



Glaucoma 2019 Updates Glaucoma Medical Therapy

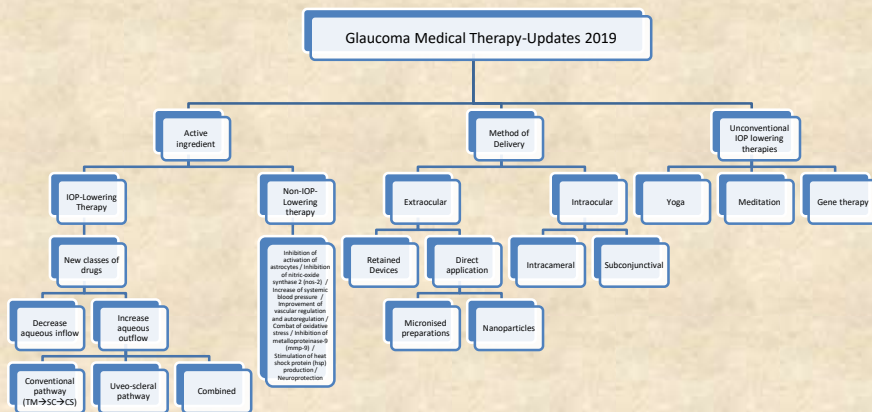
By

Nader Bayoumi, MD, PhD, FRCS(Glasgow)

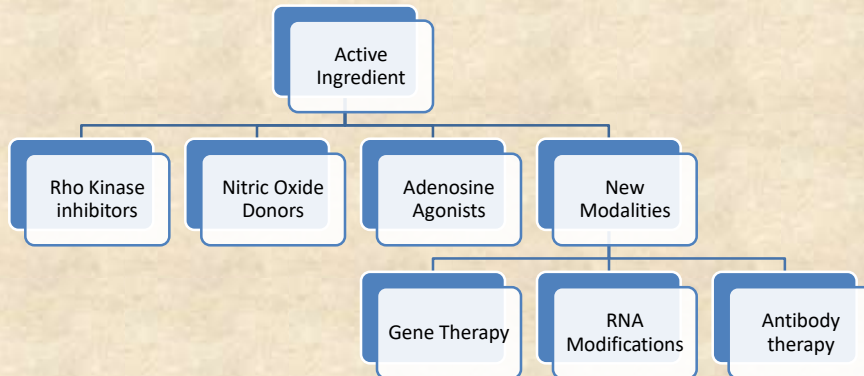
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Financial interest: None

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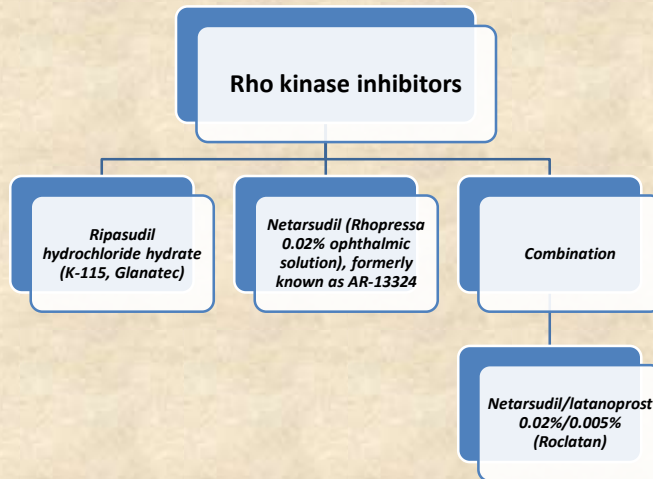
- **Rho kinase inhibitors**
 - **Chemistry**
 - Are serine/threonine kinases
 - **Function**
 - They regulate contraction of smooth muscle, vascular endothelial, and other cell types
 - Selective ROCK inhibitors can enhance fluid outflow through the TM
 - **Mechanism of Action**
 - Selective ROCK inhibitors can enhance fluid outflow through the TM by inhibiting TM/SC cellular contraction.
 - Inhibition of norepinephrine transporter (NET) provides persistent stimulation of α 2-adrenergic receptors, resulting in a decreased intracellular concentration of cyclic adenosine monophosphate in the nonpigmented ciliary epithelium and thus decreased aqueous humor production by the ciliary body.
 - Inhibition of ROCK possibly possesses a third mechanism to decrease IOP, by decreasing episcleral venous pressure (EVP) as shown in rabbits. This latter mechanism is hypothesized for humans, based on subsets of normotensive subjects who attained posttreatment IOP less than or equal to 10 mm Hg. Recent preclinical studies have also shown that netardusil could have an antifibrotic effect on the TM.

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- **Rho kinase inhibitors**

- **Preparations**

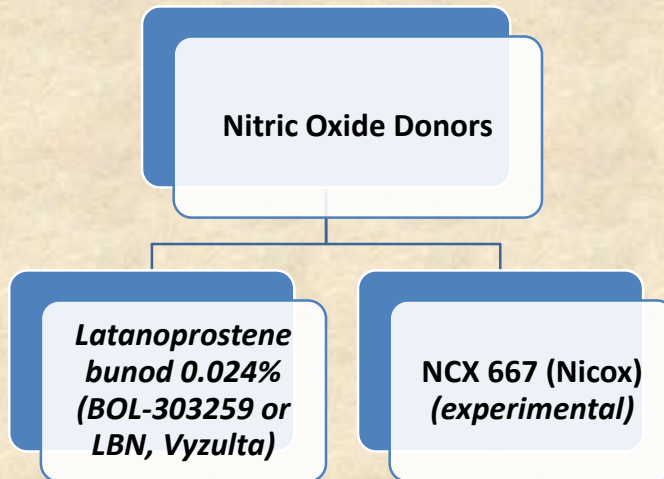
- **Ripasudil hydrochloride hydrate (K-115, Glanatec):**
 - is a specific ROCK inhibitor that has been approved for use in Japan since 2014.
 - Used primarily as an adjunctive agent
 - **Netarsudil (Rhopressa 0.02% ophthalmic solution), formerly known as AR-13324:**
 - is a once-daily small molecule inhibitor of ROCK and norepinephrine transporters (NET).
 - Topical adverse events → cornea verticillata
 - **Netarsudil/latanoprost 0.02%/0.005% (Roclatan)**
 - combines Rhopressa with latanoprost, the most widely prescribed prostaglandin analogue.
 - Dual pharmacological mechanism of action → it may benefit all components of aqueous humor dynamics, i.e. formation and clearance (both via uveoscleral and trabecular outflow)

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- **Nitric Oxide Donors**

- **Latanoprostene bunod 0.024% (BOL-303259 or LBN, Vyzulta)**

- combines 2 mechanisms and 2 targets into 1 molecule →

- **Chemistry**

- is a NO donating prostaglandin F_{2α} agonist

- **Mechanism of Action**

- Is metabolized in situ to latanoprost acid and butanediol mononitrate, an NO donating moiety → Nitric oxide serves as a signaling molecule using cyclic guanosine monophosphate (GMP) as a second messenger to initiate a series of events that results in structural/functional changes that result in an overall relaxation of the TM and inner wall of SC and the ciliary muscle + reduce the formation of aqueous humor by acting on ion transporters including Na,K-ATPase in the ciliary processes

- **NCX 667 (Nicox) (experimental)**

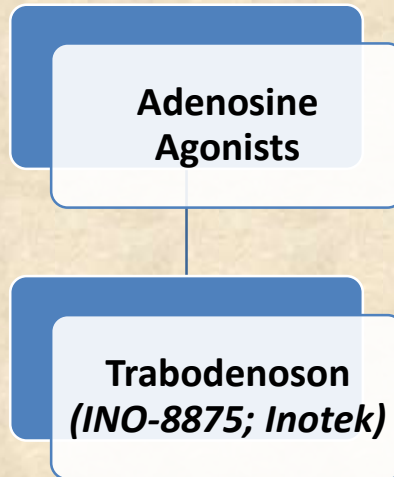
- is another NO donor shown to reduce IOP while being well-tolerated in both normotensive rabbits and laser-induced ocular hypertensive cynomolgus monkeys.

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- **Adenosine Agonists**

- **Trabodenoson (INO-8875; Inotek) →**

- **Chemistry**

- is a highly selective adenosine A1 receptor agonist

- **Mechanism of Action**

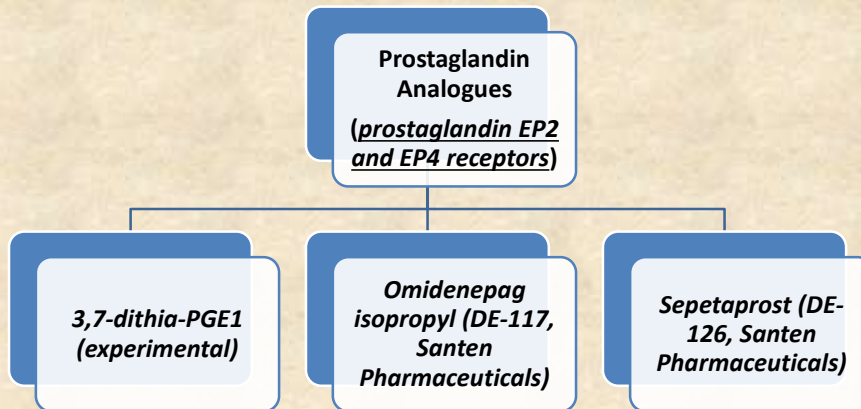
- engenders an upregulation of protease A and matrix metalloproteinase-2 (MMP-2) in target cells. The proteases digest and remove hydrolyzed collagen type IV, a major component of the resistive ECM in the TM. (Levels of MMP-2 increase in response to mechanical stretch, induced by increased pressure in perfused human anterior segment organ cultures (HOCAS)).
 - Treatment with trabodenoson does not affect the rate of aqueous humor production. **Initial ocular hypertension** induced by topical adenosine agonists in cynomolgus monkeys is likely associated with the activation of *adenosine A2 receptors*, whereas subsequent hypotensive effects seem to be mediated by *adenosine A1 receptors* and are due to increased outflow facility.

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- **Prostaglandin Analogues**

- Other prostaglandin analogs (PGAs) currently in development target the **prostaglandin EP2 and EP4 receptors**
- Agonist-sensitive EP1, EP2, and EP4 receptors are present in TM cells and EP1–EP4 receptors are present in SC cells
 → EP1 and EP3 receptor activation increase cell stiffness, whereas EP2 and EP4 agonists dose-dependently decrease cell stiffness → As TM and SC from glaucomatous eyes are stiffer than age-matched normal controls, EP2 and EP4 agonists became candidates for IOP lowering via **decreasing cell stiffness and enhancing of outflow through the conventional drainage pathway.**

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- **Prostaglandin Analogues**

- **3,7-dithia-PGE1 (experimental)**

- Selective EP4 receptor agonist
- reduced IOP and total outflow resistance in monkeys without affecting uveoscleral outflow or aqueous flow, indicating that the reduced total outflow resistance represented enhanced trabecular outflow.

- **Omidenepag isopropyl (DE-117, Santen Pharmaceuticals)**

- the 0.002% dosage proved more effective than latanoprost 0.005% at week 1 and provided similar reduction in IOP to latanoprost through week 4.
- Conjunctival hyperemia, episcleral hyperemia, mild and transient photophobia, and eye pain were reported in 14.3% of patients in the trial, with no adverse events reported in the control eyes.

- **Sepetaprost (DE-126, Santen Pharmaceuticals) →**

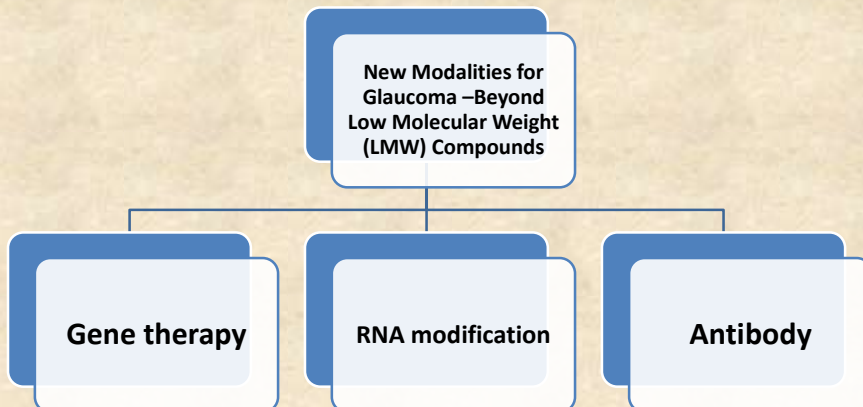
- is an FP- and EP3 receptor dual agonist. Targeting EP3 receptors in the TM and ciliary muscle may **facilitate outflow of aqueous humor through the TM pathway** (although this seems counter-intuitive to the EP3 TM-stiffening effects described above) in addition to the uveoscleral pathway, for an additive effect to lower IOP.

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- **New Modalities for Glaucoma –Beyond Low Molecular Weight (LMW) Compounds**
 - Gene therapy
 - RNA modification
 - Antibody

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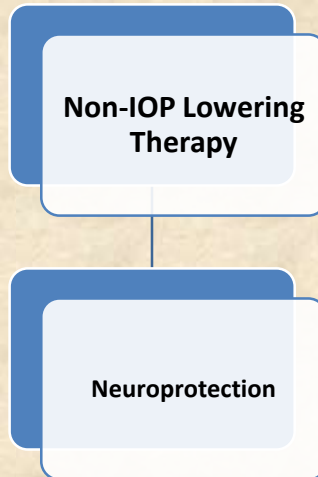
- **Targeted CRISPR-Cas9 gene editing**
 - Experimental
 - More detailed evaluations are required from these cell-based therapeutic studies, including: 1) determining the fate of the transplanted cells in the eye and rest of the body, 2) investigating if they restore the outflow pathway to a healthy state, and 3) determining if they de-differentiate over time and thus only temporarily modify and maintain outflow.
- **Small interfering RNA (siRNA)**
 - **Bamosiran (SYL040012)**
 - targeting the β -adrenergic receptor (= timolol)
- **antisense oligonucleotides (ASO)**
 - **ISTH0036**
 - an antisense oligonucleotide selectively targeting TGF- β 2
 - is administered as an intravitreal injection
 - While the initial clinical evaluation of this molecule was done in conjunction with glaucoma filtration surgery (trabeculectomy), it is unclear if the IOP lowering effects observed were due to reduction of postsurgical fibrotic overgrowth or improvements in the function of the trabecular meshwork irrespective of the surgical procedure

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- **Neuroprotection**
- **Introduction to Neuroprotection and Related Therapies: Frontiers Revisited**
- **Clinical Trials**
 - 1. Study of NT-501 Encapsulated Cell Therapy (ECT) for Glaucoma Neuroprotection and Vision Restoration (<https://clinicaltrials.gov/ct2/show/NCT02862938>)
 - 2. Single-dose Study of ANX007 in Participants With Primary Open-angle Glaucoma (<https://clinicaltrials.gov/ct2/show/NCT03488550>)
 - 3. Study to Evaluate Safety and Efficacy of rhNGF Eye Drops Solution Versus Vehicle in Patients With Glaucoma (NGF-Glaucoma) (<https://clinicaltrials.gov/ct2/show/NCT02855450>)

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- **Neuroprotection**
- **Introduction to Neuroprotection and Related Therapies: Frontiers Revisited**
- **Clinical Trials**
 - For the NT-501 ECT trial, the investigators are determining the efficacy of an **intravitreal implantation of genetically modified human cells to secrete ciliary neurotrophic factor (CNTF)**, which is shown to be neuroprotective in preclinical models of retinal degeneration and glaucoma. The primary outcome of this trial is a change in visual field through 6 months measured by any of the following indices, visual field index, mean deviation and pointwise linear regression. In addition, several novel exploratory endpoints including, structural measures of retinal nerve fiber/ RGC layer thickness, contrast sensitivity, and changes to optic nerve head are being evaluated. Assessments will be continued at 12 and 24 months. The anticipated completion of this study is in 2020. A positive outcome from this study will provide considerable guidance to the field of glaucoma neuroprotection in terms of the role/ contribution of trophic factors in preserving RGC structure and function as well as the use of novel interventional endpoints, which may be used in lieu, or along with, visual field assessments in future neuroprotection trials.

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- **Neuroprotection**
- **Introduction to Neuroprotection and Related Therapies: Frontiers Revisited**
- **Clinical Trials**
 - Annexon Biosciences has recently completed a phase I open label single-dose escalation study that is evaluating safety, tolerability, and systemic pharmacokinetic effects of **an intravitreal injection of ANX007, an antibody against complement C1qa protein** in patients with POAG. There are several lines of evidence to suggest that C1qa plays a neurodestructive and/or neuromodulatory role in dendritic and synaptic pruning in development and aging, as well as in glaucoma, and other neuropathies including Alzheimer's disease. In this small trial (n = 15 participants), pharmacokinetics will be assessed by measuring serum concentrations of ANX007. In addition, serum will be assessed for anti-drug antibodies as a means of assessing immunogenicity after a single IVT injection. Duration of the study was 56 days and results are pending.

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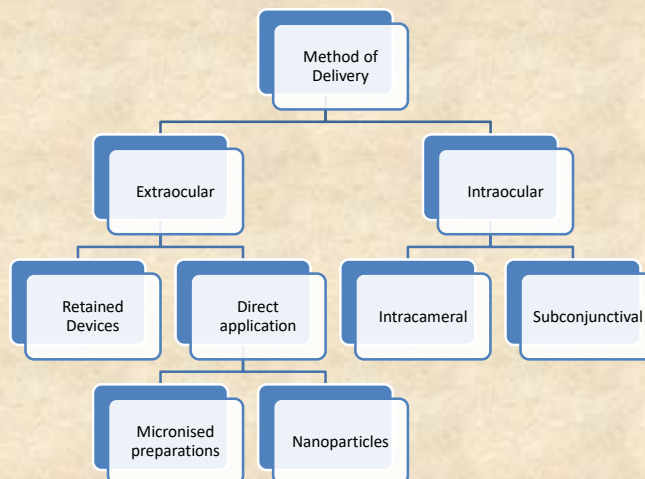
- **Neuroprotection**
- **Introduction to Neuroprotection and Related Therapies: Frontiers Revisited**
- **Clinical Trials**
 - Topical ocular administration of **recombinant human nerve growth factor (rhNGF)** is the subject of another interventional clinical trial in patients with glaucoma. NGF signalling has been implicated in promoting RGC survival in preclinical models of glaucoma, and a recent report revealed that rhNGF was well tolerated up to 180 mg/mL up to 8 weeks of TID dosing. In the upcoming clinical trial, primary outcome measures to be evaluated at week 8 include IOP, safety, and visual acuity. Changes to various electroretinography functional readouts and dilated fundus ophthalmoscopy to assess optic nerve, cup-to-disc ratio and other anatomical parameters. Are also being monitored as secondary outcome measures. The study consists of 60 participants. To date no data have been reported with regard to the pharmacokinetics of topically applied rhNGF, and an open question persists on whether therapeutic levels of rhNGF can reach the retina. Traditionally, topical applied biologics have had limited ability to reach the retina with only a few exceptions as mentioned above.

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- **Method of delivery**
- **Drug Delivery Implants for Glaucoma Management**
- **Indications**
 - For patients with poor adherence to topical drop management
 - Those around the globe with limited access to an ophthalmologist

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- **Method of delivery**
- **Drug Delivery Implants for Glaucoma Management**
 - **Extraocular**
 - Retained devices
- **Sustained Release Formulations and Devices**
 - Characteristics of an *ideal* sustained release system for lowering IOP would include:
 - 1) A duration of efficacy of ≥ 6 months, with IOP lowering that is non-inferior to topical ocular prostaglandin agonist therapy. Thus, the use of a β -blocker (e.g. timolol) as an active comparator should be avoided.
 - 2) An ocular AE profile equal to or better than that observed with topical ocular prostaglandin agonist therapy.
 - 3) A bio-erodible system to minimize the need for an invasive removal procedure.
 - 4) An installation or injection procedure that can be performed "office" rather than in an operating suite.
 - 5) The active pharmaceutical ingredient must confer sustained IOP lowering independent of factors like circadian rhythm and aqueous humor formation

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- **Method of delivery**
- ***The bimatoprost ring (Allergan)***
 - is a device that rests on the surface of the eye, under the eyelids, and releases bimatoprost
- ***The topical ophthalmic drug delivery device (TODDD) (Amorphex Therapeutics)***
 - is a soft, flexible device that floats on the tear film, completely concealed under the eyelid
 - It can be easily replaced by patients themselves and has the potential for carrying not only IOP management drugs, but also treatment for ocular allergies and other ocular disorders
 - The TODDD loaded with timolol has completed phase 2a clinical trials, where it demonstrated safety, comfort, retention, and uninterrupted efficacy in reducing IOP for 180 days
- **Direct application**
 - Nanoparticles
 - Microdoses

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- **Method of delivery**
- **Latanoprost with high precision, piezo-print microdose delivery**
 - single 8- μ L microdoses of 0.005% latanoprost (0.4 μ g; μ Rx-latanoprost)
 - Microdosing of 0.4 μ g of μ Rx-latanoprost achieved significant IOP reduction. Lower ocular exposure with topical prostaglandin analog microdosing can enable new therapeutic opportunities for optimizing glaucoma treatment.
 - Microdosing may also be beneficial in reducing ocular side effects associated with excessive drug product and preservatives often used to treat chronic ocular diseases such as glaucoma.



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- **Method of delivery**
- **Intraocular**
 - Intracameral
- **bimatoprost sustained-release (SR) biodegradable, intracameral implant**
 - currently in a phase 3 trial
 - In its phase 1/2 trial, a single bimatoprost SR implant reduced IOP in 92% of glaucoma patients at 4 months by 7.2–9.5 mm Hg, whereas pooled fellow eyes receiving once-daily topical bimatoprost 0.03% had a reduction of 8.4 mm Hg
 - The implant demonstrated a favorable safety profile.
- **ENV515 (Envisia)(travoprost)**
 - is an intracamerally injected biodegradable proprietary *Particle Replication In Non-Wetting Templates* (PRINT) **nanoparticle** with an extended release formulation of *travoprost*.
 - In a phase 2 trial in glaucoma patients, a single administration of ENV515 demonstrated IOP lowering comparable with the topical prostaglandin analogues latanoprost and bimatoprost and topical timolol maleate 0.5% ophthalmic solution for the entire 9-month evaluation period
 - ENV515 was well-tolerated with no serious adverse events or changes in corneal endothelial cell counts or corneal thickness.

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- **Method of delivery**
- **Intraocular**
 - Intracameral
- **The PolyActiva implant**
 - involves the covalent attachment of latanoprost acid to a monomer unit via a selectively labile linker. The drug-monomer is polymerized with suitable comonomers, or polymer segments, to give the final polymeric prodrug
 - A major advantage of a conjugate system is the opportunity to eliminate a burst release, which is an inherent issue with most, if not all, polymer systems relying on erosion/diffusion for release.
- **iDose (Glaukos)(travoprost)**
 - is another sustained release travoprost intraocular implant at the phase 2 clinical trial stage
 - The titanium implant is comparable in size to the company's proprietary microinvasive glaucoma surgery devices.
 - To implant, the device is passed across the anterior chamber, and the anchor portion is advanced through the TM into scleral tissue where it is designed to elute therapeutic levels of medication for extended periods of time.

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- **Method of delivery**
- **Intraocular**
 - Subconjunctival
- ***Subconjunctival implants or depots***
 - **Advantages**
 - should reduce the potential for corneal endothelium adverse events
 - In addition, subconjunctival injections are generally viewed as less invasive than an intracameral injection
 - **Disadvantages**
 - A disadvantage of subconjunctival injections relative to intracameral implantation is that the drug administration is likely to be further away from the putative sites of action, and the ocular safety profile (e.g. hyperemia in the case of a prostaglandin agonist) may be similar to, or even enhanced, compared that of topical ocular drops

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- **Method of delivery**
- **Intraocular**
 - Subconjunctival
- ***Subconjunctival implants or depots***
- ***liposomal depot formulation of latanoprost***
 - Peregrine Ophthalmic is developing a liposomal depot formulation of latanoprost. Unlike other extra- and intraocular systems described above, this approach does not employ a monolithic implant or device, but instead relies on **nanoliposomes**. The advantage of implanting a liposomal, or nano/microparticle, formulation into the subconjunctival place is twofold:
 - 1) the nanoliposomes enable a relatively small gauge needle (30G) compared to that typically required for implants (e.g. BimatoprostSR employs a 28Gneedle (68)), and
 - 2) the suspension formulation maximizes the amount of drug that can be loaded into the subconjunctival space (e.g. 100 μ L injection affording \sim 1.2 mg of latanoprost), which is far larger than the intracameral space (75,76).

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- **Method of delivery**
- **Intraocular**
 - Subconjunctival
- **Subconjunctival implants or depots**
- **liposomal depot formulation of latanoprost**
 - The *Peregrine* liposomes are ~100 nm in diameter and are primarily composed of L- α -phosphatidylcholine derived from chicken eggs (EggPC). The hydrophobic properties of latanoprost enables it to reside in the lipid bilayer of the liposome affording high drug loading efficiency (94%) and a total drug load of ~ 1 mg/mL. The same hydrophobic properties of latanoprost that enable efficient drug loading also contribute to the limited rate of partitioning out of the liposome and into the surrounding aqueous environment of the subconjunctival space. This slow partitioning enabled a statistically significant IOP reduction $\geq 20\%$ over a 3 month period in a small clinical trial of 6 patients. While the initial data with the Peregrine system are encouraging it is unclear how dependent this approach is to the particular physicochemical properties of latanoprost and whether different drug classes would also be viable options.

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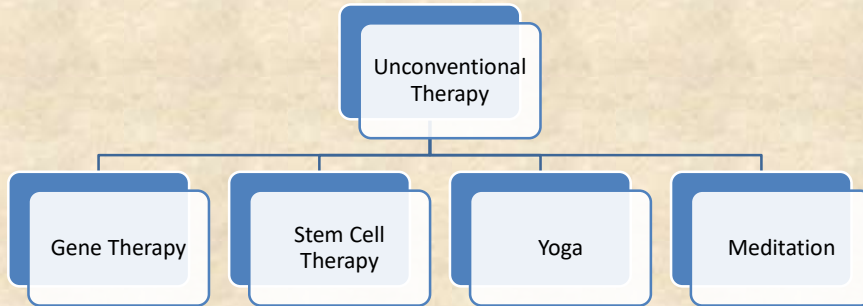
- **Method of delivery**
- **Intraocular**
 - Subconjunctival
- **Subconjunctival implants or depots**
- **latanoprost loaded bioerodible version of Durasert™ rod implant**
 - are larger monolithic implants
 - EyePoint, in collaboration with Pfizer, had been exploring a latanoprost loaded bioerodible version of its Durasert™ rod implant which is similar to their marketed IVT implant Iluvien®. However, that trial appears to have been stopped prematurely and no additional information is currently available
- **VS101 latanoprost insert (Eye-D)**
 - The third subconjunctival system is currently being developed by BioLight Lifesciences; their VS101 latanoprost insert (Eye-D) has not yet been described in peer reviewed literature, but appears to be a non-degradable insert that is placed under the conjunctiva after an incision has been made

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- **The goal of gene therapy**
 - is to reprogram target cells to up-or downregulate a biochemical/physiological process by up- or downregulating production of a specific substance within specific cells.
- **Viral vectors**
 - Adenoviral (AdV)
 - adeno-associated viral (AAV)
 - self-complementary adeno-associated viral (scAAV)
 - herpes simplex viral (HSV)
 - retroviral vectors (RV)
- **Target tissues**
 - The rhoA and rho kinase pathway may be an effective target for gene therapy. This pathway modulates the actin cytoskeleton, cell adhesive interactions, ECM formation, and TM actomyosin contraction

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- **Stem Cell Therapy**
- **The goal of stem cell therapy**
 - is to replace or regenerate damaged and dead tissue
 - Trabecular meshwork and JCT cell counts are lower in medically untreated POAG eyes than in age-matched normals and decrease with age in both at essentially the same rate.
 - Differentiated induced pluripotent stem cells (iPSCs) grown in TM cell culture medium could repopulate the cell depletion model. (When transplanted, the TM-medium conditioned iPSCs became similar to TM cells in morphology and expression patterns, leading to the restoration of IOP homeostatic function.)
 - In the future, iPSCs developed from patient-specific skin fibroblasts to avoid immune rejection phenomena could be a treatment option for older patients with more advanced glaucoma

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- Unconventional IOP lowering therapies
 - Yoga
 - Meditation
- **Yoga**
 - Hypothesis
 - The *yoga*-based *Tratak kriya* leads to contraction and relaxation of ciliary muscles leading to increased outflow of aqueous humor, thus lowering the IOP in glaucoma patients. Studies like a single-blind randomized study which found significant reduction in IOP of glaucoma patients after 10 min of reading books as compared to those with gaze fixed at a point 6 m away suggest that whenever contraction in ciliary muscle is induced by near accommodation of eyes or by drugs, the pore size in the trabecular meshwork increases which may increase the outflow. During far accommodation, the ciliary muscles relax, decreasing the trabecular meshwork's pore size, whereas it increases the uveoscleral outflow as the humor crosses between the epithelium's devoid surface of ciliary muscle fibers. Therefore, *Tratak kriya* might reduce IOP in glaucoma by increasing the outflow through both trabecular and uveoscleral pathways. Practicing controlled yogic breathing causes increased self-awareness and relaxes mind which might lead to decreased stress. Reduced IOP and stress might improve QoL of glaucoma patients.

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- Unconventional IOP lowering therapies
 - Yoga
 - Meditation
- **Meditation**
 - we evaluated whether mindfulness-based stress reduction can lower IOP and normalize typical stress biomarkers.
 - In a prospective, randomized trial 90 POAG patients (180 eyes; age above 45 y) were assigned to a waitlist control or mindfulness meditation group which practiced daily for 21 days. We measured IOP (primary endpoint), quality of life (QOL), stress-related serum biomarkers [cortisol, β -endorphins, IL6, TNF- α , brain-derived neurotrophic factor (BDNF), reactive oxygen species (ROS), total antioxidant capacity (TAC)], and whole genome expression.
 - Between-group comparisons revealed significantly lowered IOP in meditators (OD: 18.8 to 12.7, OS 19.0 to 13.1 mm Hg) which correlated with significantly lowered stress-Biomarker levels including cortisol (497.3 to 392.3 ng/mL), IL6 (2.8 to 1.5 ng/mL), TNF- α (57.1 to 45.4 pg/mL), ROS (1625 to 987 RLU/min/104 neutrophils), and elevated β -endorphins (38.4 to 52.7 pg/mL), BDNF (56.1 to 83.9 ng/mL), and TAC (5.9 to 9.3) (all $P < 0.001$). These changes correlated well with gene expression profiling. Meditators improved in QOL ($P < 0.05$).
 - A short course of mindfulness-based stress reduction by meditation in POAG, reduces IOP, improves QOL, normalizes stress biomarkers, and positively modifies gene expression. Mindfulness meditation can be recommended as adjunctive **therapy** for POAG.

Thank You