WHITEPAPER

Targeting the Trabecular Meshwork, Schlemm's Canal and the Collector Channels

The Evolution of Canaloplasty and the iTrack™ Canaloplasty Microcatheter

As our understanding of the pathogenesis of glaucoma has evolved, the role of the proximal versus distal portions of the conventional outflow pathway as therapeutic targets has generated growing interest. It is well understood that the trabecular meshwork, specifically the extracellular matrix filling the open space of the juxtacanalicular connective tissue (JCT) is the primary site of outflow resistance in the conventional outflow pathway.[1] It is also known that glaucomatous pathology can cause significant outflow resistance in distal pathways.[2] Greater contractility of Schlemm's canal has been shown to increase outflow resistance.[3,4,5] Further, the canal in eyes with primary open angle glaucoma (POAG) tends to be shorter, narrowed, and often collapsed, reducing the area of active flow.[3,4,5] Another significant cause of increased outflow resistance in POAG eyes is herniations of the trabecular meshwork obstructing up to 90% of collector channels.[6]

Armed with improved understanding of the function and physiology of the proximal and distal outflow pathways in glaucomatous eyes, an increasing number of surgeons are turning to ab-interno canaloplasty to target each segment of the conventional outflow pathway; trabecular meshwork, Schlemm's canal, and the collector channels.

Introduced in 2005 and approved by the FDA in 2008, canaloplasty with the iTrack™ microcatheter has evolved to be a procedure with high utility in the treatment of glaucoma. It is indicated in a wide variety of glaucoma types including; POAG, pigmentary (PG), pseudoexfoliation (PXF) and ocular hypertension. It can be performed either in conjunction with cataract surgery or as a stand-alone procedure.

First conceived through an ab-externo approach as an alternative to trabeculectomy, surgeons have developed an ab-interno canaloplasty technique that is conjunctiva and sclera sparing and thus can be deployed earlier in the disease process.

Schlemm's Canal and the Collector Channels as Therapeutic Targets

Aqueous outflow through the conventional pathway passes first from the anterior chamber through the uveal and corneoscleral trabecular meshwork, consisting of the uveal and corneoscleral meshwork beams and the juxtacanalicular connective tissue [JCT]. It then passes through endothelium and into the lumen of Schlemm's canal. Aqueous egresses from the canal through ostia into collector channels, aqueous veins, and ultimately the venous system. 70-90% of aqueous humor flows through the conventional outflow pathway,[1] which is the target for the majority of pharmaceutical, laser and minimally invasive glaucoma surgery (MIGS) glaucoma treatments.

There are numerous physical and biochemical factors which regulate outflow within the conventional outflow pathway, including gene expression, endothelial pore formation, protein activity, and signalling mediators such as cytokines and nitric oxide.[7] Resistance to outflow can occur in any portion of the conventional outflow pathway.

The Proximal Outflow System

In human eyes, up to 75% of the resistance to aqueous humor outflow is localized within the trabecular meshwork.[1] The juxtacanalicular portion of the trabecular meshwork, which lies immediately adjacent to Schlemm's canal and comprises a thin strip of connective tissue covered by a monolayer of endothelial cells, is thought to account for the majority of reduced outflow facility within the trabecular meshwork of POAG eyes.[1]

Studies using fluorescent beads have shown that aqueous outflow is segmental; only a fraction of the trabecular meshwork is actively involved in outflow facility at any given time.[8] Further, the more darkly pigmented portion of the trabecular meshwork adjacent to collector channel ostia, where the flow of aqueous and the phagocytosed pigment are greater, correlates with greater active flow into Schlemm's canal.[8] This indicates that preferential flow pathways are present near the entrances of collector channels – and thus suggests that pigment may serve as a useful biomarker to identify the area(s) of active flow within the trabecular meshwork.[8]

In the trabecular meshwork of POAG eyes, the accumulation of extracellular matrix proteins and banded fibrillar elements compromise the function of the trabecular meshwork and lead to pathologic changes that increase resistance to outflow.[9,10] Alterations in the glycosaminoglycans that comprise the extracellular matrix have also been shown to play a role in the progression of POAG. Of the glycosaminoglycans, a reduction in hyaluronic acid and an increase in chondrontin sulfate exert the most notable impact on POAG progression.[15] The trabecular meshwork endothelial cells are dynamic, however, and initiate a homeostatic response to adjust outflow resistance in response to sustained imbalances in IOP[9-11] that result from changes to the glycosaminoglycans. Research by Knepper et al suggests that the trabecular meshwork endothelial cells counteract these imbalances in IOP via the regulation of hyaluronic acid levels within the outflow pathway.[15] The ability of the trabecular meshwork in POAG eyes to mediate hyaluronic acid levels, and thus IOP, is compromised by a reduction in the number of functioning trabecular meshwork endothelial cells, however.[12-14] In the case of trabecular excision procedures, the removal of trabecular meshwork cells in POAG eyes has been suggested to further compound the inability of the trabecular meshwork to regulate hyaluronic acid levels, in addition to inducing postoperative inflammation with angle scarring.[7]

"The more darkly pigmented portion of the trabecular meshwork adjacent to collector channel ostia, where the flow of aqueous and the phagocytosed pigment are greater, correlates with greater active flow into Schlemm's canal."

Hyaluronic Acid and the Pathogenesis of Glaucoma

- Hyaluronic acid is a necessary substrate of the biophysiological architecture of a healthy aqueous outflow system and plays a pivotal role in the maintenance of extracellular matrix, including the trabecular meshwork. Specifically, hyaluronic acid interreacts with cell surface receptors in Schlemm's canal – CD44, RHAMM and ICAM-1 – to promote cell motility, adhesion, and proliferation.[38]
- The depletion of hyaluronic acid has been linked to POAG.[16] A study by Knepper et al found that the amount of hyaluronic acid in the POAG trabecular meshwork was 77% less than that in the normal trabecular meshwork (P<.02), with hyaluronic acid detected in only 4 of the 10 studied POAG trabecular meshworks.[15]
- High levels of matrix metalloproteinases (MMPs) have been demonstrated to clear the deposition of extracellular matrix in the trabecular meshwork, thus facilitating the outflow of aqueous humor.[17] Decreased hyaluronic acid levels reduce the activity of the MMP-2 and MMP-9 gylcosaminoglycans, which are necessary in the normal clearing and maintenance of extracellular matrix.[18]
- It is thus hypothesized that, in the trabecular meshwork cells of POAG patients, reduced hyaluronic acid levels can lead to down-regulation of MMPs, therefore contributing to the disruption of the extracellular matrix and, subsequently, development of POAG.[19] In the absence of hyaluronic acid its receptor, CD44, becomes unbound and alters into sCD44, which is cytotoxic to trabecular meshwork cells.[20]

The Distal Outflow System

Schlemm's Canal

Schlemm's canal performs an important homeostatic function in maintaining the flow of aqueous humor via the conventional outflow pathway. It interacts with the aqueous return to the venous system, and thus directly impacts flow through the distal portion of the conventional outflow system.

It has been demonstrated that Schlemm's canal becomes narrower or collapsed with elevated IOP, which correlates with a decrease in outflow facility.[4,21] Experimental studies dating back to 1973 by Johnstone et al suggest that, as IOP increases, the canal becomes narrower.[4,22] This is caused by the expansion of the trabecular meshwork into the lumen of the canal.[4,22] More recently, research by Allingham et al has shown that a reduction in Schlemm's canal dimensions may account for approximately 50% of the decrease in outflow facility observed in POAG eyes.[4]

Using novel three-dimensional micro-computed tomography (3D micro-CT), Hann and colleagues assessed Schlemm's canal volume and collector channel orifice area, diameter and number, in cases of both glaucomatous and non-glaucomatous eyes.[23] They concluded that decreased outflow facility in POAG eyes may be due to a decrease in Schlemm's canal area and an increase in total occlusions, which reduces the number of patent collector channels available for aqueous outflow. Their findings also confirmed the reduced homeostatic function of Schlemm's canal in glaucomatous eyes.[23]

The Collector Channels

The collector channels are a segment of the conventional

outflow pathway, connecting Schlemm's canal with the episcleral venous system. Randomly distributed around the circumference of the eye, there is a higher density of collector channels in the inferonasal quadrant of the eye.[24] Studies have also noted variability in the orifice size of collector channels, ranging between 5-50 microns.[24-26] The drainage of aqueous humor occurs preferentially through the trabecular meshwork near the collector channels.[26] It has also been noted that not all of the collector channels are involved in active flow at a given time.[27]

According to studies undertaken in human POAG eyes by Haiyan Gong, MD, PhD, an increase in IOP causes the trabecular meshwork to herniate into the ostia of the collector channels, blocking the flow of aqueous.[6] Gong and colleagues have shown that up to 90% of collector channels may be blocked with herniated trabecular meshwork in POAG eyes, resulting in reduced outflow facility.[6] Further, these blockages may become progressively worse as IOP rises.[6]

Targeting the Proximal and Distal Outflow Pathway with Canaloplasty

Canaloplasty was conceptualized by Robert Stegmann, MD, Professor and Chairman of Ophthalmology at the Medical University of South Africa. In his earlier work developing hyaluronic acid-based ophthalmic viscosurgical devices (OVDs), Stegmann observed that the injection of sodium hyaluronate into the closed angle of patients opened the angle. From this observation Stegmann et al concluded that sodium hyaluronate acted as a physical barrier to the fibrinogen/fibrin cycle, allowing closed angles to be opened – and to remain open permanently – thus counteracting increased IOP.[28-30] He postulated that POAG could be treated by OVD expansion of Schlemm's canal and the distal outflow system[31] – and thus began his pioneering work in viscocanalostomy.

Stegmann conceptualized the insertion of a metal cannula into Schlemm's canal via an ab-externo scleral dissection, through which high-molecular weight sodium hyaluronate (HA) was injected into the canal. The cannula, which was not flexible, could only be extended into Schlemm's canal a limited distance and thus could only dilate a limited portion of the canal on either side of the incision. Despite the technical challenges associated with this initial cannula design, the early results were promising. Stegmann and colleagues demonstrated that high-molecular weight, HA-based OVD increased the diameter of Schlemm's canal in glaucomatous eyes from 25-30 microns to 230 microns.[32] Additionally, during viscocanalostomy OVD was seen to displace blood from aqueous veins, suggesting an improvement in outflow facility.[32]

Previous experiments in post-mortem primate eyes had shown that injection of a non-viscous material such as saline solution into Schlemm's canal did not result in dilation of the canal,[33] even when the episcleral venous system was occluded to provide resistance to outflow.

The positive early findings by Stegmann et al were corroborated by Murray Johnstone, MD and colleagues, who reported changes in outflow facility following the injection of high-molecular weight, HA-based OVD (Healon GV, Johnson & Johnson) into Schlemm's canal via a process of viscodilation.[31] One of the first systematic in vitro examinations of the histologic effects of viscodilation of Schlemm's canal, the work by Johnstone et al showed that Schlemm's canal was dilated with increased anteroposterior length and height in treated eyes relative to untreated controls.[34] Johnstone and colleagues showed that the collector channels were also widely dilated following viscodilation. They thus concluded that OVD delivery created sufficient hydrostatic force to widely dilate Schlemm's canal and the collector channels.

Johnstone also demonstrated that cannulation of Schlemm's canal, combined with viscodilation, disrupted the endothelial lining of the anterior and posterior walls of the canal.[31] He theorized that these disruptions would increase communication and aqueous flow between the juxtacanalicular space and the lumen of Schlemm's canal, further contributing to an improvement in outflow facility.[31] Johnstone also postulated that disruption of the posterior wall

provides for direct communication between the lumen of Schlemm's canal and the tissues of the ciliary muscle, thereby enhancing uveoscleral outflow.[31]

Another important finding from Johnstone et al was the proximal effect of viscodilation.[31] In primate eyes, dilation of Schlemm's canal extended circumferentially from 4-12 mm beyond the tip of the cannula, while in human eyes Schlemm's canal was dilated 6-14 mm beyond the tip of the cannula.[34] This therefore suggested that, in order to effectively viscodilate the full circumference of the outflow pathway, delivery of OVD would be required for the full 360° of Schlemm's canal. Stegmann conceived the first flexible microcatheter to facilitate catheterization and pressurized viscodilation of the entire 360° of Schlemm's canal – thus began his pioneering work in canaloplasty.

During the canaloplasty procedure, a flexible microcatheter catheterizes 360° of Schlemm's canal. This is an important distinction from the former viscocanalostomy procedure, in which a metal cannula accessed only 180° of the canal. Once the microcatheter has circumnavigated the entirety of Schlemm's canal, it is slowly withdrawn as high-molecular weight HA-based OVD is delivered along the entire length of Schlemm's canal. As per the work by Stegmann and Johnstone[1-3], the use of high-molecular weight OVD is necessary to ensure dilation of Schlemm's canal and sufficient hydrostatic force to improve outflow facility in both Schlemm's canal and the collector

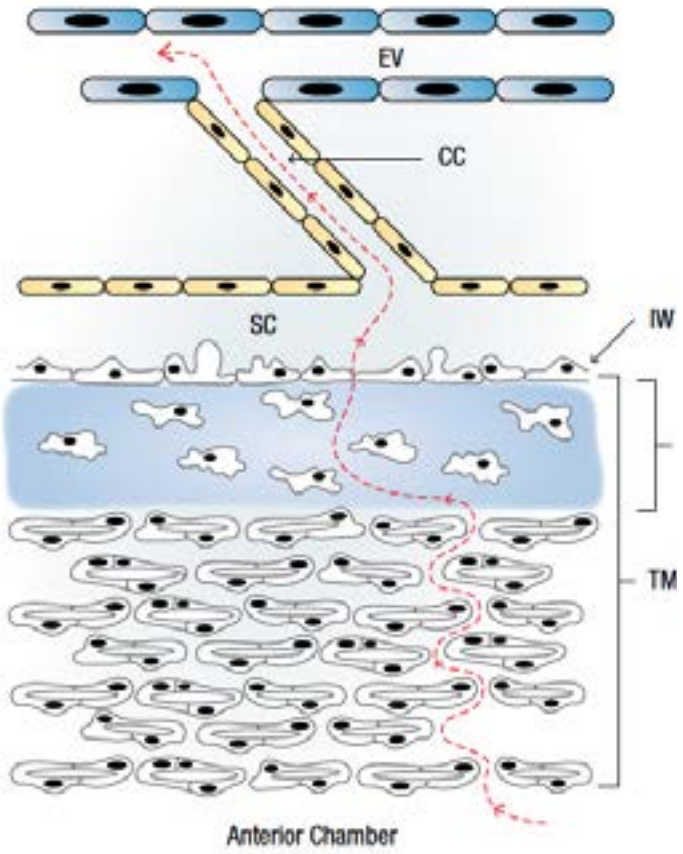


Figure 1: Schematic illustrating the major components of the conventional outflow pathway. Aqueous humor (red dashed line) flows through the initial portion of the trabecular meshwork (TM), juxtacanalicular connective tissue (JCT) region, inner wall of Schlemm canal (IW), Schlemm canal (SC), collector channel (CC), and finally reaches the episcleral vein (EV). Reproduced from J Cataract Refract Surg 2014; 40:1263–1272.

TRABECULAR MESHWORK (TM)

75% of the resistance to aqueous humor outflow is localized within the trabecular meshwork.[1]

SCHLEMM'S CANAL (SC)

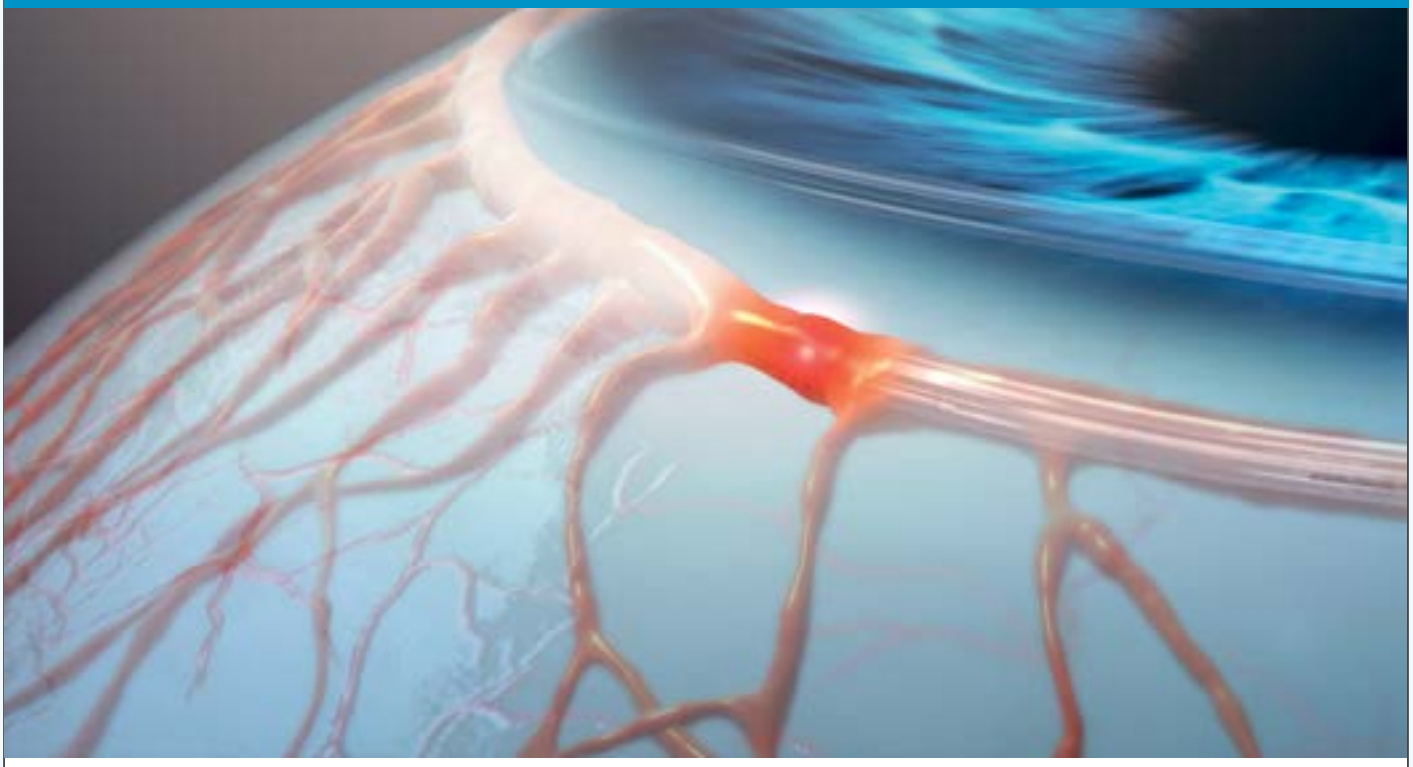
Schlemm's canal becomes narrower or collapsed with elevated IOP, which may account for approximately 50% of the decrease in outflow facility observed in glaucomatous eyes.[4]

COLLECTOR CHANNELS (CC)

Up to 90% of collector channels may be blocked in POAG eyes.[6]

CANALOPLASTY, MECHANISM OF ACTION

Canaloplasty is suggested to improve outflow facility via three key mechanisms: 1. Mechanical, 2. Hydrostatic and, 3. Biophysical.



1. **Mechanical**: As noted earlier, the dimensions of the lumen of Schlemm's canal are smaller in glaucomatous eyes and correlate with reduced outflow facility.[4] Herniations of the juxtacanalicular tissue into collector channels are more frequently observed in glaucomatous eyes than in age-matched, non-glaucomatous eyes.[34,18] During canaloplasty, 360° catheterization of Schlemm's canal mechanically breaks adhesions within the canal and pushes herniations of trabecular meshwork out of the collector channel ostia.

2. **Hydrostatic:** Hydrostatic pressure caused by the delivery of HA-based OVD into Schlemm's canal during pressurized viscodilation has been shown to stretch the trabecular meshwork, with possible creation of microperforations into the anterior chamber.[34] This dilates Schlemm's canal and the collector channels,[7,31] as evidenced by visible blanching of the aqueous veins.[7]

3. **Biophysical:** It is theorized that the pressurized delivery of HA-based OVD into Schlemm's canal may bind with sCD44, reversing the cytotoxicity present in POAG. This would improve the cellular function and architecture of the outflow system, thus improving outflow facility.

channels. Upon completion of 360° viscodilation, the microcatheter is extracted from Schlemm's canal at the initial surgical site. In cases of severe glaucoma, Stegmann conceived an additional treatment step in which a 10-0 Prolene suture is towed around the entire circumference of Schlemm's canal and tied, to distend and stent the trabecular meshwork.

"...in human eyes Schlemm's canal was dilated 6-14 mm beyond the tip of the cannula.[34] This therefore suggested that, in order to effectively viscodilate the full circumference of the outflow pathway, delivery of OVD would be required for the full 360° of Schlemm's canal."

The World's First Canaloplasty Microcatheter, iTrack™

Building upon the pioneering scientific and clinical work by Stegmann and Johnstone[1-3,33] the next step in the evolution of canaloplasty encompassed the design and development of a flexible microcatheter capable of safely and efficiently circumnavigating the entire 360° of Schlemm's canal and delivering OVD under pressure.

Led by Ronald Yamamoto, the team at iScience Interventional, Inc., undertook a series of laboratory assessments in perfused enucleated human eyes to validate the overall effect on outflow facility, including dilation of Schlemm's canal, with a prototype iTrack™ canaloplasty microcatheter.[4]

A series of matched pairs (n=14) of control and catheterized eyes were included in the assessment. The catheterized eyes had previously undergone catheterization and expansion of Schlemm's canal. Using a constant pressure perfusion apparatus, outflow facility was measured over a 24-hour period. A statistically significant increase in outflow facility was observed in the catheterized eyes. In contrast, the control eyes showed a gradual decrease in outflow facility. Refer to Table 1.

A high-resolution ultrasound was used to measure the dimensions of Schlemm's canal prior to and following catheterization and pressurized viscodilation. Measurements of the cross-sectional area of Schlemm's canal were extracted from a series of images acquired at 10° intervals before and after expansion. On average, the diameter of Schlemm's canal increased from 150 microns to 300 microns in the catheterized eyes.[35] The high-resolution ultrasound imaging also showed dilation of the collector channel ostia, as well as stretching/thinning of the juxtacanicular tissue.[35]

TABLE 1: A COMPARISON OF OUTFLOW FACILITY[4]
(p<0.001, paired two-sided T-test)

Mean +/- SD outflow facility after 24 hours of perfusion	
CATHETERIZED EYES	**0.17 +/-0.09 ul/min/mm²**
CONTROL EYES	**0.09 +/-0.07 ul/min/mm²**

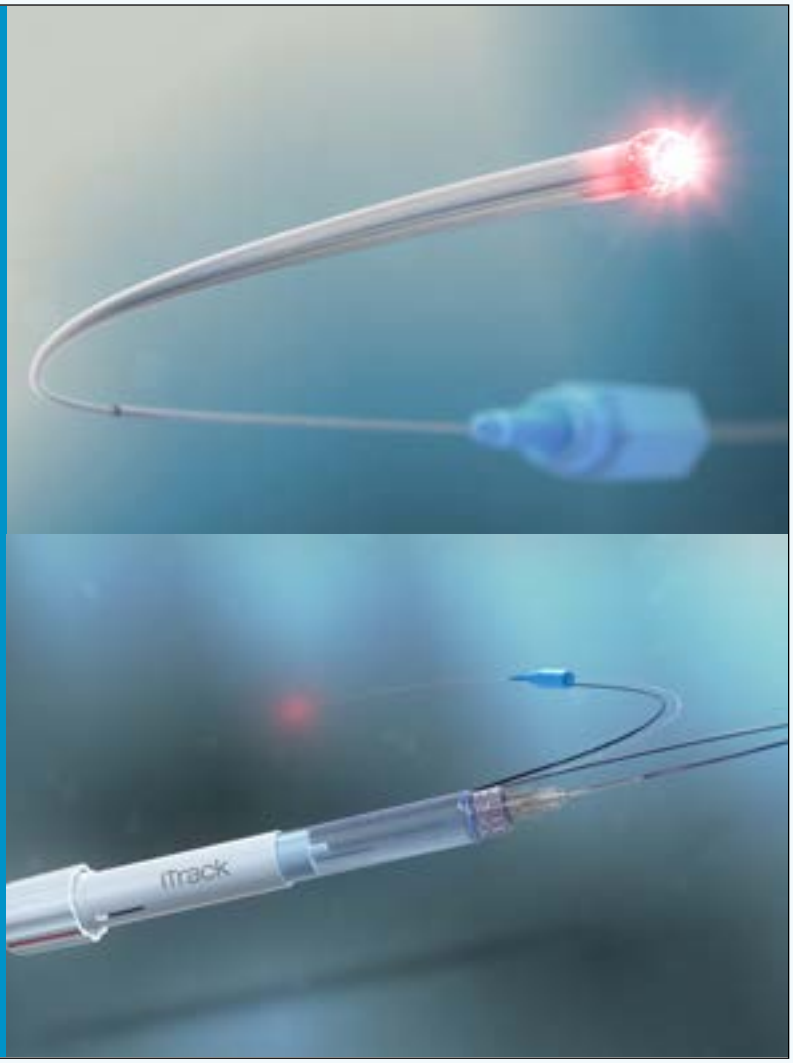
Noting the proximal effect of viscodilation previously reported by Johnstone et al,[31-33] Yamamoto and the engineering team designed the iTrack™ microcatheter to circumnavigate the full 360° of Schlemm's canal.

Further, noting the high viscosity and dynamic flow of the OVD required for canaloplasty, a specialized injector referred to as the ViscoInjector™ was designed to deliver precise microquantities of high-molecular weight, HA-based OVD at a constant pressure. This was an important consideration in ensuring consistent, reproducible clinical outcomes. It was also necessary that the surgeon be able to adjust the amount of OVD delivered, to account for differences in patient pathology and the OVD molecular weight. The number of microboluses of OVD delivered via the ViscoInjector™ and therefore the amount of viscodilation performed could be changed.

With the prototype iTrack™ and ViscoInjector™ designs in place, a series of tests were conducted with Healon GV (now Healon GV Pro, Johnson & Johnson) and Healon (now Healon Pro, Johnson & Johnson) to assess the volume of OVD delivered.[36] The testing incorporated a robotically controlled ViscoInjector™ simulating the delivery of OVD into Schlemm's canal. The volume of OVD delivered was 2.8 microliters per microbolus equating to more than 100 microliters over the full circumference of Schlemm's canal. Additional testing validated the pressurized delivery of OVD

TAKING A CLOSER LOOK AT ITRACK™

The iTrack™ microcatheter (pictured top right) features a polymer shaft with a diameter of 250 microns with a slightly larger atraumatic tip. It has a lubricious coating to facilitate smooth passage through Schlemm's canal. Within the internal lumen of the microcatheter is a nitinol guide wire for strength and an optical fiber for visualization. The optical fiber is attached to the iLumin™ which lights the tip of the microcatheter, making its position visible during circumnavigation of Schlemm's canal. This helps to safeguard against misdirection into the suprachoroidal space or the collector channels. The microcatheter connects to the ViscoInjector™ (pictured bottom right) with a luerlock, which permits pressurized viscodilation of +100 microliters of OVD over 360 degrees of Schlemm's canal.



via the iTrack™ microcatheter and ViscoInjector™. The combination of OVD volume and pressurized delivery are fundamental to the canaloplasty procedure, and cause stretching of the trabecular meshwork, displacement of herniations out of collector channel ostia and enlargement of all outflow channels. As evidenced by Trypan Blue Venography,[37] and the clinical observation of blanching of aqueous veins, the iTrack™ delivers sufficient volume and pressure of OVD to dilate Schlemm's canal and the collector channels and improve outflow through the episcleral venous system. OVD delivered in lower volume or at lower pressure may pass through the patent collector channels without impacting on the areas of outflow resistance.

"Noting the proximal effect of viscodilation previously reported by Johnstone et al,[31-33] Yamamoto and the engineering team designed the iTrack™ microcatheter to circumnavigate the full 360° of Schlemm's canal."

Conclusion

Responsible for the majority of aqueous outflow facility, the conventional outflow pathway continues to be a key therapeutic target in POAG patients. There is growing awareness of the need to optimize the homeostatic physiology of the outflow pathway to better manage the course of OAG over the patient's lifespan. Treatments must ideally enhance outflow facility by restoring more normal function to both proximal and distal portions of the conventional outflow pathway – and without tissue destruction or artificial stenting. They should restore homeostatic function of the trabecular meshwork, Schlemm's canal and the collector channels and thus help to counteract elevations and fluctuations in IOP. For example, a treatment which targets reduced outflow facility in the trabecular meshwork, but fails to remove blockages within the collector channels, will have limited clinical utility.

Comprising a process of 360° catheterization of Schlemm's canal followed by pressurized viscodilation of the canal with high molecular-weight, HA-based OVD, the multimodal mechanism of ab-interno canaloplasty may help to restore the outflow facility and homeostatic function of the trabecular meshwork, Schlemm's canal and collector channels. This makes it a highly effective treatment in the majority of mild to moderate OAG patients, irrespective of where the point(s) of outflow obstruction reside. Further, the ability of ab-interno canaloplasty to re-establish the conventional outflow pathway without the disruption or removal of tissue, and without the use of a permanent implant, offers significant utility in clinical practice. The iTrack™ microcatheter is the only device specifically designed and FDA approved to perform canaloplasty.

REFERENCES

1. Manik Goel, Renata G Picciani, Richard K Lee, and Sanjoy K Bhattacharya. Aqueous Humor Dynamics: A Review. Open Ophthalmol J. 2010; 4: 52–59.
2. Swaminathan et al, Aqueous outflow: Segmental and distal flow J Cataract Refract Surg.2014 August; 40(8): 1263–1272
3. Hong J, Xu J, Wei A, et al. Spectral-domain optical coherence tomographic assessment of Schlemm's canal in Chinese subjects with primary open-angle glaucoma. Ophthalmology. 2013;120(4):709-715.
4. Allingham RR, de Kater AW, Ethier CR. Schlemm's canal and primary open angle glaucoma: correlation between Schlemm's canal dimensions and outflow facility. Exp Eye Res. 1996;62(1):101-109.
5. Hann CR, Vercnocke AJ, Bentley MD, Jorgensen SM, Fautsch MP. Anatomic changes in Schlemm's canal and collector channels in normal and primary open-angle glaucoma eyes using low and high perfusion pressures. Invest Ophthalmol Vis Sci. 2014;55(9):5834-5841.
6. Cha ED, Xu J, Gong H. Variations in active areas of aqueous humor outflow through the trabecular outflow pathway. Presented at ARVO 2015.
7. Fellman RL, Grover, DS. Episcleral venous fluid wave in the living human eye adjacent to microinvasive glaucoma surgery (MIGS) supports laboratory research: Outflow is limited circumferentially, conserved distally, and favored inferonasally. J Glaucoma. 2019;28:139–45.
8. Gong H and Francis A: Schlemm's Canal and Collector Channels as Therapeutic Targets. In Innovations in Glaucoma Surgery, Samples JR and Ahmed I eds. Chapter 1, page 3-25, Springer New York, 2014.
9. Acott TS, Kelley MJ. Extracellular matrix in the trabecular meshwork. Exp Eye Res. 2008;86:543–561.
10. Acott TS, Kelley MJ, Keller KE, Vranka JA, Abu-Hassan DW, et al. Intraocular pressure homeostasis: maintaining balance in a high-pressure environment. J Ocul Pharmacol Ther. 2014;30:94–101.
11. Bradley JM, Kelley MJ, Zhu X, Anderssohn AM, Alexander JP, et al. Effects of mechanical stretching on trabecular matrix metalloproteinases. Invest Ophthalmol Vis Sci. 2001;42:1505–1513.
12. Alvarado J, Murphy C, Juster R. Trabecular meshwork cellularity in primary open-angle glaucoma and nonglaucomatous normals. Ophthalmology. 1984;91:564–579.
13. Alvarado J, Murphy C, Polansky J, Juster R. Age-related changes in trabecular meshwork cellularity. Invest Ophthalmol Vis Sci. 1981;21:714–727.
14. Grierson I, Howes RC. Age-related depletion of the cell population in the human trabecular meshwork. Eye (Lond) 1987;1:204–210.
15. Knepper PA, Goossens W, Hvizd M, Palmberg PF. Glycosaminoglycans of the human trabecular meshwork in primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 1996;37(7):1360-1367.
16. Navajas EV, Martins JR, Melo LA, Jr., Saraiva VS, Dietrich CP, Nader HB, et al. Concentration of hyaluronic acid in primary open-angle glaucoma aqueous humor. Exp Eye Res. 2005;80(6):853-857.
17. Umihira J, Nagata S, Nohara M, Hanai T, Usuda N, Segawa K. Localization of elastin in the normal and glaucomatous human trabecular meshwork. Invest Ophthalmol Vis Sci. 1994;35(2):486-494.
18. Hann CR, Vercnocke AJ, Bentley MD, Jorgensen SM, Fautsch MP. Anatomic changes in Schlemm's canal and collector channels in normal and primary open-angle glaucoma eyes using low and high perfusion pressures. Invest Ophthalmol Vis Sci. 2014;55(9):5834-5841.
19. Guo MS, Wu YY, Liang ZB. Hyaluronic acid increases MMP-2 and MMP-9 expressions in cultured trabecular meshwork cells from patients with primary open-angle glaucoma. Mol Vis. 2012;18:1175-1181.
20. Green KA, Yue BY, Samples JR, Knepper PA. Glaucoma Research and Clinical Advances: 2016-2018. In: Knepper PA, Samples JR, eds. Trabecular meshwork cell death in primary open-angle glaucoma. Amsterdam, The Netherlands: Kugler Publications; 2016:1-16.
21. Battista SA, Lu Z, Hofmann S, Freddo TF, Overby DR, Gong H. Reduction of the available area for Aqueous humor outflow and increase in meshwork herniations into collector channels following acute IOP elevation in bovine eyes. Invest. Ophthalmol Vis Sci 2008; 49:5346–5352/
22. Johnstone MA, Grant WG. Pressure-dependent changes in structures of the aqueous outflow system of human and monkey eyes. Am J Ophthalmol. 1973;75:365–383
23. Cheryl R. Hann; Andrew J. Vercnocke; Michael D. Bentley; Steven M. Jorgensen; Michael P. Fautsch Anatomic Changes in Schlemm's Canal and Collector Channels in Normal and Primary Open-Angle Glaucoma Eyes Using Low and High Perfusion Pressures. Investigative Ophthalmology & Visual Science September 2014, Vol.55, 5834-5841.
24. Dvorak-Theobald G. Further studies on the canal of Schlemm; its anastomoses and anatomic relations. Am J Ophthalmol. 1955;39(4 Pt 2):65–89.
25. Rohen JW, Rentsch FJ. Morphology of Schlemm's canal and related vessels in the human eye. Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1968;176(4):309–29.
26. Hann CR, Bentley MD, Vercnocke A, Ritman EL, Fautsch MP. Imaging the aqueous humor outfl ow pathway in human eyes by three-dimensional micro-computed tomography (3D micro-CT). Exp Eye Res. 2011;92(2):104–11.
27. Yang C-Y, Liu Y, Lu Z, Ren R and Gong H. Effects of Y27632 on aqueous humor outflow facility with changes in hydrodynamic pattern and morphology in human eyes. Invest Ophthalmol Vis Sci. 2013;54(8):5859-70.
28. Gillies MC, Su T. Cytokines, fibrosis and the failure of glaucoma filtration surgery. Aust NZ J Ophthalmol 1991; 19:299-304
29. Del Vecchio PJ, Bizios R, Holleran LA, et al. Inhibition of human sderal fibroblast proliferation with heparin. Invest Ophthalmol Vis Sci 1988; 29:1272-1276
30. Iverson DA, Katsura H, Harmer MK, Blumenkranz MS. Inhibition bf intraocular fibrin formation following infusion of low-molecular-weight heparin during vitrectomy. Arch Ophthalmol 1991; 109:405-409
31. Smit BA, Johnstone MA. Effects of viscoelastic injection into Schlemm's canal in primate and human eyes: potential relevance to viscocanalostomy. Ophthalmology. 2002;109(4):786-792.
32. Stegmann R, Pienaar A, Miller D. Viscocanalostomy for open-angle glaucoma in black African patients. J Cataract Refract Surg. 1999;25(3):316-322.
33. Johnstone MA, Grant WM. Microsurgery of Schlemm's canal and the human aqueous outflow system. Am J Ophthalmol 1973;76:906–17.
34. Grieshaber MC, Pienaar A, Olivier J, Stegmann R. Clinical evaluation of the aqueous outflow system in primary open-angle glaucoma for canaloplasty. Invest Ophthalmol Vis Sci. 2010;51(3):1498-1504.
35. M.R. Hee; S.R. Conston; R.K. Yamamoto. Outflow facility after 180 degree catheterization and distal expansion of Schlemm's Canal in perfused cadaver eyes. Investigative Ophthalmology & Visual Science May 2004, Vol.45, 984. Presented at ARVO 2004. https://iovs.arvojournals.org/article.aspx?articleid=2406791
36. Data on file, Nova Eye, Inc. Available upon request.
37. Docherty G, Gooi P. Canaloplasty, GATT & Trypan Blue Venography. Review of Ophthalmology. 6 Oct 2020.
38. Entwistle, J., etal. , HA receptors: regulators of signalling to the cytoskeleton. J Cell Biochem, 1996. 61(4): p. 569-7

CONTRAINDICATIONS: The iTrack™ canaloplasty microcatheter is not intended to be used for catheterization and viscodilation of Schlemm's canal to reduce intraocular pressure in eyes of patients with the following conditions: neovascular glaucoma; angle closure glaucoma; and, previous surgery with resultant scarring of Schlemm's canal.

ADVERSE EVENTS: Possible adverse events with the use of the iTrack™ canaloplasty microcatheter include, but are not limited to: hyphema, elevated IOP, Descemet's membrane detachment, shallow or at anterior chamber, hypotony, trabecular meshwork rupture, choroidal effusion, Peripheral Anterior Synechiae (PAS) and iris prolapse.

WARNINGS: The iTrack™ canaloplasty microcatheter is intended for one time use only. DO NOT re-sterilize and/or reuse, as this can compromise device performance and increase the risk of cross contamination due to inappropriate reprocessing.

PRECAUTIONS: The iTrack™ canaloplasty microcatheter should be used only by physicians trained in ophthalmic surgery. Knowledge of surgical techniques, proper use of the surgical instruments, and post-operative patient management are considerations essential to a successful outcome.