzbowska J, Wierzbowska R, Iskander DR. Assessing efficacy of canaloplasty using continuous 24-hour monitoring of ocular dimensional changes. *Invest Ophthalmol Vis Sci.* 2016; 57: 2533-2542.
- [27] Richter GM, Coleman AL. Minimally invasive glaucoma surgery: current status and future prospects. *Clin. Ophthalmol.* 2016; 10: 189-206.
- [28] Manasses DT, AU L. The new era of glaucoma micro-stent surgery. *Ophthalmol Ther.* 2016; DOI 10.1007/s40123-016-0054-6.
- [29] Battle JF, Fantes F, Riss I, Pinchuk L, Albuquerque R, Kato YP, Arrieta E, Peralta AC, Palmberg P, Parrish RK, Weber BA, Parel J-M. Three-year follow-up of a novel aqueous humor microshunt. *J Glaucoma* 2016; 25: 58-65.
- [30] SooHoo JR, Seibold LK, Radcliffe NM, Kahook MY. Minimally invasive glaucoma surgery: current implants and future innovations. *Can J Ophthalmol.* 2014; 49: 528-533.
- [31] Ferguson TJ, Berdahl JP, Schweitzer JA, Sudhagoni R. Evaluation of a trabecular micro-bypass stent in pseudophakic patients with open-angle glaucoma. *J Glaucoma* 2016; 25: 896-900.

- [32] Burgoyne CF, Downs JC, Bellezza AJ, Suh J-KF, Hart RT. The optic nerve head as a biomechanical structure; a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. *Prog Retinal Eye Res.* 2005; 24: 39-73.
- [33] Hollander H, Makarov F, Stefani FH, Stone J. Evidence of constriction of optic axons at the lamina cribrosa in the normotensive eye in humans and other mammals. *Ophthalmic Res.* 1995; 27: 296-309.
- [34] Broadway DC, Drance SM. Glaucoma and vasospasm. *Br J Ophthalmol.* 1998; 82, 862-870.
- [35] Cull G, Told R, Burgoyne CF, Thompson S, Firtune B, Wang L. Compromized optic nerve blood flow and autoregulation secondary to neural degeneration. *Invest Ophthalmol Vis Sci.* 2015; 56: 7286-7292.
- [36] Flammer J, Orgul S. Optic nerve blood-flow abnormalities in glaucoma. *Prog Retin Eye Res.* 1998; 17: 267-289.
- [37] Park SC, Brumm J, Furlanetto RL, Netto C, Liu Y, Tello C, Liebmann JM, Ritch R. Lamina cribrosa depth in different stages of glaucoma. *Invest Ophthalmol Vis Sci.* 2015; 56: 2059-2064.
- [38] Pasquale LR. Vascular and autonomic dysfunction in primary open-angle glaucoma. *Curr Opin Ophthalmol.* 2016; 27: 94-101.
- [39] Park H-Y L, Lee K-II, Lee K, Shin HY, Park CK. Torsion of the optic nerve head is a prominent feature of normal-tension glaucoma. *Invest Ophthalmol Vis Sci.* 2015; 156-163.
- [40] Girard MJA, Tun TA, Husain R, Acharyya S, Haaland BA, Wei X, Mari JM, Perera SA, Baskan M, Aung T, Strouthidis NG. Lamina cribrosa visibility using optical coherence tomography: comparison of devices and effects of image enhancement techniques. *Invest Ophthalmol Vis Sci.* 2015; 56: 865-874.
- [41] Kim T-W, Kagemann L, Girard MJA, Strouthidis NG, Sung KR, Leung CK, Schuman JS, Wollstein G. Imaging of the lamina cribrosa in glaucoma: perspectives of pathogenesis and clinical applications. *Curr Eye Res.* 2013; 38: 903-909.
- [42] Sigal IA, Wang B, Strouthidis NG, Akagi T, Girard MJA. Recent advances in OCT imaging of the lamina cribrosa. *Br J Ophthalmol.* 2014; 98: ii34-ii39.
- [43] Bradley JM, Kelley MJ, Zhu X, Anderson AM, Alexander JP, Acott TS. Effects of mechanical stretching on trabecular matrix metalloproteinases. *Invest. Ophthalmol. Vis. Sci.* 2001; 42: 15015-1513.
- [44] Downs JC, Roberts MD, Sigal IA. Glaucomatous cupping of the lamina cribrosa: a review of the evidence for active progressive remodeling as a mechanism. *Exp Eye Res.* 2011; 93: 133-140.
- [45] Kanakamedala P, Harris A, Sierky B, Tying A, Muchnik M, Eckert G, Tobe LA. Optic nerve head morphology in glaucoma patients of African descent is strongly correlated to retinal blood flow. *Br J Ophthalmol.* 2014; 98: 1551-1554.
- [46] Shiga Y, Omodaka K, Kunikata H, Ryu M, Tsuda S, et al. Waveform analysis of ocular blood flow and the early detection of normal tension glaucoma. *Invest Ophthalmol Vis Sci.* 2013; 54: 7699-7706.
- [47] Thomas D, Papadopoulou O, Doshi R, Kapin MA, Sharif NA. Retinal ATP and phosphorus metabolites: reduction by hypoxia and recovery with MK-801 and diltiazem. *Med Sci Res.* 2000; 28: 87-91.
- [48] Tezel G. Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. *Prog Retina Eye Res.* 2006; 25: 490-513.
- [49] McElnea EM, Quill B, Docherty NG *et al.*, Oxidative stress, mitochondrial dysfunction and calcium overload in human lamina cribrosa cells from glaucoma donors. *Mol Vis.* 2011; 17: 1182-1191.
- [50] Osborne NN, Nunez-Alvarez C, Joglar B, Del Olmo-Aguado S. Glaucoma: focus on mitochondria in relation to pathogenesis and neuroprotection. *Eur J Pharmacol.* 2016; 787: 127-133.
- [51] Coughlin L, Morrison RS, Horner PJ, Inman DM. Mitochondrial morphology differences and mitophagy deficits in murine glaucomatous optic nerve. *Invest Ophthalmol Vis Sci.* 2015; 56: 1437-1446.
- [52] Calkins DJ, Horner PJ. The cell and molecular biology of glaucoma: axonopathy and the brain. *Invest Ophthalmol Vis Sci.* 2012; 53: 2482-2484.
- [53] Prassana G, Krishnamoorthy R, Yorio T. 2011. Endothelin, astrocytes and glaucoma. *Exp Eye Res.* 2011; 93: 170-177.
- [54] Von Zee CL, Langert KA, Stubbs EB. Transforming growth factor- β 2 induces synthesis and secretion of endothelin-1 in human trabecular meshwork cells. *Invest Ophthalmol Vis Sci.* 2012; 53: 5279-5286.
- [55] Levin LA. Extrapolation of animal models of optic nerve injury to clinical trial design. *J Glaucoma* 2004; 13: 1-5.
- [56] Levin LA. Animal and cell culture models of glaucoma for studying neuroprotection. *Eur J Ophthalmol.* 2001; 11 (Suppl 2): S23-S29.
- [57] Chintala SK, Putris N, Geno M. Activation of TLR3 promotes the degeneration of retinal ganglion cells by upregulating the protein levels of JNK3. *Invest Ophthalmol Vis Sci.* 2015; 56: 505-514.
- [58] Nickell RW, Howell GR, Soto I, John SWM. Under pressure: cellular and molecular responses during glaucoma, a common neurodegeneration with axonopathy. *Ann Rev Neurosci.* 2012; 35: 153-179.
- [59] O'Hare F, Rance G, McKenrick AM, Crowston JG. Is primary open-angle glaucoma part of a generalized sensory neurodegeneration? A review of the evidence. *Clin Expt Ophthalmol.* 2012; 40: 895-905.
- [60] Pfeiffer N, Lamparter J, Gericke A, Grus FH, Hoffmann EM, Wahl J. Neuroprotection of medical IOP-lowering therapy. *Cell Tissue Res.* 2013; 353: 245-251.
- [61] Pease ME, McKinnon SJ, Quigley HA, Kerrigan-Baumrind LA, Zack DJ. Obstructed axonal transport of BDNF and its receptor TrkB in experimental glaucoma. *Invest Ophthalmol Vis Sci.* 2000; 41: 764-774.
- [62] Martinez-del-La-Casa J, Cifuentes-Conoreia P, Berrozpe C, Sastre M, Polo V, Moreno-Montanes J, Garcia-Feijoo J. Diagnostic ability of macular nerve fiber layer thickness using new segmentation software in glaucoma suspects. *Invest Ophthalmol Vis Sci.* 2014; 55: 8343-8348.

- [63] Musch DC, Gillespie BW, Lichter PR, Niziol LM, Janz NK. Visual field progression in the Collaborative Initial Glaucoma Treatment Study: the impact of treatment and other baseline factors. *Ophthalmol.* 2009; 116: 200-207.
- [64] Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. *Ophthalmol.* 2008; 115: 1123-129.e3.
- [65] Chen MF, Chui TYP, Alhadeff P, Rosen RB, Ritch R, Dubra A, Hood DC. Adaptive optic imaging of healthy and abnormal regions of retinal nerve fiber bundles of patients with glaucoma. *Invest Ophthalmol Vis Sci.* 2015; 56: 674-681.
- [66] Yang H, Lockwood H, Williams G, Libertaux V, Downs C, Gardiner SK, Burgoyne CF. The connective tissue components of optic nerve head cupping in monkey experimental glaucoma part 1: global change. *Invest Ophthalmol Vis Sci.* 2015; 56: 7661-7678.
- [67] Krizaj D, Ryskamp DA, Tian N, Tezel G, Mitchell CH, Slepak VZ, Shestopalov VI. From mechanosensitivity to inflammatory responses: new players in the pathology of glaucoma. *Curr Eye Res.* 2013; 39:105-19.
- [68] Quigley HA, Dunklberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol.* 1989; 107: 453-464.
- [69] Sponsel WE, Growth SL, Satangi N, Maddess T, Reilly MA. Refined data analysis provides clinical evidence for central nervous system control of chronic glaucomatous neurodegeneration. *Trans Vis Sci Tech.* 2014; 3: 1-13.
- [70] Yucel YH, Zhang Q, Gupta N, Kaufman PL, Weinreb RN. Loss of neurons in magnocellular and parvocellular layers of the lateral geniculate nucleus in glaucoma. *Arch Ophthalmol.* 2000; 118: 378-384.
- [71] Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. *Ophthalmol.* 2008; 115: 763-768.
- [72] Wostyn P, De Groot V, Van Dam D, Audenaert K, Esriel K, De Deyn P. Glaucoma and the role of cerebrospinal fluid dynamics. *Invest Ophthalmol Vis Sci.* 2015; 56: 6630-6631.
- [73] Beidoe G, Mousa S. Current primary open-angle glaucoma treatments and future directions. *Clin Ophthalmol.* 2012; 6: 1699-1707.
- [74] Koutsonas A, Walter P, Roessler G, Plange N. Implantation of a novel telemetric intraocular pressure sensor in patients with glaucoma (ARGOS Study): 1-year results. *Invest Ophthalmol Vis Sci.* 2015; 56: 1063-1069.
- [75] Resende AF, Yung ES, Waisbourd M, Katz LJ. Monitoring intraocular pressure in glaucoma: current recommendations and emerging cutting-edge technologies. *Expert Rev Ophthalmol.* 2015; 10: 563-76.
- [76] Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol.* 1998; 126: 498-505.
- [77] Mallick J, Devi L, Malik P, Mallick J. Update on normal tension glaucoma. *J Ophthalmic Vis Res.* 2016; 11: 204-208.
- [78] Kersey T, Clement C, Bloom P, Cordeiro MF. New trends in glaucoma risk, diagnosis and management. *Ind J Med Res.* 2013; 137: 659-668.
- [79] Kaufman PL, Rasmussen CA. Advances in glaucoma treatment and management: outflow drugs. *Invest Ophthalmol Vis Sci.* 2012; 53: 2495-2500.
- [80] Jonas JB. Role of cerebrospinal fluid pressure in the pathogenesis of glaucoma. *Acta Ophthalmologica* 2011; 89: 505-514.
- [81] Ammar DA, Hamweyah K, Kahook MY. 2012. Antioxidants protect trabecular meshwork cells from hydrogen peroxide-induced cell death. *Trans Vis Sci Tech.* 1(1):4.
- [82] Drace C, Williams G, Kelly CR, Sharif NA. Methods for treating glaucoma comprising administering α -lipoic acid. *US Patent* 2010; 7718697.
- [83] Melena J, Stanton D, Osborne NN. Comparative effects of antiglaucoma drugs on voltage-dependent calcium channels. *Graefes Arch Clin Exp Ophthalmol* 2001; 239:522-530.
- [84] Mayama C. Calcium channels and their blockers in intraocular pressure and glaucoma. *Eur J Pharmacol.* 2014; 739: 96-105.
- [85] Noro T, Namekata K, Azuchi Y, Kimura A, Guo X, Harade C, Nakano T, Tsuneoka H, Harada T. Spermidine ameliorates neurodegeneration in a mouse model of normal tension glaucoma. *Invest Ophthalmol Vis Sci.* 2015; 56: 5012-5019.
- [86] Sharif NA, Xu SX. Human retina contains polyamine-sensitive [3 H]-ifenprodil binding sites: implications for neuroprotection? *Br J. Ophthalmol.* 1999; 83, 236-240.
- [87] Chang EE, Goldberg JL. Glaucoma 2.0: neuroprotection, neuroregeneration, neuroenhancement. *Ophthalmol.* 2012; 119, 979-986.
- [88] Gupta SK, Agarwal R, Galpalli ND, Srivasta S, Agrawal SS, Saxena R. Comparative efficacy of pilocarpine, timolol and latanoprost in experimental models of glaucoma. *Meth Find Exp Clin Pharmacol.* 2007; 29: 665-671.
- [89] Desantis L. Preclinical overview of brinzolamide. *Surv Ophthalmol.* 2000; (Supp. 2), S119-S129.
- [90] Sharif NA, Xu SX, Crider JY, McLaughlin M, Davis TL. Levobetaxolol (BetaxonTM) and other β -adrenergic antagonists: preclinical pharmacology, IOP-lowering activity and sites of action in human eyes. *J. Ocular Pharmacol Ther.* 2001; 17: 305-317.
- [91] Sharif NA, Xu SX. Binding affinities of ocular hypotensive β -blockers levobetaxolol, levobunolol and timolol at endogenous guinea pig β -adrenoceptors. *J. Ocular Pharmacol Ther.* 2004; 20: 93-99.
- [92] Osborne SA, Montgomery DM, Morris D, McKay IC. Alphagan allergy may increase the propensity for multiple eye-drop allergy. *Eye*, 2005; 19: 129-137.
- [93] Hellberg MR, McLaughlin MA, Sharif NA, DeSantis L, et al. 2002. Identification and characterization of the ocular hypotensive efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist, and AL-6598, a DP prostaglandin receptor agonist. *Surv. Ophthalmol.* 2002; (Suppl #1). 47: S13-S33.
- [94] Camras CB, Sharif NA, Wax MB, Stjernshantz J. Bimatoprost, the prodrug of a prostaglandin analogue. *Br J. Ophthalmol.* 2008; 92: 862-863.

- [95] Sharif NA, Klimko P. Update and commentary on the prodrug bimatoprost and a putative prostamide receptor. *Expert Rev Ophthalmol.*; 2009; 4: 477-489.
- [96] Sharif NA, Kelly CR, Crider JY. Human trabecular meshwork cell responses induced by bimatoprost, travoprost, unoprostone, and other FP prostaglandin receptor agonist analogues. *Invest. Ophthalmol. Vis. Sci.* 2003; 44: 715-721.
- [97] Kopeczynski CC, Epstein DL. Emerging trabecular outflow drugs. *J Ocular Pharmacol Ther.*, 2014; 30: 85-87.
- [98] Henderson AJ, Hadden M, Guo C, Douglas N, Decornez H, Hellberg MR, Rusinko A, McLaughlin M, Sharif NA, Drace C, Patil R. 2,3-Diaminopyrines as rho kinase inhibitors. *Bioorgan Med Chem Lett.* 2010; 20: 1137-1140.
- [99] Ramachandran C, Patil RV, Combrink K, Sharif NA, Srinivas SP. Rho-Rho kinase pathway in the actomyosin contraction and cell-matrix adhesion in immortalized human trabecular meshwork cells. *Mol Vision* 2011; 17: 1877-1890.
- [100] Cavet M, Vittitow JL, Impagnatello F, Ongini E, Bastia E. Nitric oxide (NO): an emerging target for the treatment of glaucoma. *Invest Ophthalmol Vis Sci.* 2014; 55: 5005-5015.
- [101] Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of Latanoprostene Bunod 0.024% and Timolol Maleate 0.5% in open-angle glaucoma or ocular hypertension: The LUNAR Study. *Am J Ophthalmol.* 2016; 168: 250-259.
- [102] Myers JS, Sall KN, Dubnier H, McVicar W, Rich C, Baumgartner RA. A dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of 2 and 4 weeks of twice-daily ocular trabodenoson in adults with ocular hypertension or primary open-angle glaucoma. *J Ocular Pharmacol Ther.* 2016; 32: 555-562.
- [103] Baiza-Duran LM, Alvarez-Delgado J, Contreras-Rubio AY, Medrano-Palafox J, De Luca-Brown A, Casab-Rueda H., et al. 2009. The efficacy and safety of two-fixed combinations: timolol-dorzolamide-brimonidine versus timolol-dorzolamide. A prospective, randomized, double-masked, multicenter, 6-month clinical trial. *Ann Ophthalmol.* 41: 174-178.
- [104] Hollo G, Topouzis F, Fechtner RD. Fixed-combination intraocular pressure-lowering therapy for glaucoma and ocular hypertension: advantages in clinical practice. *Expert Opin Pharmacother.* 2014; 15: 1737-1747.
- [105] Ellis D, Scheibler L, Sharif NA. Prostaglandin conjugates and derivatives for treating glaucoma and ocular hypertension. 2017; *US Patent 9604949 B2*.
- [106] Johnson TV, Tomarev SI. Rodent models of glaucoma. *Brain Res Bull.* 2010; 81: 349-358.
- [107] Sharif NA, McLaughlin MA, Kelly CR, Katoli P, Drace C, et al. Cabergoline: pharmacology, ocular hypotensive studies in multiple species, and aqueous humor dynamic modulation in Cynomolgus monkey eyes. *Exp Eye Res.* 2009; 88: 386-397.
- [108] Yan Z, Tian Z, Chen H, Deng S, Lin J, Liao H, Yang X, Zhuo Y. Analysis of a method establishing a model with more stable chronic glaucoma in rhesus monkeys. *Exp Eye Res.* 2015; 131: 56-62.
- [109] Fingert JH, Clark AF, Craig JE, Alward WL, Snibson GR, McLaughlin MA, Tuttle L, Mackay DA, et al. Evaluation of the myocilin (MYOC) glaucoma gene in monkey and human steroid-induced ocular hypertension. *Invest Ophthalmol Vis Sci.* 2001; 42: 145-152.
- [110] Kirihaara T, Iwamura R, Yoneda K, Kawabata-Odani N, Shimazaki A, Kawazu K. DE-117, a selective EP₂ agonist, lowered intraocular pressure in animal models. *Invest Ophthalmol Vis Sci.* 2015; 56: 5709.
- [111] Cordeiro MF, Guo L, Luong V, Harding G, Wang W, Jones HE, Moss SE, Sillito AM, Fitzke FW. Real-time imaging of single nerve cell apoptosis in retinal neurodegeneration. *Proc Natl Acad Sci USA* 2004; 101:13352-13356.
- [112] Mayordomo-Febrer A, Lopez-Murcia, Morales-Tatay JM, Monleon-Salvado D. Metabolomics of the aqueous humor in the rat glaucoma model induced by a series of intracameral sodium hyaluronate injection. *Exp Eye Res.* 2015; 131: 84-92.
- [113] Chowdhury UR, Madden BJ, Charlesworth MC, Fautsch MP. 2010. Proteome analysis of human aqueous humor. *Invest Ophthalmol Vis Sci.* 51: 4921-4931.
- [114] Todani A, Behlau I, Fava MA, Cade F, Cherfan DG, Zakka FR, Jakobiec FA, Gao Y, Dohlman CH, Melki SA. Intraocular pressure measurement by radio wave telemetry. *Invest Ophthalmol Vis Sci.* 2011; 52:9573-80.
- [115] Zhu H, Crabb DP, Ho T, Garway-Heath GF. More accurate modeling of visual field progression in glaucoma: ANSWERS. *Invest Ophthalmol Vis Sci.* 2015; 56: 6077-6083.
- [116] Dismuke WM, Sharif NA, Ellis DZ. Human trabecular meshwork cell volume decrease by NO-independent soluble guanylate cyclase activators YC-1 and BAY-58-2667 involves the BK_{Ca} ion channel. *Invest. Ophthalmol Vis Sci.* 2009; 50: 3353-3359.
- [117] Dismuke WM, Sharif NA, Ellis DZ. Endogenous regulation of human Schlemm's canal cell volume by nitric oxide signaling. *Invest. Ophthalmol Vis Sci.* 2010; 51: 5817-5824.
- [118] Salvi A, Bankhele P, Jamil J, Kulkarni-Chitnis M, Njie-Mbye Y-F, Ohia SE, Opere CA. Effect of hydrogen sulfide donors on intraocular pressure in rabbits. *J. Ocular Pharmacol. Ther.* 2016; 32: 371-375.
- [119] Ge P, Navarro ID, Kessler MM, Bernier SG, Perl NR, Sarno R, Masferrer J, Hannig G, Stamer DW. The soluble guanylate cyclase stimulator IWP-953 increases conventional outflow facility in mouse eye. *Invest Ophthalmol Vis Sci.* 2016; 57: 1317-1326.
- [120] Prasanna G, Fortner J, Xiang C, Zhang E, Carreiro S, Anderson S, Sartnurak S, Wu G, Gukasyan H, Niesman M, Nair S, Rui E, Lafontaine J, Almaden CD, Wells P, Krauss A. Ocular pharmacokinetics and hypotensive activity of PF-04475270, an EP₄ prostaglandin agonist in preclinical models. *Exp Eye Res.* 2009; 89: 608-17.
- [121] Sharif NA, Williams GW, Crider JY, Xu SX, Davis TL. Molecular pharmacology of the ocular hypotensive DP/EP₂ class prostaglandin AL-6598 and localization of DP and EP₂ receptor sites in human eyes. *J. Ocular Pharmacol. Ther.* 2004; 20: 489-508.

- [122] Prasanna G, Carreiro S, Anderson S, Gukasyan H, Sartnurak S, Younis H, Gale D, Xiang C, Wells P, Dinh D, Almaden S, Fortner J, Toris C, Niesman M, Lafontaine J, Krauss A. Effect of PF-04217329 a prodrug of a selective prostaglandin EP₂ agonist on intraocular pressure in preclinical models of glaucoma. *Exp Eye Res.* 2011; 93: 256-264.
- [123] Ihekoromadu N, Lu F, Iwamura R, Yoneda K, Kawabata-Odani N, Shams NK. Safety and Efficacy of DE-117, a Selective EP₂ Agonist in a Phase 2a Study. *Invest Ophthalmol Vis Sci.* 2015; 56: 5708.
- [124] May JA, Dantanarayana AP, Zinke PW, McLaughlin MA, Sharif NA. 1-((S)-2-Aminopropyl)-1H-indazol-6-ol: A potent peripherally acting 5-HT₂ receptor agonist with ocular hypotensive activity. *J. Med. Chem.* 2006; 49: 318-328.
- [125] Sharif NA, McLaughlin MA, Kelly CR. AL-34662: a potent, selective, and efficacious ocular hypotensive serotonin-2 receptor agonist. *J. Ocular Pharmacol. Ther.* 2007; 23: 1-13.
- [126] May JA, Sharif NA, McLaughlin MA, Chen H-H, Severns BS, Kelly CR, Holt WF, Young R, Glennon RA, Hellberg MR, Dean TR. Ocular hypotensive response in non-human primates of (R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydropyrano[2,3-g]indazol-8-ol a selective 5-HT₂ receptor agonist. *J. Med. Chem.* 2015; 58: 8818-8833.
- [127] Suto F, Rowe-Rendleman CL, Ouchi T, Jamil A, Wood A, Ward CL. A novel dual agonist of EP₃ and FP receptors for OAG and OHT: safety, pharmacokinetics, and pharmacodynamics of ONO-9054 in healthy volunteers. *Invest Ophthalmol. Vis Sci.* 2015; 56: 7963-7970.
- [128] Yamane S, Karakawa T, Nakayama S, Nagai K, Moriuyuki K, Neki S, Suto F, Kambe T, Kawabata K. IOP-lowering effect of ONO-9054, a novel dual agonist of prostanoid EP₃ and FP receptors, in monkeys. *Invest Ophthalmol Vis Sci.* 2015; 56: 2547-2552.
- [129] Wang RF, Podos SM, Mittag TW, Yokoyoma T. Effect of CS-088, an angiotensin AT₁ receptor antagonist, on intraocular pressure in glaucomatous monkey eyes. *Exp Eye Res.* 2005; 80: 629-632.
- [130] Vaajanen A, Vapaatalo H, Kautiainen H, Oksala O. 2008. Angiotensin (1-7) reduces intraocular pressure in the normotensive rabbit eye. *Invest Ophthalmol Vis Sci.* 2008; 49: 2557-2562.
- [131] Foureux G, Nogueira JC, Nogueira BS, Fulgencio GO, Menezes GB, Fernandes SOA et al. Antiglaucomatous effects of the activation of intrinsic angiotensin-converting enzyme 2. *Invest Ophthalmol Vis Sci.* 2013; 54: 4296-4306.
- [132] Agarwal R, Krasilnikova AK, Safinaz RI, Agarwal P, Ismail NM. Mechanisms of angiotensin converting enzyme inhibitor-induced IOP reduction in normotensive rats. *Eur J Pharmacol.* 2014; 730: 8-13.
- [133] Holappa M, Vapaatalo H, Vaajanen A. Ocular renin-angiotensin system with special reference to the anterior part of the eye. *W J Ophthalmol.* 2015; 5: 110-124.
- [134] Ma JX, Song Q, Hatcher HC, Crouch RK, Chao L, Chao J. Expression and cellular localization of the kallikrein-kinin system in human ocular tissues. *Exp Eye Res.* 1996; 63: 19-26.
- [135] Sharif NA, Xu SX. Pharmacological characterization of bradykinin receptors coupled to phosphoinositide turnover in SV40-immortalized human trabecular meshwork cells. *Exp Eye Res.* 1996; 63: 631-637.
- [136] Webb JG, Husain S, Yates PW, Crosson CE. Kinin modulation of conventional outflow facility in bovine eye. *J Ocular Pharmacol Ther.* 2006; 22: 310-316.
- [137] Webb JG, Yang X, Crosson CE. Expression of the kallikrein/kinin system in human anterior segment. *Exp Eye Res.* 2009; 89: 126-132.
- [138] Webb JG, Yang X, Crosson CE. Bradykinin activation of extracellular signal-regulated kinases in human trabecular meshwork cells. *Exp Eye Res.* 2011; 92: 495-501.
- [139] Sharif NA. Use of non-peptidic bradykinin receptor agonists to treat ocular hypertension and glaucoma. *US Patent* 2012; 8173668.
- [140] Combrink K, Mohapatra S, Hellberg MR, Sharif NA, Prasanna G, et al. Bradykinin receptor agonists and uses thereof to treat ocular hypertension and glaucoma. *US Patent* 2012; 8252793.
- [141] Prasanna G, Sharif NA, Li B, Hellberg M, Krause T, Yacoub S, Scott D, Kelly C, Pang IH, Combrink K. BK2A78: a novel non-peptide bradykinin B₂ agonist lowers intraocular pressure (IOP) in ocular hypertensive Cynomolgus monkeys. *Assoc Res Vis Ophthalmol.* 2014; Abst. # 2883.
- [142] Sharif NA, Xu S, Li L, Katoli P, Kelly C, Wang Y, Cao S, Patil R, Klekar L, Scott D, Husain S. Protein expression, biochemical pharmacology of signal transduction, and relation to IOP modulation by bradykinin B₂-receptors in ciliary muscle. *Mol Vision* 2013; 19: 1356-1370.
- [143] Sharif NA, Wang Y, Katoli P, Xu S, Kelly CR, Li L. Human non-pigmented ciliary epithelium bradykinin B₂-receptors: receptor localization, pharmacological characterization of intracellular Ca²⁺ mobilization, and prostaglandin secretion. *Curr Eye Res.* 2014; 39: 378-389.
- [144] Sharif NA, Katoli P, Kelly CR, Li L, Xu S, Wang Y, Klekar L, Earnest D, Yacoub S, Hamilton G, Jacobson N, Shepard AR, Ellis D. Trabecular meshwork bradykinin receptors: mRNA levels, immunohistochemical visualization, signaling processes pharmacology and linkage to IOP changes. *J. Ocular Pharmacol Ther.* 2014; 30: 21-34.
- [145] Sharif NA, Li L, Peng Y, Katoli P, Xu S, Veltman J, Li B, Scott D, Wax M, Gallar J, Acosta C, Belmonte C. Preclinical pharmacology, ocular tolerability and ocular hypotensive efficacy of a novel non-peptide bradykinin mimetic small molecule. *Exp Eye Res.* 2014; 128: 170-180.
- [146] Sharif NA, Katoli P, Scott D, Li L, Kelly CR, Xu S, Husain S, Toris C, Crosson C. FR-190997, a non-peptide bradykinin B₂-receptor partial agonist, is a potent and efficacious intraocular pressure lowering agent in ocular hypertensive cynomolgus monkeys. *Drug Develop Res.* 2014; 75: 211-223.
- [147] Whitcup SM. Clinical trials in neuroprotection. *Prog Brain Res.* 2008; 173: 323-335.
- [148] Neufeld AH, Kawai SI, Das S, Vora S, Gachie E, Connor JR, et al. Loss of retinal ganglion cells following retinal ischemia: The role of inducible nitric oxide synthase. *Exp Eye Res* 2002; 75: 521-528.
- [149] Wood JP, DeSantis L, Chao HM, Osborne NN. Topically applied betaxolol attenuates ischemia-induced effects to the rat retina and stimulates BDNF mRNA. *Exp Eye Res.* 2001; 72: 79-86.

- [150] Gao H, Qiao X, Cantor LB, WuDunn D. Up-regulation of brain-derived neurotrophic factor expression by brimonidine in rat retinal ganglion cells. *Arch. Ophthalmol.* 2002; 120: 797-803.
- [151] Chadder GJ. Advances in glaucoma treatment and management: neurotrophic agents. *Invest Ophthalmol Vis Sci.* 2012; 53: 2501-2505.
- [152] Saylor M, McLoon LK, Harrison AR, Lee MS. Experimental and clinical evidence for brimonidine as an optic nerve and retinal neuroprotective agent: an evidence-based review. *Arch Ophthalmol.* 2009; 12: 402-406.
- [153] Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. *Am J Ophthalmol.* 2011; 151: 671-681.
- [154] Osborne NN, Cazervielle C, Carvalho AL, Larsen AK, DeSantis L. *In vivo* and *in vitro* experiments show that betaxolol is retinal neuroprotective agent. *Brain Res.* 1997; 751: 113-123.
- [155] Agarwal N, Martin E, Krishnamoorthy RR, Landers R, Wen R, Krueger S, Kapin MA, Collier RJ. Levobetaxolol-induced Up-regulation of retinal bFGF and CNTF mRNAs and preservation of retinal function against a photic-induced retinopathy. *Exp Eye Res.* 2002; 74: 445-53.
- [156] Abdul Y, Akhter N, Husain S. Delta opioid agonist SNC-121 protects retinal ganglion cell function in a chronic ocular hypertensive rat model. *Invest Ophthalmol Vis Sci.* 2013; 54: 1816-1828.
- [157] Burgess LG, Uppal K, Walker DI, Roberson RM, Tran V, Parks MB, Wade EA, May AT, Umfress AC, Jarrell KL, Stanley BOC, Kuchtey J, Jones DP, Brantley MA. Metabolome-wide association study of primary open angle glaucoma. *Invest Ophthalmol Vis Sci.* 2015; 56: 5020-5028.
- [158] Wiederholt M, Thieme H, Stumpff F. The regulation of trabecular meshwork and ciliary muscle contractility. *Prog. Retinal Eye Res.* 2000; 19: 271-295.
- [159] Chowdhury UR, Hann CR, Stamer DW, Fautsch MP. Aqueous humor outflow: dynamics and disease. *Invest Ophthalmol Vis Sci.* 2015; 56: 2993-3003.
- [160] Tam ALC, Gupta N, Zhang Z, Yucel YH. Latanoprost stimulates ocular lymphatic drainage: an in vivo nanotracer study. *Trans Vis Sci Tech.* 2013; 2 (5): 3.
- [161] Liu JHK, Slight JR, Vittitow JL, Sforzolini BS, Weinreb RN. Efficacy of Latanoprostene Bunod 0.024% compared with Timolol 0.5% in lowering intraocular pressure over 24 hours. *AmJ Ophthalmol.* 2016; 169: 249-257.
- [162] Luna C, Li G, Huang J, Qiu J, Wu J, Yuan F, Epsteins DL, Gonzalez P. Regulation of trabecular meshwork cell contraction and intraocular pressure by MiR-200c. *PLoS One* 2012; 7: 251688.
- [163] Johnson TV, Martin KR. Cell transplantation approaches to retinal ganglion cell neuroprotection in glaucoma. *Curr Opin Pharmacol.* 2013; 13: 78-82.
- [164] Chamling X, Sluch SM, Zack DJ. The potential of human stem cells for the study and treatment of glaucoma. *Invest Ophthalmol Vis Sci.* 2016; 57: ORSFi1-ORSFi6.
- [165] Harrison BA, Whitlock NA, Voronkov MV, Almstead ZY, Gu K-J, Allen J, Gopinathan S, et al. Novel class of LIM-kinase inhibitors for the treatment of ocular hypertension and associated glaucoma. *J Med Chem.* 2009; 52: 6515-6518.
- [166] Kirihaara T, Shimazaki A, Nakamura M, Miyawaki N. Ocular hypotensive efficacy of Src-family tyrosine kinase inhibitors via different cellular actions from Rock inhibitors. *Exp Eye Res.* 2014; 119: 97-105.
- [167] Takashima Y, Taniguchi T, Yoshida M, Haque MS, Igaki T, Itoh H, Nakao K, Honda Y, Yoshimura N. Ocular hypotension induced by intravitreally injected C-type natriuretic peptide. *Exp Eye Res.* 1998; 66: 89-96.
- [168] Potter DE, Russell KR, Manhiyani M. Bremazocine increases C-type natriuretic peptide levels in aqueous humor and enhances outflow facility. *J Pharmacol Exp Ther.* 2004; 309: 548-553.
- [169] Novack GD. Cannabinoids for treatment of glaucoma. *Curr Opin Ophthalmol.* 2016; 27: 146-150.
- [170] Faulkner R, Sharif NA, Orr S, Craven R, Moster M, Sall K, Whitson J, Bethem R, Curtis M, Dahlin D. Aqueous humor concentrations of bimatoprost free acid, bimatoprost and travoprost free acid in cataract surgical patients administered multiple topical ocular doses of LUMIGAN® or TRAVATAN®. *J. Ocular Pharmacol Ther.* 2010; 26: 147-156.
- [171] Chiou GC, Li B. Ocular hypotensive actions of serotonin antagonist-ketanserin analogs. *J Ocular Pharmacol.* 1992; 8: 11-21.
- [172] Civan MM. The fall and rise of active chloride transport: implications for regulation of intraocular pressure. *J Exp Zool A Comp Exp Biol.* 2003; 300: 5-13.
- [173] Katz A, Tal DM, Heller D, Habeck M, Ben Zeev E, Rabah B, Bar Kana Y, Marcovich AL, Karlisch SJD. Digoxin derivatives with selectivity for the isoform of Na⁺K⁺-ATPase potentially reduce intraocular pressure. *Proc Nat Acad. Sci. (USA)* 2016; 112: 13723-13728.
- [174] Ogidigben MJ, Potter DE. Comparative effects of alpha-2 and DA-2 agonists on intraocular pressure in pigmented and nonpigmented rabbits. *J Ocul Pharmacol.* 1993; 9:187-99.
- [175] Tanna AP, Rademaker AW, Stewart WC, Feldman RM. Meta-analysis of the efficacy and safety of alpha2-adrenergic agonists, beta-adrenergic antagonists, and topical carbonic anhydrase inhibitors with prostaglandin analogs. *Arch Ophthalmol.* 2010; 128: 825-33.
- [176] Chidlow G, DeSantis LM, Sharif NA, Osborne NN. The characteristics of [³H] 5-hydroxytryptamine binding to iris-ciliary body of the rabbit. *Invest. Ophthalmol. Vis Sci.* 1995; 36: 2238-2245.
- [177] Chidlow G, Nash MS, DeSantis L, Osborne NN. The 5-HT_{1A} Receptor agonist 8-OH-DPAT lowers intraocular pressure in normotensive NZW rabbits. *Exp Eye Res.* 1999; 69: 587-593.
- [178] Sharif NA. Novel potential treatment modalities for ocular hypertension: focus on angiotensin and bradykinin system axes. *J. Ocular Pharmacol Ther.* 2015; 31: 131-145.
- [179] Sharif NA, Patil R, Li L, Husain S. Human ciliary muscle cell responses to kinins: activation of ERK1/2 and pro-matrix metalloproteinases secretion. *World J. Ophthalmol.* 2016; 6: 20-27.
- [180] Patil R, Xu S, Rusinko A, Feng Z, Katoli P, May JA, Hellberg M, Sharif NA, Wax M, Irigoyen M, Clarke M, et al. Rapid identification of novel inhibitors of aquaporin-1 channel by high-throughput screening. *Chem. Biol Drug Design* 2016; 87: 794-805.