New Horizons in Glaucoma

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Disclosures

- Consultant
  - Alcon, Aerie Pharmaceuticals, Allergan, Bausch & Lomb, Carl Zeiss Meditec, Glaukos, Heidelberg Engineering, Topcon

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What's New, What's Next in Glaucoma

- Can a biomarker be developed to more easily diagnose glaucoma?
- How Often does glaucoma occur?
- IOP
  - 24-Hour IOP
    - Devices now FDA approved to measure 24-hour IOP
  - Ocular Perfusion Pressure
    - Including blood pressure in equation to measure blood flow to optic nerve
  - Role of hysteresis in glaucoma risk
    - Biomechanical property that is associated with risk
  - Cerebrospinal fluid pressure and translaminar pressure difference
    - One explanation for why glaucoma may develop at low IOP

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What's New, What's Next in Glaucoma

- Optic Nerve/RNFL/Posterior pole
  - What changes first – RNFL or optic nerve or macula
    - Important to get measurements from all areas b/c some changes and other don't, depending upon the individual
  - Confocal Scanning Laser Ophthalmoscopy-improved form of retinal photography
  - Advances in Optical Coherence Tomography
    - Faster units with better resolution
    - Swept Source OCT
    - OCT angiography
  - Modifying how the OCT RNFL results are displayed
    - Flipping the TSNIT that allows easier detection subtle loss and improved structure-function
    - Improved Methods for Structure-Function
- Visual fields
  - Role of central fields in diagnosing and monitoring glaucoma
    - 10-2 pattern with 2^{0} spacing
  - Faster tests
  - Structure –Function
    - Incorporating fields with imaging results
    - Incorporating fields with retinal photography

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What's New and What's Next in Glaucoma

- Therapy
  - Generics
  - Do glaucoma medications work around the clock
    - FDA does not require 24 hour testing
  - Fixed combination agents have moved up to 2^{nd} line agents
  - New glaucoma surgical devices such as Xen implant, Cypass, iStent
    - MIGS type devices
  - New Medications
  - New drug delivery devices

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IOP

- 24-Hour IOP
- Ocular perfusion pressure
  - Diastolic blood pressure minus IOP
  - Cut off is b/w 30 and 50
- Role of hysteresis in glaucoma risk
- CSF and glaucoma risk

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The difficulty in using IOP as a marker of disease is how much it varies and how difficult it is to detect elevated IOP

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24-Hour IOP Monitoring

- How do we evaluate IOP if we are only measuring it briefly in office?
- Three approaches to measure IOP over 24 hour period
  - Self tonometry
  - Permanent continuous IOP monitoring
  - Temporary continuous IOP monitoring
    - Measures a marker of progression, not IOP variation

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Permanent Continuous Monitoring

- Provide daytime and nighttime IOP measurements through self-contained implant
- Accessed remotely with wireless technology
- Ideal for advanced glaucoma
- Would not be measuring the surface but rather taking IOP measurements directly inside the eye
  - Subject to less noise
- Incorporates telemetric IOP device with IOL
- Digital signal sent form IOL to external device
- Alarm raised at certain point
- Long-term stability is unknown

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Triggerfish Contact Lens IOP Device

- The lens is designed to provide a more accurate assessment of IOP
- Lens worn for 24 hours and discarded
- Consists of a clear, silicone contact lens ringed by a strain gauge and a microprocessor and antenna that transmits data to an external receiver
- The gauge continuously monitors the shape of the cornea, indicating greater or lesser intraocular pressure
- Information about IOP fluctuations is immediately transmitted via radio frequencies from the lens' microprocessor to a recording receiver
- The microprocessor is powered by an induction loop which uses a magnetic field around the eye to generate the tiny amounts of required electricity
  - Induction loops are also used to power hearing-aid implants

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Self Tonometry

- Patients would monitor their IOP over time with easy-to-use devices
- Easiest approach in regards to continuous monitoring
- Adapt current device such as Noncontact tonometer or Rebound tonometer
- May be difficult for some patients to perform
- Not easy to obtain 24 hour IOP

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Cerebrospinal Fluid Pressure (CSF) and Glaucoma

- The third part of the pressure equation is CSF
- IOP, Blood Pressure and CSF
  - All inter-related and anyone out of balance may lead to glaucoma
- Recent work has shown that low CSF may be contributory to the development of glaucoma
  - Translaminar pressure differential
    - Takes into account the IOP and CSF
  - May explain pathogenesis for normal tension glaucoma

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OCT

- First generation – Time Domain
  - Zeiss Stratus COT
- Second generation – Spectral Domain
  - Several manufacturers including Optovue (RTVue), Zeiss Cirrus, Heidelberg Spectralis, Topcon Maestro
- Next generation – Swept Source
  - Only one FDA approved device – Topcon Triton

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Currently Approved OCT Devices

- Full approval including NDB
  - Optovue RTVue, Avanti and iVue
  - Carl Zeiss Meditec Cirrus and Cirrus Photo
  - Heidelberg Spectralis
  - Topcon Maestro
  - Topcon Triton – Swept Source

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Advantages of Flipping the RNFL

- TSNIT was an arbitrary designation 25 years ago
- Temporal region is most important part of curve and with NITSN, region is not broken up and loss more obvious
- Easier to recognize structure-function correlation
  - RNFL loss correlates easily with field loss
- Easier to understand if macula area may be involved and central field loss present
  - Is there a reduction in RNFL within the central 8^0

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Macula Testing in Glaucoma

- Imaging to detect glaucoma damage has concentrated around RNFL and optic nerve evaluation
- Complicating the assessment of the optic nerve when evaluating for glaucoma damage is:
  - High variability of the ONH size and shape
    - Even among healthy individuals
  - Wide range of optic cup shapes and sizes
  - Variable size and configuration of blood vessels
  - Variable angle of penetration into the eyeball of the optic nerve (tilted disc)
  - Parapapillary changes such as atrophy
- These are the reasons why it is difficult to detect early glaucomatous damage

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Macula Testing in Glaucoma

- Imaging allows measurement of features that are not possible otherwise
  - Imaging can detect changes in the macular region
  - The eye has about 1 million retinal ganglion cells, and their numbers are densest in the macula
    - about six cells deep
  - About 50% of ganglion cells are in the central 4.5 mm of the retina
    - an area that represents only 7% of the total retinal area
  - This area is not well covered in most visual field testing

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Peripapillary Atrophy(PPA) and Glaucoma

- PPA more common and greater in OAG
- Degree of PPA correlates with optic disk damage
- Location of PPA correlates with location of optic disk damage
- Location of PPA correlates with location of visual field defects
- Is it a primary phenomenon?
  - parapapillary atrophy occurs first and leads to loss of neurons
- Is it a secondary phenomenon?
  - result of retinal ganglion cell death and/or other changes to optic nerve head

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Measuring Blood Flow

- Ocular blood flow and optic nerve injury have been linked
- The question still not answered is which comes first
- Can a device be developed that provides reproducible, quantitative, objective assessment of retinal and optic nerve blood flow
  - Both global and local
  - Does not require expert operator
  - Measurement should correlate with structure and function

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Measuring Blood Flow

- There have been numerous devices to measure blood flow over the years
  - Varying degrees of invasiveness, accuracy and precision
    - From injectable dyes to ultrasonography to laser
  - Poorly reproducible or variations in acquisition of data
- Optical Coherence Tomography Angiography
  - Used to map retinal and superficial optic nerve vasculature and blood flow
  - Not clear if there is a floor effect
  - Is technique useful from early to advanced disease?
- Superficial vascular layer is the first area affected by glaucoma

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What is OCT-A?

- New, non-invasive imaging without the use of dyes
- Uses motion contrast imaging to high-resolution volumetric blood flow to generate angiographic images quickly
- Uses differences in OCT B-scan signal intensity taken at same location to construct map of blood flow
- Looking at erythrocyte movement in vessels
- Requires high imaging speeds along with eye tracking

- Do not visualize vessel wall but rather flow inside the walls
- Do not see dye staining, pooling or leakage
- En-face images can be scrolled from internal limiting membrane to the choroid
- Looking at flow at a fixed point in time
- Can correlate structure and functional information since OCT-A are registered to OCT B-Scans

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OCT Angiography (OCTA)

- Non-invasive imaging modality that allows detection of blood flow and three-dimensional reconstruction of blood vessels using signal decorrelation between consecutive transverse cross-sectional OCT scans
- OCTA is computed by comparing on pixel-by-pixel basis repeated B-scans acquired at the same retinal location in rapid succession
- Rationale is in non-mobile tissue the reflected signal will be stationary
  - Thus the repeated B-scans will be identical
  - Inside the vasculature, moving erythrocytes cause a time-dependent backscattering of the OCT signal which is seen as differences in the repeated B-scans

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OCT Angiography (OCT-A)

- Analysis is done by either
  - Amplitude decorrelation
    - Changes in OCT signal
  - Doppler OCT which is a phased-based tool
    - Quantify axial blood flow that is parallel to direction of acquisition device
- Analysis allows OCTA images to be analyzed with en-face or cross-sectional images
  - View based upon depth

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Glaucoma Therapy
An Overview

- Chronic disease that can be difficult to control
  - Person has the disease for the rest of their life
- Treatment often requires multiple medications and surgeries
- Treatment endpoints are poorly defined
- Treatment endpoints often difficult to achieve, even when defined
- Medication adherence challenges are common
  - Patients have difficulties taking medications for long periods of time
- Continuing need for new therapies and drug delivery techniques

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What's New and What's Next in Glaucoma

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  - Do glaucoma medications work around the clock
    - FDA does not require 24 hour testing
  - Fixed combination agents have moved up to 2nd line agents
  - New glaucoma surgical devices such as Xen implant, Cypass, iStent
    - MIGS type devices
  - New Medications
  - New drug delivery devices

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Glaucoma Therapy Update

- In future, similar to cardiologists we may discuss with our patients smoking cessation, altering diet, weight loss, and increased physical activity as additional therapies for glaucoma
- Many of the new therapies will revolve around drug delivery directly into the eye via some form of injection (doctor) or insertion (patient)

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Glaucoma Therapy Update

- There are currently 6 main classes of IOP-lowering medications
- Each works by altering 1 or more aspects of aqueous humor flow
- Beta-blockers and carbonic anhydrase inhibitors reduce the rate of aqueous production
- Prostaglandins increase outflow through the uveoscleral pathway
- Alpha-adrenergic agonists lower IOP by a dual mechanism
  - reducing aqueous production and increasing uveoscleral outflow
- None of these drugs works at the site of outflow impairment—the TM
- Miotic class of drugs do increase trabecular outflow, but only indirectly through actions on the ciliary muscle
  - not through any direct effects on the TM itself
  - generally poorly tolerated and not widely used in modern practice
- There has been an unmet need for an IOP-lowering medication that works at the TM
  - the main site of outflow obstruction in glaucomatous eyes

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Glaucoma Therapy Update

- Trend in topical eyedrop therapeutics is combination compounds with multiple targets and mechanisms of action (MOA) with single daily dosing
- Targets will include trabecular meshwork and uveoscleral outflow, aqueous humor production and episcleral venous pressure (EVP)
- Stem cell and gene therapy are being developed but are years away from clinical use

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Topical Glaucoma Treatments

BRAND NAME/ MNFR	GENERIC NAME	CONCENTRATION/ BOTTLE SIZE
Beta Blockers Betagan/Allergan	levobunolol HCL	0.25% - 5mL, 10mL; 0.5% - 2mL, 5mL, 10mL, 15mL
Betimol/Vistakon	timolol hemihydrate	0.25% - 5mL; 0.5% - 5mL, 10mL, 15mL
Betoptic-S/Alcon	betaxaolol HCL	0.25% - 2.5mL, 5mL, 10mL, 15mL
Istalol/Ista	timolol maleate	0.5% - 5mL
Timoptic/Aton Pharma	timolol maleate	0.25% - 5mL, 10mL, 15mL; 0.5% - 5mL, 10mL, 15mL
Timoptic (preservative-free)/Aton Pharma	timolol maleate	0.25% - unit dose; 0.5% - unit dose
Timoptic-XE/Aton Pharma	timolol maleate	0.25% - 2.5mL, 5mL; 0.5% - 2.5mL, 5mL
Prostaglandin Analogs Lumigan/Allergan	bimatoprost	0.01% - 2.5mL, 5mL, 7.5mL
Rescula/Sucampo	unoprostone	0.15% - 2.5mL, 5mL
Travatan Z/Alcon	travoprost	0.004% - 2.5mL, 5mL
Generic	latanoprost	0.005% - 2.5mL
Zioptan/Merck	tafluprost	2.5mL
Prostaglandin + Nitric Oxide Vyzulta/Bausch + Lomb	latanoprostene Bunod	0.024% - 5 mL

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Topical Glaucoma Treatments

BRAND NAME/ MNFR	GENERIC NAME	CONCENTRATION/ BOTTLE SIZE
Alpha Agonists Generic	brimonidine	0.1%, 0.15% - 5mL, 10mL, 15mL
Alphagan P/Allergan	brimonidine	0.1%, 0.15% - 5mL, 10mL, 15mL
Iopidine/Alcon	apraclonidine	0.5% - 5mL, 10mL; 1% - unit dose
Carbonic Anhydrase Inhibitors Azopt/Alcon	brinzolamide	1% - 5mL, 10mL, 15mL
Trusopt/Merck	dorzolamide	2% - 5mL, 10mL
Rho kinase Inhibitors (ROCK inhibitor) Rhopressa/Aerie	Netarsudil	0.02% - 2.5mL
Combination Glaucoma Medications Combigan/Allergan	brimonidine/timolol	0.2%/0.5% - 5mL, 10mL
Simbrinza/Alcon	Brinzolamide/brimonidine	1%/0.2% - 8 mL
Cosopt PF/Merck Generic	dorzolamide/timolol	2%/0.5% - 5mL, 10mL

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New Drugs

- Latanoprost bunod
  - Approved November 2017
  - Nitric oxide donating Prostaglandin F2α
  - Vyzulta Bausch & Lomb
- Rho Kinase Inhibitors
  - Approved December 2017
  - Netarsudil 0.02%
  - Rhopressa
  - Aerie
- Rho Kinase Inhibitors and latanoprost
  - Roclatan
  - Aerie
  - 1st quarter 2019
- Lumigan SR
  - Sustained release bimatoprost implant
  - Phase III
- OTX-TP
  - Sustained release travoprost punctal plug
  - Ocular Therapeutix
- Xelpros (latanoprost BAK-free eye drops)
  - Sun Ophthalmics
  - 1st quarter 2018
  - Multi-dose PF bottle

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Latanoprostone bunod (Vyzulta)

- 0.024% used once daily to reduced IOP
  - Bausch & Lomb
  - Waiting for FDA approval
- Metabolized to latanoprost acid plus butanediol mononitrate
- Butanediol mononitrate is a nitric-oxide donating moiety NO molecule attached to latanoprost backbone to provide dual action
- Works over 24 hour period with >35% IOP reduction
- One molecule leads to IOP reduction via the uveoscleral and trabecular meshwork pathways
- NO is a signaling molecule that regulates outflow facility via the TM
- Can dilate blood vessels
- Modulates TM contractility, cell adhesion and the cytoskeleton leading to reduced IOP
- Medication acts on both the
  - Uveoscleral outflow pathway by altering the extracellular matrix in the ciliary muscle and the sclera
  - Trabecular meshwork outflow by inhibiting actomyosin contractility in trabecular meshwork cells thereby relaxing the meshwork

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New Medication
Rho Kinase Inhibitors

- Rho kinase inhibitors
  - Rhopressa
- Reduce cellular stiffness in trabecular meshwork
  - Target trabecular meshwork cells to enhance outflow
  - May offer neuroprotective as well as anti inflammatory effects
  - Aerie
- Side effects
  - Hyperemia (conjunctival hemorrahges
  - Corneal verticillata
- Efficacy similar to timolol
- Once per day

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New Glaucoma Medications

- Aerie Pharmaceuticals
  - Dual action Rho kinase (ROCK) + norepinephrine transport (NET) inhibitor (Netarsudil 0.02%) - Rhopressa
    - AR-13324 lowers IOP by enhance outflow through TM (ROCK) and inhibit aqueous production (NET)
    - Also believed to reduce episcleral venous pressure which may allow it to better reduce IOP when it is below 21 mm Hg
  - Once per day dosage
  - Hyperemia is most common side effect found in studies to date

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Nertarsudil – Side Effects

Cornea verticillata (lipid micro-deposits in the corneal epithelial layer)
- Asymptomatic
- Only visible via biomicroscopy evaluation
- Benign corneal deposits (phospholipidosis) are a familiar outcome with other drugs such as amiodarone

- Conjunctival hemorrahges
  - 20%
  - Intermittent
  - No symptoms

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Rocklatan

- Combination of Rhopressa with latanoprost
- Dosed once daily with significant IOP lowering
- Triple action ROCK + NET + latanoprost (Roclatan)
  - PG324 fixed combination of AR-13324 and latanoprost
    - Additional IOP reduction through uveoscleral outflow
- Few systemic side effects
- Limited ocular side effects
- Expected 1st quarter 2019

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Drug Delivery Devices

- Problem – poor adherence in patients taking their medications as directed
  - Common with chronic disease such as glaucoma
  - Estimated 40% or higher of medicines not taken
- Plan - develop therapeutic methods that are independent of patient and delivered by doctor
- Modalities include devices that reside on ocular surface, slow-release depots that are injected into the eye, and punctal plugs that deliver drugs directly into tear film

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New Methods for Drug Delivery

- Patient's don't adhere well to instilling drops
- Eyedrops have drawbacks
  - Relatively inefficient in that large volume is placed in small space
  - Relies on patient's ability to comply and administer drops correctly
- Objectives of new drug delivery methods
  - Ensure drug delivered to the site of action in the eye
  - Reduce side effects of topical medications
  - Improve compliance
  - Improve clinical outcomes
  - Methods may be
    - patient centered and noninvasive or doctor centered and invasive

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Drug Delivery

- An ideal sustained release drug delivery system should be able to encapsulate and deliver the necessary drug to the target tissues at a therapeutic level without any detriment to the drug
- Drug encapsulation should be as high as possible to minimize loss and unless it is specifically desired, the initial burst of drug release should be kept to a minimum
- By modifying various biomaterials, it is possible to achieve sustained drug delivery to both the anterior and posterior segments of the eye

- Ocular Surface
  - Contact lens
  - Punctal plug
- Sclera
- Anterior chamber
- Intravitreal
- Subconjunctival/subchoroidal

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Ocular Drug Delivery Key Points

- Easy to place and easy to remove
- Tolerable
- Consistent efficacy
  - Works close to eye drop with improved compliance
  - Can it work better?
- Cosmetically invisible
- Stays in place
  - At least 90 days
- Use in multiple disease states

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Drug Delivery Systems for Glaucoma

- Amorphex Therapeutics
  - A polymer, similar to a contact lens, that contains the drug and sits under the upper eyelid
  - Releases the drug over several months
- Envisa Therapeutics
  - Implantable extended-release device
- pSivida and SKS Ocular
  - Delivery devices

- Kala Pharmaceuticals
  - Drops that can get into the eye more easily
- Ocular Therapeutix
  - Tear duct plugs containing medication
- Foresight - Helios
- Mati Therapeutics Inc.
  - Punctal plug device
- Graybug
  - Sustained release

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Platforms delivered outside the eye

- Helios (ForSight Vision 5) - Allergan
  - Bimatoprost-laden plymer-matrix insert embedded in compliant ring
- TODDD (Topical Ophthalmic Drug Delivery Device; Vista Scientific)
  - Nonerodible solid matrix under the eyelid embedded with a drug
  - Amoerphex Therapeutics
  - Most of the company's work has focused on timolol and prostaglandins.
- Punctal plugs:
  - Ocular Therapeutix (OTX-TP) is an intracanicular depot that dissolves over time
  - Mati Therapeutics (L-PPDS) is a latanoprost punctal plug delievery system
  - Kayla Pharmaceuticals
    - Drops that allow medication to get into the eye more effectively.
- Phenylboronic-Acid based polymeric micelles for mucoadhesive anterior segment ocular drug delivery

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Platforms Delivered inside the eye

- Bimatoprost SR
  - Bimatoprost sustained-release implant (Allergan)
  - Currently in Phase 3 clinical trials.
- ENV515 -Envisia Therapeutics
  - Implantable biodegradable polymer drug delivery system using extended-release travoprost using engineered highly-precise microparticles and nanoparticles
- GrayBug microparticle
  - Polymer-based intraocular delivery technologies that would allow customizable sustained release of all therapeutic classes
- pSivida
  - Delivery devices or technology to allow a constant delivery of medication over months or years
- Ohr Pharmaceutical
  - Inject micro- or nanoparticles into the eye that would then release a glaucoma drug/drugs over an extended period of time
- ClearSide Biomedical, Inc.
  - Use of microneedles to inject medication into a specific spot for it to be most effective

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Sustained Release Devices

- Questions to be considered:
  - Comfortability of device
  - Effectivity
    - Will it replace drops altogether or be replacement of one medication
    - Will OD's be granted rights to insert?
- What is taking so long?
  - Technicalities: Invention, investment, research
  - Modality and barriers within the eye itself
  - Comfortability/Usability for patients

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Drug-Loaded Contact Lenses

- Approximately 35 million individuals in US wear contact lenses
- If a person requires glaucoma therapy and wear CLs, request individual to discontinue CL wear, at least while administering drug
  - This may impact on adherence of medication
- If CL is to contain medication, this combination must be as safe and effective as CL and drug is used singly
  - Cannot impact upon refractive properties of lens
  - Concern for preservatives concentrating in CL or concentrating in tear layer between CL and cornea

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Drug-Loaded Contact Lenses
Simplistic Concept That Has Not Worked

- Soak CL in lens storage solution with drug
  - Hydrophilic matrix of soft CL absorbs drug and then releases it by simple diffusion
  - Limited by drug kinetics which leads to rapid diffusion
  - Diffusion varies drug to drug, often in under one hour
  - Medication with preservatives may cloud CL or effect oxygen permeability
- Issues with both forms
  - Want linear release which is difficult to achieve
- New Codes for 2016
  - 0365T Drug eluting contact lenses

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Drug-Loaded Contact Lenses
Drug Loading Strategies

- Use colloidal nanoparticles or molecular imprinting
  - Sub-micron size particles either coated with or encapsulating drug
    - Liposomes
    - Colloidal gold or silver
    - Once CL is placed on eye, drug diffuses into tear layer
    - Packing of drug in colloidal allows for more sustained delivery
  - Drug imprinting
    - Modifies contact lens material to allow drug molecule to sit within hydrogel complex
    - Allows higher drug load than simple diffusion

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Punctal Plug Drug Delivery Devices

- Insert slow-release medication depot into the punctum using a punctal plug
  - Plug may dissolved over time, be replenished or replaced
- Advantages
  - Track record of safety in using punctal plugs for dry eye
  - Minimally invasive and low-risk
  - Leverage existing medications used to treat glaucoma

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Punctal Plug Drug Delivery Devices

- Disadvantages
  - Prone to fall out over time which is not acceptable for chronic condition where months occur b/w visits
    - Need to overcome this problem such as improving patient awareness that plug has fallen out
  - Drug delivery is passive depending upon tears to wash into the plug reservoir and transport active drug back into the tear film
    - In cases of severe dry eye or lid anatomy pathologies, plug may not deliver drug in predictable manner
  - Current medications may not be ideal for drug delivery
    - Plug may not hold enough
    - Pulsed dosing as seen with topical use versus constant delivery with depot may lead to different efficacy
      - Prostaglandin not as effective when used in constant manner
- Efficacy varies from slightly less than timolol to close to a PG

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Punctal Plug Drug Delivery Devices

- Mati Therapeutics
  - Evolute
  - QLT started this work and has modified device to improve retention
  - Retention up to 95% depending if lower or upper punctum is used
  - Engaged in phase 2 trial with latanoprost
- Ocular Therapeutix
  - Using travoprost with 88% retention rate at 75 days
    - Phase 3 trial ongoing
  - Also working with allergy and steroid depot

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Sustained-release Travoprost

- OTX-TP, Ocular Therapeutix
- Intracanalicular depot composed of polyethylene glycol hydrogel and drug-containing micro particles
- Sustained release prostaglandin analogs for the treatment of glaucoma and ocular hypertension
- Once drug placed in tear drainage system, the hydrogel expands to conform to surrounding tissue
- The plug resides within the canaliculus, delivering travoprost to the ocular surface for up to 90 days
- Reduce or eliminate the need for daily dosing.
- Reduces need of patient to take a medication
- Fluorescein is incorporated to serve as a visualization aid

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Sustained-release Travoprost Punctal Plug

- Sustained release prostaglandin analogs for the treatment of glaucoma and ocular hypertension.
- Inserted non-invasively through the punctum
- The plug resides within the canaliculus, delivering travoprost to the ocular surface for up to 90 days
- Reduce or eliminate the need for daily dosing
- Travoprost encapsulated in microparticles which are suspended in a dried polyethlene glycol resorbable hydrogel rod
- Hydrolysis of the microparticles mediates sustained release
- The product also contains a visualization aid (fluorescein) to monitor retention over the treatment period.
- After therapy is complete, the hydrogel resorbs and exits the nasolacrimal system, so there is no need for removal.
- Preservative - free

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Mati Therapeutics

- "Evolute" Silicone Punctal Plug Device Used with Latanoprost w 5-6 mm Hg reduction
- Concern with plugs is retention, patient comfort and ease of insertion
  - 92-96% retention rate over 90 – 120 days
  - Easily removable if need be
- Long term efficacy also a concern
- Punctal opening – constant
- Elution in one direction into tear film due to valve
- Surface area exposed – constant
- Travoporst is the drug of choice for punctal plugs b/c of greater efficacy

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Amorphex Therapeutics

TODDD (Topical Ophthalmic Drug Delivery Device; Vista Scientific)

Nonerodible solid matrix under the eyelid embedded with a drug

Amoerphex Therapeutics

Most of the company's work has focused on timolol and prostaglandins

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Bimatoprost SR

- Allergan
- Sustained release bioerodible implant that lasts 4-6 months with similar efficacy to eyedrops
- Small disolvable pellet is injected into the anterior chamber
  - Sits in/near the angle that resorbs over time
- Can be performed in the office
- Insert can be visualized in the inferior angle
- Ensures patient compliance
- Phase III trial underway comparing SR to timolol
- Will there ever be a need for removal?
- Could it cause cataracts?

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Bimatoprost SR Study Results

- Baseline IOP 25.2mm Hg
- Mean IOP reduction ranged from 7.2-9.5mm Hg at week 16
- Fellow eye IOP reduction 8.4 mm Hg with topical Bimatoprost eyedrops once daily
- Rescue therapy needed in 8% at week 16
- IOP reduction seen through 6 months
- At 6 moths, 71% did not require rescue therapy or a 2nd injection

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Glaucoma Surgery

- Minimally Invasive Glaucoma Surgery (MIGS)
  - Increasing from $13 Million in 2013 to $70 million in 2015
  - Objective is for reduced complications compared to trabeculectomy with nearly similar IOP reduction
  - New MIGS type devices in development
    - To be approved over the next several years
    - Istent inject and iStent Supra (Glaukos), Ivantis (Hydrus), CyPass Micro-stent (Trascend Medical), AqueSys (Allergan)

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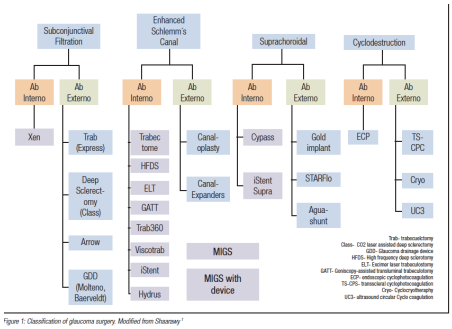

Figure 1: Classification of glaucoma surgery. Modified from Shaarawy[1]

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Minimally or Micro- Invasive Glaucoma Surgery - MIGS

- Glaukos Trabecular Micro-bypass stent (iStent)
  - June 2012 FDA approval
  - Designed to create a permanent opening from the anterior chamber to Schlemms canal
  - Designed to fit and remain in Schlemms canal
  - Titanium device 1 mm in length consisting of inlet or snorkel end connected at right angle to implantation portion, which has a pointed end to facilitate entry into canal
  - Theoretic advantages
    - Open a pathway into Schlemms canal
- Tiny titanium devices that drains aqueous fluid from the anterior chamber
- Minimally traumatic, conjunctiva sparing *ab-interno* procedure
  - performed through a clear corneal micro-incision under 2.0mm
- The objective is to achieve IOP in the mid-teens and reduce medication use
  - leaving the door open for more invasive surgical alternatives if required in the future
- It is approved for use during cataract surgery in the 20% of cataract patients that are treated with medications to reduce intraocular pressure (IOP)

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Micro-invasive Glaucoma Surgery MIGS

- MIGS devices under development using a Schlemm's canal outflow target include
  - *Hydrus Microstent* from Ivantis Inc.
  - *iStent inject* from Glaukos
- *Hydrus* is a flexible curved scaffold made from elastic Nitinol that spans three clock-hours of the canal and gently dilates it
  - designed to be inserted into Schlemm's canal and open the channel to allow blocked fluid to flow more freely
  - targeting multiple collector channels to reduce resistance to outflow

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Xen Gel Stent

- IOP lowering device already approved in Europe, Canada and some other countries
  - Allergan
- A soft, permanent, minimally invasive ocular shunt (MIGS or micro-invasive glaucoma surgery device) that is implanted in the anterior chamber of the eye to facilitate the continuous flow of aqueous humor into the subconjunctival space
- The ocular shunt is manufactured from gelatin (45 µm internal diameter)
- The implant is 6mm in length and nearly as thin as a strand of human hair.

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Xen Gel Stent

- Implanted through a small 27-gauge needle, single use, pre-loaded proprietary injector using an ab interno (from inside the eye) approach
- The surgeon first advances the needle through the peripheral cornea and across the anterior chamber towards the target area. The needle is then advanced through the trabecular meshwork and sclera and is visualized as it enters the subconjunctival space. The implant is then released and the needle is removed from the eye.
- When implanted, it creates a better outflow of aqueous fluid from the anterior chamber of the eye into the non-dissected tissue of the subconjunctival space
- This procedure is minimally invasive
- The gelatin material is non-inflammatory with minimal stress on the surrounding tissue and doesn't migrate once placed
- The surgery leaves all other options open for future use if needed, and it can be repeated

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Summary

- Many developments in terms of new diagnostic devices
  - IOP measuring
  - OCT imaging
  - Visual Fields
- And therapeutic entities
  - Medications
  - Surgical advances

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