Advances in Glaucoma Therapy

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New Technologies In Glaucoma Diagnosis

Caveat for all Imaging devices
Ganglion Cell Anatomy

Overlay allows you to pinpoint pathology

Ganglion Cell Analysis: How Accurate Is It?

- **DIAGNOSTIC ACCURACY AND REPRODUCIBILITY**
  - Tan et al
  - Across-sectional study, the researchers employed existing data from patients enrolled in the Advanced Imaging for Glaucoma Study. Participants were categorized into three groups: normal (65 eyes), perimetric glaucoma (78 eyes), and preperimetric glaucoma (52 eyes).
  - With regard to reproducibility, the GCC parameters outperformed (smaller coefficients of variation) RNFL parameters in normal ($P = .0002$) and perimetric glaucomatous ($P > .001$) eyes but not preperimetric glaucomatous ($P = .11$) eyes.

Ganglion Cell VF Pathology

- Analysis of VF in RGC loss in Glaucoma
  - 24-2 protocol has 6 degrees separation allowing for thinning the RGC to be missed to due point placement.
  - Drazdo et al; Vision Research 2007
  - 10-2 testing substantially improves correlation with RGC analysis
  - Hood and Hub; Vis Sci 2011
  - Stamper (1984) identified the relationship between NTG and macular damage with typically near fixation visual field loss.
  - Heijl & Lundqvist 1984
  - 45 patients followed from normal to abnormal VF's using test points at 5,10,15 & 20 degrees from fixation.
  - Largest number at 15 degrees but a surprising number at 5 degrees confirming Hood's work showing that early damage occurs in the macula as well as more traditional arcuate zones.

The New Way: RNFL, Optic Disc & GCC Analysis

- Macular pathology
  - AMD
  - ERM
  - VMT
  - VMA
- Peripheral Pathology
  - Early VF loss outside of macular region
Assess change in RNFL and GCC thickness over time.

RNFL Rate of Change = -1.00 µ/Year

GCC Rate of Change = -1.93 µ/Year

Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness.

Ganglion Cell Analysis

Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness.

BACKGROUND:
Post-mortem analyses of multiple sclerosis (MS) eyes demonstrate prominent retinal ganglion cell layer (GCL) loss, in addition to related axonal retinal nerve fiber layer (RNFL) loss. Despite this, clinical correlations of retinal neuronal layers remain largely unexplored in MS.

RESULTS:
Ganglion cell analysis (GCC) was thinner in relapsing-remitting MS (RRMS; n = 96, 71.6 µm), secondary progressive MS (SPMS; n = 20, 66.4 µm) and primary progressive MS (PPMS; n = 16, 74.1 µm) than in healthy controls (81.8 µm; p < 0.001 for all). GCC thickness was most decreased in SPMS, and although GCC thickness correlated significantly with disease duration, after adjusting for this, GCC thickness remained significantly lower in SPMS than RRMS. GCC thickness correlated significantly, and better than RNFL thickness, with EDSS, high-contrast, 2.5% low-contrast and 1.25% low-contrast letter acuity in MS. 13.6% of patients also demonstrated inner or outer nuclear layer thinning.

CONCLUSIONS:
OCT segmentation demonstrates in vivo GCC thinning in all MS subtypes. GCC thickness demonstrates better structure-function correlations (with vision and disability) in MS than RNFL thickness. In addition to commonly observed RNFL/GCC thinning, retinal inner and outer nuclear layer thinning also occur in MS.
Updated Guided Progression Analysis (GPA™)
Optic Nerve Head information now included

- Average Cup-to-Disc Ratio plotted on graph with rate of change information.
- RNFL/ONH Summary includes item “Average Cup-to-Disc Progression”.
- Printout includes an optional second page with table of values, including Rim Area, Disc Area, Average & Vertical Cup-to-Disc Ratio and Cup Volume. Each cell of the table can be color coded if change is detected.
- Miscellaneous updates to the report design.

The New Way: Angle Measurement with OCT

Myopia = “Red Disease”
Tracking the Elusive Diurnal!

- Sensimed: Swiss medical device company. Jean-Marc Wismer CEO
- Device is called Triggerfish
- Tracks fluid pressure in the eye and beams data to palm size recorder.
- Uses a circular antenna taped around the eye and connected to a battery powered portable recorder.
- Transmits radio frequency energy to an ultra thin gold ring in the CL. This powers a chip embedded in the lens.
- Additionally on the lens in an ultra thin platinum ring that stretches in response in variation in eye shape secondary to pressure.
- Available in Europe. Primary trial at University Hospitals of Geneva

Sensimed “Triggerfish”

How does it work?
SENSIMED Triggerfish® provides an automated recording of continuous ocular dimensional changes over 24 hours. This safe and sensitive system is non-invasive and practical. Installation and removal on the patient is simple and is executed by the healthcare professional. It is furthermore outpatient compatible.

Technologies in the Diagnosis and Management of Glaucoma

IOL Tonometry

http://www.launchpnt.com/portfolio/biomedical/intraocular-pressure-sensor

Surgical Continuous IOP Monitoring Device

- Nature Medicine 2014
  - Yossi Mandel, Bar-Ilan/ Stephen Quake, Stanford
  - Utilizes a variable float tube in the IOL
  - Smart Phone app allows acquisition of data
  - Anticipated in 2-3 years

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

Icare Home Tonometry

- Waiting FDA approval
- Person would have device provided from eye doctor to use for 24 hours
- Measurements sent to eye doctor for review
- Issue with reimbursement
- Dependent upon ability of individual to take accurate readings
Icare HOME tonometer

- IOP, date, time, eye recognition (right/left) and measurement quality are all stored in the internal memory.
- Data is transferred to a PC for further analysis by the prescribing physician.
- New features: positioning light, automatic eye recognition system, series or single measurements, new user interface panel.

**Light**

Red and green light signals help patients correctly position the tonometer.

- Correct alignment
- Incorrect alignment
- Incorrect alignment

**Icare® EyeSmart: Automatic Eye Recognition**

The tonometer includes an automatic eye recognition system that identifies which eye is being measured.

- Two infrared LED transmitters below probe (1)
- One infrared LED sensor above probe (2)
- The infrared light is reflected from nose back to the sensor
- The sensor knows from which transmitter the reflected infrared light came from and thus which eye, right or left, was measured
- The resulting eye indication is stored into the memory of the tonometer

**New User Interface Panel**

- Simple Indicator Lights and Audible Alerts
- Interpretation only by a health care professional
- Does not display the IOP measurement

- Mitigating concerns that the patient or caregiver might improperly use the information provided by the device
Some materials contain naturally autofluorescent components of a molecule that can be visualized if illuminated by a specific excitation wavelength. No autofluorescence when illuminated with white light. Emitting light when illuminated with excitation wavelength.

**Normal FAF distribution**

- Optic nerve head: absence of autofluorescent material.
- Retinal blood vessels: absorption phenomena by blood contents.
- Foveal area: absorption from luteal pigment.
- Parapapillary area: mildly decreased intensity maybe caused by increased melanin deposition and lower density of LF granules in central RPE cells.

**ONH Drusen**

**Parapapillary Autofluorescence**

Important tool for early diagnosis?

- Advanced Glaucoma
  - Histological LF accumulation parapapillary region
  - POAG, PSXG, NTG, OHT

  \[ \text{↑} \text{FAF signal in parapapillary atrophic zone} \]
  - Increased intensity in blue on yellow VEP pattern (OHT)
  - LF correlated w. stage of progression.

**Glucoma and Lipofuscin**
THE ROLE OF CORNEAL HYSTERESIS
an indicator for glaucoma progression risk

Corneal Hysteresis: No Longer "Novel"
- Technology is at a "tipping point"
- 12 years of clinical studies support CH as an in vivo indicator of corneal biomechanics
- Clinical evidence for the utility of CH in glaucoma comes from >400 publications with data from >52,000 patients

Publications about Corneal Biomechanics
1990 - 2014
Introduction of ORA
Ocular Response Analyzer Technology
- 2002: Clinical research with ORA commences
- 2005: The 1st generation ORA was made commercially available
- 2012: Generation II ORA was launched
- 3rd Generation "ORA G3" introduced September 2015

Measures:
- Corneal Hysteresis (CH)
- Goldmann-correlated IOP (IOPg)
- Corneal compensated IOP (IOPCC)

The only in vivo measurement of corneal/ocular biomechanics
- Function of viscoelastic damping
- Not a characterization of stiffness
- Provides insight into ocular properties that were not previously understood or conceived of

Ocular Response Analyzer Technology
The instrument
- 2002: Clinical research with ORA commences
- 2005: The 1st generation ORA was made commercially available
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- 3rd Generation "ORA G3" introduced September 2015

Corneal Hysteresis
- A measurement that characterizes response to application and removal of force (load/unload)
- Found in materials or systems that do not instantly follow forces applied to them but react slowly, or dissipate a portion of the applied energy
- More than 7500 papers published on hysteresis in a variety of medical fields
- Various tissues and structures (tendon, lung, arteries, etc.)


Sir James Alfred Ewing
Identified the phenomenon of hysteresis and coined the term in 1890

Hysteresis Loop
- Sir James Alfred Ewing identified the phenomenon of hysteresis and coined the term in 1890
- A measurement that characterizes response to application and removal of force (load/unload)
- Found in materials or systems that do not instantly follow forces applied to them but react slowly, or dissipate a portion of the applied energy
- More than 7500 papers published on hysteresis in a variety of medical fields
- Various tissues and structures (tendon, lung, arteries, etc.)
- The importance of Corneal visco-elasticity had been discussed and reported prior to the ORA

Ocular Response Analyzer Technology
Bi-direction Applanation Signal
- The only in vivo measurement of corneal/ocular biomechanics
- Function of viscoelastic damping
- Not a characterization of stiffness
- Provides insight into ocular properties that were not previously understood or conceived of

Clinical Evidence – Study 1
Corneal Hysteresis found to be associated with progression

- The first observational study to investigate the relationship of Corneal Hysteresis to a variety of other parameters in a glaucoma population
- 230 POAG or suspected POAG patients were included in the study
- POAG was defined by a reliable visual field that was abnormal according to OHTS criteria, with an optic nerve image, photo, or CDR thought to be consistent with the field damage by a fellowship-trained glaucoma specialist.
- GAT, OSTA, CCT and Axial Length measurements (IOL master) were recorded
- Among patients with three or more reliable fields over three or more years, or with five reliable fields in less than three years, progression was defined as having achieved the OHTS standard of “conversion” (previously normal), or (previously damaged as evidenced by an abnormal GHT or PSD) having worsened by 1 dB or greater per year in either MD or PSD.

Clinical Evidence – Study 2
CH associated with progression in NTG eyes

- A retrospective study to investigate the clinical significance of Corneal Hysteresis in patients with glaucoma treated with topical glaucoma medications
- 82 eyes of 53 NTG patients meeting typical clinical criteria of normal tension glaucoma were included.
- Significant was defined at the point of and throughout duration of the study.
- CH was measured using the Ocular Response Analyzer Technology (ORA).
- CH was measured in mmHg.
- CH values were determined to be associated with progression.

Clinical Evidence - Study 2
CH associated with progression in NTG eyes

- Of the 39 eyes with low CH, 26 (66.7%) showed progression (18.5% damage while (12.1%) showed no progression).
- Of the 43 eyes with high CH, 15 (34.9%) showed progression of VF damage, whereas 29 (67.4%) showed no progression.

Clinical Evidence – Study 1
Corneal Hysteresis found to be associated with progression

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**Conclusions:** Corneal Hysteresis was the parameter most associated with progressive field worsening.

CH: Average Values in Normal Subjects

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Clinical Evidence – Study 3
CH Associated with Asymmetric Glaucoma Progression

- Investigated the relationship between CH and asymmetric POAG
- In a prospective cross-sectional study, ORA parameters were measured in 117 POAG patients with asymmetric visual fields (VF).
- VF testing was performed with a static, automated, achromatic perimeter (24-2 test pattern, MA II, model 750). Carl Zeiss Meditec, Inc) using the SITA-standard program.
- Asymmetry was defined as a 5-point difference between OD and OS using the (AGIS) scoring system.
- Pearson correlation coefficients were used to determine correlation of various parameters with the AGIS score. Receiver operating characteristic (ROC) curves were plotted for ORA and other glaucoma risk factors.

Baseline characteristics obtained on the date of the first VF test entered in the regression were:
- age
- sex
- VF MD and PSD, CCT, and baseline IOP
- CCT was calculated as the average of 3 measurements using ultrasound pachymetry
- Baseline CH was calculated using the optical coherence tomography (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany)
- Only eyes that followed up KF was calculated as the average of 3 measurements using ultrasound pachymetry
- The mean of the minimum values of the right and left eyes was calculated for each parameter
- Determination of the eyes follow up KF was calculated as the average of 3 measurements using ultrasound pachymetry
- Only eyes withitus SITA Standard 24-2 visual field (VF) tests were included (N=153 eyes)
- Patients were typically seen at 3-month intervals and each test was repeated at the clinic’s discretion.
- Automated pointwise linear regression analysis was used to determine VF progression.

Clinical Evidence – Study 4
CH Associated with Rate of VF Progression

- A retrospective study to investigate the correlation between central corneal thickness (CCT) and central hysteresis (CH) and their relationship with the rate of visual field (VF) change.
- Baseline characteristics obtained on the date of the first VF test entered in the regression were:
- age
- sex
- VF MD and PSD, CCT, and baseline IOP
- CCT was calculated as the average of 3 measurements using ultrasound pachymetry
- Baseline CH was calculated using the optical coherence tomography (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany)
- Only eyes withitus SITA Standard 24-2 visual field (VF) tests were included (N=153 eyes)
- Patients were typically seen at 3-month intervals and each test was repeated at the clinic’s discretion.
- Automated pointwise linear regression analysis was used to determine VF progression.

Clinical Evidence – Study 3
CH Associated with Asymmetric Glaucoma Progression

Time-adjusted logistic regression with VF Progression as Binary Outcome

- ORA Corneal Compensated IOP, CRF = ORA Corneal Resistance Factor, SE = Spherical Equivalent, CCT = Central Corneal Thickness
- The above information might be of interest for glaucoma patients with increased deformation of the optic nerve during transient IOP elevations in glaucoma patients but NOT in normal controls.

Clinical Evidence – Study 4
CH Associated with Rate of VF Progression

Clinical Evidence – Study 3
CH Associated with Asymmetric Glaucoma Progression

CH Associated with Asymmetric Glaucoma Progression

CH was the best discriminative index for the worse eye in asymmetric ONH.

CH lower in 80% of worse eyes.

Clinical Evidence – Study 4
CH Associated with Rate of VF Progression

CH and the structural continuum
CH is associated with ONH Deformability & RNFL Analysis

- Lower CH is associated with decreased RNFL
- CH deformation occurred before RNFL thinning in a significant proportion of patients with glaucoma
- CH was more closely related to visual field mean deviation than to structural markers of glaucoma damage as measured by SD-OCT

ONH deformability is associated with glaucoma. CH is associated with ONH deformability. CH is more associated with VF defect than structural markers of glaucoma as measured by SD-OCT.
**Key Benefits**

**Corneal Compensated IOP (IOPcc):**

**Evaluation of the Influence of Corneal Biomechanical Properties on Intraocular Pressure Measurements Using the Ocular Response Analyzer.**

Felipe A. Medeiros, MD and Robert N. Weinreb, MD


**Conclusions:**

- IOPg agrees with Goldmann.
- IOPcc provides an estimate of IOP that is less influenced by corneal properties than those provided by GAT.
- IOPcc is clinically superior to GAT, other NCTs, and iCare because it is a better indication of the true IOP – less correlation with CCT.

**IOPcc Key Benefit #1**

**IOPcc is less influenced by the cornea**

**IOPcc Key Benefit #2**

**IOPcc is superior for glaucoma risk assessment**

**Electrophysiology in Glaucoma**

Electrophysiology objectively measures **strength and speed** of the visual signal to the brain (VEP) or retina (PERG).

**Clinical Applications of Electrophysiology in Ophthalmology**

**ISEEV Indications**

- Inherited retinal dystrophies
- Vascular diseases including diabetes
- Opaque media or trauma
- Retro bulbar neuritis
- Unexplained visual loss
- Infant with questionable vision
- Toxic and nutritional eye disease
- Glaucoma
- Suspected intracranial lesion
“Increased pattern VEP latency was significantly correlated with both the severity and location of visual field defects and the degree of cupping and pallor of the optic disc.”

“Glaucoma has also been reported to affect the VEP by causing both reductions in amplitude and increases in latency.”

Additional Clinical Papers


How Does pERG Work?

Pattern electroretinogram (pERG) is an electrical recording of retinal function in the macula and ganglion cells stimulated by contrast-reversing patterns, usually black and white.

Pattern Electroretinogram (pERG)

- pERGs are electrical signals that are a measure of the electrophysiological activity in the ganglion cells in the retina.
- Can help improve sensitivity and specificity in diagnosing neuropathies and maculopathies like macular degeneration and glaucoma when used in conjunction with other tests.
- Can also help the clinician differentiate between retinal and optic nerve disorders when used in conjunction with Visual Evoked Potential (VEP).

Steady-state pERG

- “At higher temporal frequencies, that is, above 10 rps (5 Hz), the successive waveforms overlap and a “steady-state” PERG is evoked.”
• Per NIH and Bascom-Palmer:

In patients who are glaucoma suspects, PERG signal anticipates an equivalent loss of OCT signal by several years (as many as 8 years).”

DOI:10.1167/iovs.12-11026

Concentric Stimulus Field pERG

Information affecting the central or paracentral area of the macula and ganglion cells: AMD, Plaquenil, Diabetic Edemas

High and Low contrast

Contrast Sensitivity PERG Test

Information affecting the retina in a diffuse pattern: Chronic Open Angle Glaucoma and Diabetic Retinopathy

High Contrast

Low Contrast

New Combo Agent

• Simbrinza

SIMBRINZA
(Trinzolamide/brimonidine)

IOP Control at All Time Points at Month 3

Mean IOP Change from Baseline (mm Hg)

P ≤0.002 vs. brinzolamide or brimonidine across all time points

Katz G, et al. Three-Month Randomized Trial of Fixed-Combination Brinzolamide 1%/Brimonidine 0.2%.
7/13/2017

**GLAUCOMA DRUGS ON THE HORIZON**

**Novel Drugs in Development**

<table>
<thead>
<tr>
<th>Target</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>Adenosine receptor agonist</td>
<td>Santen, Inotek, Acucela/Otsuka</td>
</tr>
<tr>
<td>Cannabinoid receptor agonist</td>
<td>Novartis</td>
</tr>
<tr>
<td>Corticosteroid isozyme inhibitor</td>
<td>AstraZeneca, High Point/Trans Tech Pharma</td>
</tr>
<tr>
<td>Rho kinase inhibitor</td>
<td>Aerie, Kowa, Senju/Novartis</td>
</tr>
<tr>
<td>Nitric oxide donating prostaglandin</td>
<td>Bausch &amp; Lomb</td>
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**Pathways to Lower IOP**

**ROCK/NET Inhibitors**

Inhibitors of Rho Kinase (ROCK) and Norepinephrine Transporter (NET)

**Aerie Pharmaceuticals ROCK/NET Inhibitor Pipeline**

<table>
<thead>
<tr>
<th>Product Candidate</th>
<th>Development Phase</th>
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<tr>
<td>Pharamex™ – ROCK/NET inhibitor</td>
<td>Phase 2 trial began July 2014</td>
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<tr>
<td>Roclatan™ – combination of Pharamex/latanoprost</td>
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Reduces IOP by increasing trabecular outflow, decreasing aqueous production, and lowering episcleral venous pressure

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21 to 35% Mean IOP Reduction at Month 3 Across Both Studies

<table>
<thead>
<tr>
<th>Time</th>
<th>SIMBRINZA™ Suspension (%)</th>
<th>Brinzolamide (%)</th>
<th>Brimonidine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>-25.6%</td>
<td>-17.8%</td>
<td>-17.1%</td>
</tr>
<tr>
<td>10 AM</td>
<td>-34.9%</td>
<td>-22.4%</td>
<td>-25.8%</td>
</tr>
<tr>
<td>3 PM</td>
<td>-24.1%</td>
<td>-16.9%</td>
<td>-14.3%</td>
</tr>
<tr>
<td>5 PM</td>
<td>-29.7%</td>
<td>-17.7%</td>
<td>-23.9%</td>
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Across studies, SIMBRINZA™ Suspension provides 21%–35% IOP reduction.

1,2

†P ≤ 0.005 vs. brinzolamide or brimonidine across all time points


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Netarsudil 0.02% Dose-Response Curve

Rho Kinase Inhibitors

- Several molecules failed clinical trials
- One rho kinase inhibitor (Netarsudil mesylate) in Phase 3
  - Inhibits the enzyme rho kinase
  - Also inhibits norepinephrine transporter (increases adrenergic activity)
- Potentially lower IOP by three mechanisms
  - Increasing TM outflow
  - Reducing episcleral venous pressure
  - Reducing aqueous production (via NET inhibition)

Netarsudil 0.02% Conjunctival Hyperemia

Netarsudil Mesylate Development

Phase 3 Results

- ROCKET-1
  - Missed primary endpoint for full cohort
  - Was non-inferior to timolol in subset of patients with baseline IOP >25 mmHg
- ROCKET-2
  - Achieved primary endpoint (non-inferior to timolol with baseline >25 mmHg)

<table>
<thead>
<tr>
<th>N=208 total</th>
<th>Latanoprost</th>
<th>Netarsudil mesylate</th>
<th>Fixed combination</th>
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<tr>
<td>Baseline IOP</td>
<td>26.4 mmHg</td>
<td>25.4 mmHg</td>
<td>25.1 mmHg</td>
</tr>
<tr>
<td>Final IOP</td>
<td>16.4 mmHg</td>
<td>19.1 mmHg</td>
<td>16.9 mmHg</td>
</tr>
<tr>
<td>IOP Reduction</td>
<td>10.0 mmHg</td>
<td>13.3 mmHg</td>
<td>8.2 mmHg</td>
</tr>
</tbody>
</table>

Netarsudil Mesylate Development

- Phase III studies with mixed results (not yet published)
- Current development plan is in combination with latanoprost
Vyzulta (Latanoprostene Bunod)

Nitric Oxide and Glaucoma

- Patients with primary open-angle glaucoma (POAG) have lower levels of NO synthase activity in the trabecular meshwork (TM), Schlemm's canal, and ciliary muscle.
- NO donors lower IOP in normal and POAG eyes.
- A major site of action for NO donors is the TM.
- NO relaxes the TM and ciliary muscle.
- NO donors increase outflow facility in anterior segments, mediated by a decrease in TM cell volume.
- Endothelial NO synthase (eNOS) overexpression increases conventional outflow and lowers IOP in a mouse eye model.

Efficacy Results: Primary Endpoint

- Phase 2 VOYAGER study
  - At highest doses, lowered IOP 1-1.5 mmHg more than latanoprost.
  - Most common AE: pain upon instillation.

- Phase 3 APOLLO study
  - 420 subjects
  - Two groups
    - Latanoprostene-bunod
    - Timolol 0.5% BID
  - Baseline IOP
    - 25.7 mmHg for LBN
    - 25.5 mmHg for timolol
  - IOP reductions:
    - 8-9 mmHg for LBN
    - 6.5-7.5 mmHg for timolol
  - Adverse events:
    - Similar rates between groups
      - Most common:
        - Eye irritation
        - Conjunctival hyperemia

Latanoprostene-bunod

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Vyzulta

- Nitric Oxide (NO) donating prostaglandin F2α agonist that is rapidly metabolized in situ to latanoprost acid and BDMN, a NO-donating moiety.
- Exhibited potent and effective intraocular pressure (IOP)-lowering activity in 3 ocular hypertensive glaucoma animal models.

BDMN: Butanediol mononitrate.
TRABODENOSEN (INO-8875)

- Inotek
  - Adenosine-1 receptor agonist (action is on trabecular meshwork)
  - Preclinical trial demonstrated ganglion cell preservation
  - 2014 ARVO presentation
  - Primary phase in 2012 (IOP reduction of 7 mmHg at 28 days)
  - March 10, 2014 Phase II trial in conjunction with latanoprost
  - 120 patients with OHTN/POAG
  - Assess synergistic effect of Trabodenosen to Latanoprost
  - 7/19/2015 filed an S-1 with SEC for an IPO up 132.25 million

Singapore Nanyang Technology University

- 2/11/2015
  - Injectable glaucoma medication
  - Extended release Nanotechnology
  - Six patient initial trial 2013
  - Anticipated submission to US clinical trials 2016

Punctal Plugs with Latanoprost Core

MATI Therapeutics
- 44-g Latanoprost Punctal Plug Delivery System
- Phase II
- Data:
  - Mean change from baseline -3.5 mmHg
  - 36% showed reduction of >/= 5 mmHg
  - Overall goal of 90% retention/Initial 75%
  - Second generation plug 90%
  - Goal of therapy 90 days of Tx

Mati Therapeutics

- AUSTIN, Texas, Oct. 28, 2013 (GLOBE NEWSWIRE) -- Mati Therapeutics Inc. ("Mati") today announced the initiation of a Phase II trial of its L-PPDS drug delivery system in patients with ocular hypertension or primary open angle glaucoma. The study will be a U.S.-based, randomized, multi-center trial of approximately 100 patients treated with L-PPDS or timolol eye drops for up to 14 weeks. The primary end point for the study is the change from baseline in intraocular pressure (IOP). A number of secondary endpoints will also be evaluated.
  - This trial is the first trial to compare L-PPDS to timolol eye drop therapy. Results from this trial are expected by the third quarter of 2014 and will be used to determine the appropriate study design for a potential Phase III pivotal trial of L-PPDS. To date, more than 570 subjects have been treated in various L-PPDS dosing Phase II studies. The Phase II study will evaluate a 95ug formulation of latanoprost.

Ocular Therpeutix

- Phase II trial of OTX-TP2
- Hydrogel plugs that deliver travoprost
- Umhlanga Medical Center & Netcare Alberito Hospital, South Africa
- 20 patients (up to 40 eyes) with OHTN or Glaucoma
- 88% retention at one month
Contact Lens Embedded IOP Lowering Drug

- Dean Ho, UCLA Dentistry School Research Team
- Nanogel that is embedded in CL's
- IOP lowering capacity
- Uses nanotechnology with small diamonds that timolol until tear enzymes (lysozyme) activate it
- The octahedron structure of the nanodiamonds has a unique charge that binds drugs to its surface
- Chitosan, A natural polymer is used to bind the drug
- Anticipated NDA is 2016

Drug Eluting Contacts

- Harvard Medical Center Researchers
- Recipients of MIT Innovators in Life Sciences competition
- Daniel Kohane, MD, PhD (anesthesiology)
- Coating Polyactic co-glycolic acid (PLGA) is coated with films containing Polyhydroxy-methacrylate by UV polymerization
- Research is being funded by:
  - National Institute of Medical Studies
  - National Eye Institute
  - Boston KPro foundation
- Duration can be as long as 100 days
- Limitation will be the duration of CL wear

Bimatoprost Sustained Release (SR)

- Sustained release formulation of bimatoprost
- Bioerodable implant injected into AC in clinic setting
- Phase 3 study underway comparing SR to timolol

Envisia Therapeutics

- ARVO 2014
- ENV515 Intracameral Implant with a polymer implant that has an extended release formulation of travoprost
- 30% IOP lowering in beagles at 24 weeks
- CEO Ben Yerxa
- Utilizes PRINT (Particle Replication In Non-Wetting Templates) technology
- Anticipated NDA 4Q 2015

MIGS – Micro-Invasive Glaucoma Surgery

- Ab-interno approach
  - Clear corneal micro-incision (<2.0mm)
  - Conjunctival sparing
- Minimally Invasive
  - Negligible disruption of normal anatomy/physiology
  - Excellent biocompatibility
- Efficacious
  - Extremely high safety profile
  - Rapid recovery

MIGS: Not Just a Soviet Fighter Jet Anymore
Current OAG Treatment Algorithm

- Newly Diagnosed OAG Patient
- Prescription Therapy (80 – 90 days)
- Laser Trabeculoplasty
- Switch to Add Rx Therapy

Drug therapy has been the standard of care in glaucoma for over 30 years. Approximately 20% of patients may require surgery 10 to 15 years after initial diagnosis due to the disease management challenges of glaucoma and financial burden in patients and the healthcare system.

Glaucma Treatment Factors Beyond IOP Lowering Effect

- Therapy Factors
  - Dosing schedules and multiple OHT prescriptions
  - Costs, office visits, and staff time
  - Side effects and interactions

- Patient & Lifestyle Factors
  - Busy schedule, forgetfulness
  - Co-existing Conditions, Tolerance

Effect of Cataract Surgery on IOP Reduction

According to the AAO Preferred Practice Patterns, cataract surgery with IOL implantation alone results in a modest reduction in IOP of less than 2mm Hg on average.

Selective and Argon Laser Trabeculoplasty

- Compared to medications, SLT demonstrates similar IOP reductions (6–8mm Hg from baseline), safety, and tolerability, and no issues with compliance/adherence.
- Following laser trabeculoplasty, many patients require the addition of medication to maintain target IOP.

Filtering Surgery – Trabeculectomy

- “Gold standard” for glaucoma surgery – creates a “bleb” (artificial outflow pathway).
- 47% cumulative probability of failure after 5 years.
- Re-operations carry high failure rates.
- High complication rate.
- Over filtration, hypopyon, 1.2% annual risk of endophthalmitis.
- 78% increase in risk of cataracts.
- Hyphema, anterior chamber shallowing, choroidal detachment, suprachoroidal hemorrhage

Primary Source of Resistance: Diseased Trabecular Meshwork

- Abnormality of the trabecular meshwork (TM) is the primary source of elevated intraocular pressure (IOP) in open-angle glaucoma.
- 50-75% of total resistance to aqueous humor outflow is found in the juxtacanalicular tissue of the TM.
- Bypassing the TM allows access to Schlemm’s canal and the distal system in order to improve aqueous outflow through the conventional outflow pathways.
Trabeculectomy with Express Minishunt

Retrospective Case Series

- Final percent IOP lowering was similar
- Moorfields Bleb Grading System
  - Less vascularity and height but more diffuse area associated with the Ex-PRESS blebs
  - Fewer cases of early postoperative hypotony and hyphema
- Quicker visual recovery
  - The Ex-PRESS group required fewer postoperative visits compared with the trabeculectomy group (P < .000).

Ex-PRESS in prior operated eyes

- Success complete in 60(60%) and qualified in 24 (24%) eyes
- Mean IOP
  - 27.7 ± 9.2 mm Hg with 2.73 ± 1.1
  - 14.02 ± 5.1 mm Hg with 0.72 ± 1.06 drugs (p < 0.0001)
- Failure
  - Uncontrolled IOP (11%)
  - bleb needling (4%)
  - persistent hypotony (1%)

iStent\textsuperscript{\textregistered} Indication for Use

The iStent Trabecular Micro-Bypass Stent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication

Distribution of Aqueous Veins

(Among 409 Aqueous Veins)
**Aqueous Veins**

- **Recipient Episcleral Vein**
- **Aqueous Vein**

**iStent® Surgical Procedure**

- iStent rails are seated against scleral wall of Schlemm's canal
- iStent Snorkel sits parallel to the iris plane

**Co-Management Considerations**

- iStent implantation is described by CPT code 0191T
- 0191T is a Category III code (new technology)
- Category III codes do not have global periods assigned
- Carriers will not recognize:
  - Modifier -04: surgical care only
  - Modifier -55: all/part of outpatient post-operative care
- Modifier -54 and -55 can still be appended to 66984
- In localities where Medicare has a higher physician payment for 0191T than for 66984 and where the payment for 66984 is reduced by 50%, payment for 66984-55 will be reduced by 50%

**iStent® Pivotal US IDE Trial**

- Prospective, randomized, multi-centered study of POAG patients who underwent iStent + cataract surgery vs. cataract surgery alone
- 290 subjects at 29 sites
- 280 randomized subjects with cataract and mild-to-moderate OAG (1:1 randomization)
- 50 additional non-randomized subjects for safety
- **Patient population**
  - Mild-to-moderate POAG (also PXE and PDS)
  - IOP ≤ 24 mm Hg on 1-3 medications
  - Post-medication washout IOP 22–36 mm Hg
- **Efficacy endpoints**
  - Primary: IOP ≤ 21 mm Hg without medications at month 12
  - Secondary: IOP ≤ 21 mm Hg without medications at month 12
  - Follow-up through 2 years postoperative

**US IDE Trial – Primary Endpoint**

- Percent of Patients with IOP ≤ 21 mm Hg Without Medication Use

- At 12 months, 72% of iStent® subjects with IOP ≤ 21 mm Hg without medication vs. 50% with cataract surgery alone (P<0.001)

**Photo courtesy of Ike Ahmed, MD**

**Photo courtesy of Tom Samuelson, MD**
Patients implanted with a single stent in conjunction with cataract surgery had significantly greater IOP reductions from baseline (21.1%) compared to patients having cataract surgery alone (15.9%) at 12 months. At 1 year, 66% of patients in the iStent + cataract surgery group were medication-free compared to 48% with cataract surgery alone (P=0.003).

The results support iStent® as an effective treatment option for mild to moderate open angle glaucoma and cataract. Ophthalmology 2011; 118:459-467.
XEN Glaucoma Implant™ Materials and Methods

**Materials**
- Permanent, collagen derived, gelatin implant, 6 mm long
- Implant is soft, compressible, and flexible when hydrated
- Material and design mitigate traditional implant issues
  - Absence of Migration
  - Tissue-conforming
  - Non-inflammatory

**Methods**
- Pre-loaded, disposable Inserter
- Handles like IOL inserter
- Straightforward procedure
- With or without cataract surgery
- Removable and/or repeatable
- Mild, Moderate & Refractory Glaucoma

**XEN Glaucoma Implant™ Mechanism of Action**

**Ab Interno Sub-Conjunctival Drainage**
- Surgical “Gold Standard” IOP reduction in minimally invasively procedure
- Clinically proven outflow pathway
- Bypasses all potential outflow obstructions
- Conjunctiva sparing: alternative surgical options remain
- Single implant delivers desired effectiveness

**Gelatin Material is Tissue Conforming**

**Video 1: Outflow Mechanism Of Action - Rabbit Eye 6 Months Postoperative**

**XEN Animation**

**POAG Only**

<table>
<thead>
<tr>
<th>Time Post-op</th>
<th>Mean IOP</th>
<th>Mean % Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 day</td>
<td>13.9</td>
<td>-20%</td>
</tr>
<tr>
<td>1 month</td>
<td>14.0</td>
<td>-21%</td>
</tr>
<tr>
<td>3 months</td>
<td>14.1</td>
<td>-20%</td>
</tr>
<tr>
<td>6 months</td>
<td>14.2</td>
<td>-21%</td>
</tr>
<tr>
<td>12 months</td>
<td>14.5</td>
<td>-23%</td>
</tr>
<tr>
<td>18 months</td>
<td>14.6</td>
<td>-22%</td>
</tr>
<tr>
<td>24 months</td>
<td>14.7</td>
<td>-23%</td>
</tr>
<tr>
<td>30 months</td>
<td>14.8</td>
<td>-22%</td>
</tr>
<tr>
<td>36 months</td>
<td>14.9</td>
<td>-23%</td>
</tr>
</tbody>
</table>

*Mean preoperative IOP is best medicated. Patients were not washed out prior to surgery.*
**InnFocus, Inc.**

- Based in Miami, Florida
- Founded in 2004
- Biomaterials-based company
- Have worked closely with Bascom Palmer Eye Institute
- Two of the three inventors of the InnFocus MicroShunt are from BPEI
  - Francisco Fantes, M.D.
  - Jean Marie Parel, Ph.D.
- The third inventor is Leonard Pinchuk, Ph.D., D.Sc., who is the President and CEO of InnFocus.

**The Lessons Learned for Glaucoma Drainage Devices:**

- Keeping a small lumen tubular device with no reservoir open in the subconjunctival/subTenons space can be accomplished by:
  - Use of an antiproliferative drug to stop the initial insult from surgery - MMC
  - Use of a very inert biomaterial to construct the device that minimizes the long-term foreign body reaction - SIBS

**The Material:** No degradable bonds leads to minimal inflammation and fibrotic reaction

- Ultra-stable backbone with no ability for side groups to come off

**The Device:** The InnFocus MicroShunt™ (previously known as the MIDI MicroShunt™)

- Outer diameter is 350 µm
- Lumen diameter is 70 µm
- 8.5 mm long
- Matches the compliance of ocular tissue
- Conforms to the curvature of the eye
- Use of a very inert biomaterial to construct the device that minimizes the long-term foreign body reaction - SIBS

**The Device:**

- Does not require a cadaver patch
- Soft, flexible, rubbery, no erosion
- Aromatic free present
- Migration
- Peritubular leakage
- No MRI interference

---

**Initial Clinical Results: From A Multi-Center Study on Early Moderate Stage Population**

<table>
<thead>
<tr>
<th>Group</th>
<th>% Reduction</th>
<th>Mean IOP (mmHg)</th>
<th>Mean Post Op Meds</th>
<th>Mean Meds</th>
<th>Post Op Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>1.3</td>
<td>11.9±3.5</td>
<td>0.9±0.6</td>
<td>1.1±0.5</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>InnFocus MicroShunt</td>
<td>38%</td>
<td>12.0±3.5</td>
<td>0.9±0.6</td>
<td>1.1±0.5</td>
<td>1.3±0.6</td>
</tr>
</tbody>
</table>

**Initial Clinical Results: From A Multi-Center Study on Severe/Refractory Population**

<table>
<thead>
<tr>
<th>Group</th>
<th>% Reduction</th>
<th>Mean IOP (mmHg)</th>
<th>Mean Post Op Meds</th>
<th>Mean Meds</th>
<th>Post Op Meds</th>
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</tr>
</tbody>
</table>
Protocol INN-005

- **Study Objective:** The study objective is to assess the safety and effectiveness of the InnFocus MicroShunt when used to lower intraocular pressure (IOP) in subjects with primary open angle glaucoma where the IOP is not controlled when using maximum tolerated glaucoma medications.

**INN-005**

- **Phase I**
  - 2:1 treatment: control randomization
  - 102 subjects treated (approx. 170 enrolled)
  - Submit with 75 subjects at 3 month follow-up to start Phase II
- **Phase II**
  - 3:1 treatment: control randomization
  - 412 subjects treated (approx. 687 enrolled)
  - Overall Randomization of 2.8:1 and 416 subjects at 24 months follow-up after lost to follow-up