

New Tools for the Toolbox

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24 Hour Contact Lens Sensor

- Weinreib, Mansouri, Romenet
- Accurate and reproducible method to measure nyctohemeral IOP rhythm
- “Triggerfish”
- Significant rhythm detected
- Nocturnal disease nature of glaucoma
- Sleep lab studies in Obstructive sleep apnea
- Consider especially in low tension glaucoma

Glaucoma as a Two Pressure Disease

- Intracranial space and intraocular space are two fluid filled compartments separated by the lamina cribrosa
 - If pressure on one side (IOP) matters than why wouldn't pressure on the other matter?
 - CSF pressure begins to drop after age 40-50, same time when glaucoma prevalence increases
 - ICP lower in patients with normal tension glaucoma & high tension glaucoma compared to normal
 - ICP is lower in normal tension vs high tension glaucoma
 - Theory is laminar deformation caused by translaminar pressure difference of IOP & ICP
 - Squeezes axons of RGC's as they travel through nerve
 - Disrupts axonal transport leading to cell death
- Glaucoma is multifactorial and IOP is only one factor

Glaucoma Pipeline

- Intracranial cerebrospinal fluid pressure (CSF-P) is lower in glaucoma
- Trans-laminar pressure difference (TLPD)
 - $TLPD = IOP - CSFP$ (normal is 4-8mmHg)
 - Lumbar measurements not as accurate as orbital CSF-P
 - MRI offers high resolution of optic nerve diameter (OND) and sheath diameter (ONSD) and optic nerve subarachnoid space width (ONSASDW)
 - Is a reliable predictor of CSF pressure

Evolving Views on IOP

- IOP is a causal risk factor in development of glaucoma at all levels of IOP
- IOP plays a role in every eye with glaucoma
- Knowledge of IOP is not necessary to diagnose or detect progression in glaucoma
- What aspects of IOP behavior is most responsible for glaucoma progression?
 - Mean IOP/ Peak IOP/ we don't know!
- Home tonometry is coming into practice and will help identify patterns of IOP
- Ocular perfusion pressure (OPP) is a risk factor for development of glaucoma (low OPP)
 - Difference between systemic BP & IOP

New Functional Testing

- Pattern ERG (PERG) – improves with decreased IOP
- Multifocal VEP – higher flicker VEP
- Isolated Check VEP
 - Tests central vision
 - Bright Check Pattern (M-cells)
 - Dark Check Pattern (off pathway cells)
- Pupil perimetry (True Field Analyzer)
 - Computer measures pupil (involuntary) diameter in response to retinal visual stimulation

Glaucoma & the Brain

- Researchers view Glaucoma as a disease of the brain
 - Neurodegenerative disease
- Glaucoma shares common features with AD, Parkinson's and Lou Gehrig's diseases
- Offers potential for new treatments that promote nerve health, neurotrophic factors which can help at multiple places in the visual pathway
 - Neuroprotection – Ciliary neurotrophic factor (CNTF)
 - Neuroregeneration – increase axon regrowth
 - Neuroenhancement – improve support between dying RGC and surrounding cells in brain and retina

Low Tension Glaucoma

- Compromised ocular blood flow
- 50% have a cause / find it / fix it
 - Past hx transfusions, bleed, hypovolemic
 - Medications: B-blockers, digoxin, digitalis
 - MRI: orbits & brain
 - R/O all cardiovascular causes of LTG
 - CBC/anemias, CA doppler, TEE, sleep studies, coagulaopathies (PTT), overly fit (low BP)
- Treatment
 - Decrease IOP, avoid B blockers, start with PG, bromonidine, CAIs last resort
 - Ginko biloba 60mg/D: inc fluidity without affecting platelet aggregation

Characteristics of Glaucoma in Japanese Americans

- Pekmezi M ArchOphthal 2009;127(2):167
- 1732 patients in Japanese-American clinic over a ten year period
 - 112 with glaucoma, 17% HTG, 70% NTG
- Proportion of patients with NTG was 4-fold higher than those with HTG

Do Superactivated Platelets Explain Disc Hemorrhages in Glaucoma?

- Disc Hemorrhage is a poor prognostic sign in ALL studies
- University of Chicago – SAPs associated with AD, TIA, corticle stroke
- Hemorrhages of optic nerve head and nailfold capillary bed characterize POAG
- Suggest that SAPs play a role in POAG
 - POAG patients display an elevated level of activated SAPs which are hyper coagulable

Do Superactivated Platelets Explain Disc Hemorrhages in Glaucoma?

- Platelets provide role in blood coagulation and circulate until they encounter thrombogenic elements and become activated, sometimes becoming superactivated
 - Phenotypically different and possess enhanced procoagulant and prothrombogenic activity
- Videocapillaroscopy to quantify vascular changes in the nailfold region demonstrated hemorrhages in 96.8% POAG, 92.3% LTG, secondary glaucoma 75%
 - 6 fold more hemorrhages than controls but different between all 3 forms of glaucoma (?)...new screening tool or ancillary

What is the Next BIG THING?

- Latanoprostene bunod (Vyzulta) by Valeant/B&L-Nicox
 - Novel nitric oxide donating prostaglandin F2a analog
 - Decreases IOP 7.5mm-9.1mm from baseline between weeks 2 &12 in phase 3 trials
 - Superior to timolol
 - Met endpoints both primary and secondary
 - Once daily dose

What is the Next BIG THING?

- Netarsudil 0.02% (Rhopressa) by Aerie Pharma
- FIRST NEW MECHANISM OF ACTION in 20 years
- Triple action
- Inhibits rho kinase (ROCK) & norepinephrine transporter (NET), both biochemical targets for lowering IOP and reduces episcleral venous pressure (EVP) by 35%
 - ROCK inhibitors increase outflow via TM which is 80% of drainage from eye
 - NET inhibitors reduces production of aqueous
- Once daily dose

What is the Next BIG THING?

- Netarsudil 0.02% (Rhopressa) by Aerie Pharma
 - Downstream effect of small-G protein Rho
 - Potential to modify disease course by arresting fibrosis of TM
 - Suppresses activity of profibrotic proteins TGF-B2, CTGF on TM cells
 - Lowering EVP may help LTG or angle closure types
 - Theory – TM relies on aqueous percolation to supply nutrients, antioxidants
 - Diverting into uveoscleral outflow may not be good for TM long term health
- Mean IOP average reduction 6mm (?stand alone)

What is the Next BIG THING?

- Netarsudil 0.02% / latanoprost 0.05% (Roclatan) - Aerie
- Quadruple action – more impressive
 - Mean IOP 25.1 decrease to 16.5 on day 29
 - 2mm better than latanoprost alone
- Combination of triple action Rhopressa & Latanoprost
- Efficacy – superior to latanoprost
- Only glaucoma product covering full spectrum of currently known IOP lowering mechanisms of action
- Once daily dose
- SE - hyperemia

Glaucoma Market to Grow to \$3B

- 2.3 Billion grows to 3 Billion by 2023
- Projected growth in seven major markets – US, France, Germany, Italy, Spain, UK and Japan is 2.4%
- Driven by first in class drugs
- Roclatan is forecast to achieve the highest sales expected to generate 262million in 2023
- Increase attributable to introduction of new drugs between 2013 and 2023 and overall increase in glaucoma prevalence
 - Mostly due to aging society in the US

Anti-Glaucoma Agents

■ Prostaglandin Analogue

- Latanoprost (Xalatan 0.005%) generic 3/2011
- Bimatoprost (Lumigan 0.03%, Lumigan 0.01%*)
- Travaprost (Travatan Z 0.004%) – No BAK
- Tafluprost (Zioptan PF)

■ The future – 7 PGA drugs currently being developed for sustained drug delivery systems

- Nanoparticle size for injection

Latanoprost 0.005%

- Topical prostaglandin
- Indications: open angle glaucoma or ocular hypertension
- Side effects – hyperemia of conjunctiva, iris pigmentation/color change, lid erythema, eyelash growth
- Dosage: once daily at bedtime
- Advantages: monotherapy/compliance, favorable SE profile, longest track record, generic March 2011
- Available as *Xalatan*
- *Sustained release punctal plug coming soon!!*

Bimatoprost 0.03% & 0.01%**

- Topical prostaglandin
- Indications: open angle glaucoma or ocular hypertension
- Side effects – hyperemia of conjunctiva, iris pigmentation/color change, lid erythema, eyelash growth
- Dosage: once daily at bedtime
- Advantages: monotherapy/compliance, favorable SE profile with lower concentration but equal IOP lowering
 - Switch when having SE with other PGs or as first line PG
- Available as *Lumigan, Lumigan 0.01%*
- *Subconjunctival depo & external implant coming !!*

Bimatoprost 0.03% & 0.01%**

- ForSight Vision5 – Helios Insert
 - Polymer bimatoprost matrix in a soft compliant ring 26mm in diameter
 - Applied to ocular surface in office maintained under lids
 - Mean IOP reduction at 6 months of 6.5mm
- Allergan – developing Bimatoprost SR
 - The amount of drug in implant is equivalent to one drop bimatoprost
 - Safer, less drug exposure, less side effects
 - Delivered intracamerally, prefilled single use applicator
 - Drug depleted in one year, implant gone in 2 years
 - POAG pts live 16 yrs / 32 injections / leave behind benign

Travoprost 0.004%

- Topical prostaglandin
- Indications: open angle glaucoma or ocular hypertension
- Side effects – hyperemia of conjunctiva, iris pigmentation/color change, lid erythema, eyelash growth
- Dosage: once daily at bedtime
- Advantages: monotherapy/compliance, favorable SE profile, long track record
- Available as *Travatan-Z*
- *Coming soon as medicated punctal plug*

New Ideas in Glaucoma

- Minimally Invasive Glaucoma Surgery (MIGS)
 - Micro-stents emerging from trials, recent FDA approvals
 - Studies (COMPASS/phase 3) showing limited efficacy of third IOP lowering agent
 - Makes argument for MIGS after failing with two topical Rx's
 - Safer but less effective than older bigger surgeries
 - Goal – MIST/minimally intrusive sustainable therapy not maximally tolerated medical therapy
- Glaukos iStent
- Solx Gold Implant
- AqueSys XEN Gel Stent

New Ideas in Glaucoma

- Minimally Invasive Glaucoma Surgery (MIGS)
 - Endocyclophotocoagulation (ECP) / Endo Optiks
 - iTrack catheter (iScience)
- Nocturnal hypotension – risk factor for glaucoma
 - Ambulatory 24 hour BP monitoring is routine in clinical practice and can identify nocturnal dips in BP
 - Reduction in dose of blood pressure medications may be helpful
 - If PCP deems this inappropriate ingestion of salty snack like small bag of potato chips before bed may help prevent dips

Endocyclophotocoagulation -ECP

- Reduces production of aqueous fluid by utilizing laser energy to treat the ciliary processes
 - Disables some of the ciliary epithelium
 - Works on inflow production of aqueous
 - Ideal procedure to combine with cataract surgery
 - Endoscope can be inserted through same incision for cataract surgery
 - Expect 20-30% drop in IOP
 - Drop in IOP is not immediate like filtering surgery but improves with post operative decrease in inflammation
 - Requires viscoelastics out of the bag to move iris for probe

Schlemm Canal Scaffold Implant

■ Hydrus / Invantis

- Alone or in combination with cataract surgery
 - 1.5 mm incision
- Mild-moderate glaucoma
- 8 mm long device, flexible nitinol
- Enters canal, resides in canal, provides tension on inner wall

■ Results in significant, durable decreases in IOP and medication use

- Best results in combined surgery – 16.6mm/0.1 Rx @24m
- Alone results – 18.6mm / 0.5 Rx @24m
 - 70% less use of medications

Glaukos iStent Trabecular Bypass

- Smallest medical device approved by FDA
 - 1mm long, 0.33mm height, snorkle 0.25mm x 120um, 60ug
 - Nonferromagnetic titanium single use, sterile inserter
- Approved for mild-moderate glaucoma
- Placed during cataract surgery
- Spares tissues damaged by traditional procedures
- Contraindicated in NVG, PAS, primary or secondary angle closure glaucoma, angle abnormalities
- Adverse events – corneal edema, loss of BVA > 1 line, PCO, stent obstruction

360 Degree Trabeculotomy

- One use disposable device
- Alone or combined with cataract surgery
- Canaloplasty = 44% IOP reduction
- Tears and unroofing of schlemm's canal and juxtacanalicular tissue
- Average IOP decreases from 24.4mm to 13.7mm
- Topical Rxs decrease from 1.5 to 0.2 @ 12m
- Advantage – easy, outpatient, option to delay trabeculectomy, less side effects

360 Degree Trabeculotomy

- iTrack catheter 250u
- Initial use was for childhood glaucoma with poor prognosis, Failed goniotomy, infantile glaucoma after cataract surgery, infantile glaucoma associated with ocular or systemic conditions, progressive congenital glaucoma and corneal clouding
- Outcomes 87-92% successful
- Trabeculotomy codes already exist
- Formerly iScience Surgical
- Now iScience Interventional, Menlo Park CA

CyPass Micro-Stent / Transcend Medical

- Stent the supraciliary space and augments uveoscleral outflow (like iStent Supra)
- Targets suprachoroidal outflow in redirecting aqueous outflow
- Fenestrated micro-stent 6.35mm long and 510u in diameter
- Polyimide material
- Ab interno insertion is easier than other stents
- Results – reduction in IOP by 33% and 50% decrease number of medications at one year

XEN Gel Stent - AqueSys

- Gel stent is preloaded in a disposable injector with a 27-gauge needle and delivered into the non-dissected Tenon space creating a connection from the anterior chamber to the subconjunctival space
 - Bypasses Schlemm's canal entirely
- Experimental in US; Europe for mild-moderate glaucoma, & advanced w efficacy similar to trab
- Ab interno collagen pre-loaded implant of cross linked porcine gel that hydrates on insertion
 - 3 lumen sizes: 140u, 63u, 45u
 - 1mm in AC / 3mm in sclera / 2mm in subconj space
- 40% reduction in IOP at 36 months, 74% reduction in Rx
- Adverse events – hyphema, choroidal effusion

InnFocus Microshunt

- Small stent is creating a connection from the anterior chamber to the subconjunctival space
 - Bypasses Schlemm's canal entirely
- Polystyrene-block isobutylene
- Experimental in US; Europe for mild-moderate glaucoma, & advanced w efficacy similar to trab
- Ab externo approach with conjunctival dissection
- More appropriate for advanced disease requiring lower IOP
- Adverse events – hyphema, choroidal effusion

Neuroprotectants

- Memantine (NAMEDA) – blocks Na, K channels, retards apoptosis
- Brimonidine(?)
- Ciliary neurotrophic factor – CNTF phase I as implant
- BDNF – inhibits programmed cell death
- Erythropoietin- EPO
- Future is neuroprotection to improve environment and
 - neurodegeneration with stem cells
 - Neuroenhancement supports injured RGCs before they die
 - Immunobiology with T cell based vaccination

Nanosensor IOL

- Fraunhofer Institute in Germany
 - Microelectric Circuits and Systems IMS
- Implant sensor for continuous IOP monitoring
- Integrated a 2.5 by 2.6 millimeter sensor in an IOL
- The top and bottom of the sensor are electrodes
 - The top electrode is flexible, bottom of the sensor is rigid
 - When the intraocular pressure increases, the top electrode is pushed in, reducing the distance between the top and bottom of the sensor and thus increasing the capacitance
- Implant sends the pressure data to a reader that is fitted into the frame of a pair of spectacles
- An antenna in the spectacle frame supplies the sensor with the required energy via an electromagnetic field
- Currently undergoing clinical trials
- Could come available in two to three years time

Nanosensors IOP

- MIT Technology Review
- A pressure sensor to measure glaucoma IOP
- Tiny microchip implanted subretinal
- The sensor is designed to measure IOP
 - wirelessly transmit the data to computer
- One of the major obstacles in creating this type of device is designing a tiny but highly functional chip that uses very little power
 - Sensor runs on nanowatts rather than on microwatts
- The researchers began testing the implant in animals last December

Adalimumab (Abbvie) for Uveitis

- 1st & only Anti-TNF for treating NI Uveitis
- Previously approved for psoriatic arthritis
- Steroid-sparing option proven to prolong time to a disease flare and decrease visual acuity
- Indicated – treatment of NI intermediate, posterior and panuveitis
- AE – URI, sinusitis, HA, rash, reactivation of HBV
- Warnings – TNF rarely cause CNS and peripheral demyelination (MS, Optic neuritis, Guillain-Barre)
- Available as – *Humira*

Malaria Drug Delivery Device

- Science Translational Medicine study – MIT, Brigham & Women’s Hospital developed a new oral drug capsule that unfurls into a star shape that temporarily remains in stomach releasing drug for up to 2 weeks
- Especially helpful in disease treatment like malaria
 - Also HIV, Alzheimers, TB
 - Resource constrained or remote locations, long term therapy
- Modifications to “linkers” may allow treatments for months or longer
- Treating 70% with ivermectin and malarial medications would be as effective as malarial treatment for 90%

Breakthrough in Acanthamoeba

- Miltefosine (Impavido) – received orphan drug designation from FDA
- Indication – treatment of acanthamoeba keratitis

Impantable Miniature Telescope

- Prosthetic device sealed into carrier plate
 - Fused quartz crystal
 - PMMA clear carrier
 - PMMA (blue tint) light restrictor
- Vision Care Ophthalmic Technologies
 - Saratoga, CA
 - 408.872.9393

Corneal Inlays

- Trying to create surgical alternative to monovision and multifocal contact lenses
- “modified monovision”- won’t correct above -2D
 - 1.50D best
- Can use spectacles for distance and stereo-binocularity
- Placed in Pocket under LASIK flap
- Creates depth of focus & Improves reading vision
- Less distance in operative eye
- Ease of removal, exchange, repositioning
- Loss of contrast sensitivity

Effective Presbysurgery

- Must be extraocular
- Must preserve distance quality vision
- Must provide improved functioning at intermediate and near
- Should not require perpetual enhancement or revision
- Must be reversible
- Pocket techniques are viewed as superior in cornea inlay surgery as they maintain structural integrity, avoid issues of flap striation, preserve corneal nerve health, allow quicker healing

Corneal Inlays

- KAMRA (AcuFocus, Irvine CA)
 - Creates pinhole effect with 1.6mm pupil
 - Benefit – good distance is preserved OU
 - Good continuous range of vision at near
 - Decrease in night vision
 - Placed in pocket at 400um depth under LASIK flap
- Raindrop (Revision Optics, Lake Forest CA)
 - Creates depth of focus
 - Less distance vision but better near
 - Loss of contrast sensitivity, Halos at night but regain after 1 year
 - Placed directly under LASIK flap

Scleral Implants for Presbyopia

- VisAbility Implant (Refocus Group, Dallas TX)
 - 4 small clear plastic implants
 - Inserted below scleral surface
 - Vaulting of sclera lifts underlying ciliary muscle

New Era in Refractive Surgery

- Optimization – continuous improvement of a technique or technology
- Goals of a better procedure
 - Cornea remains intact
 - Flap-less / minimally invasive
 - Single system / no patient relocation
 - Less denervation / dry eye
 - Predictability

ReLEx SMILE Procedure / Zeiss

- Small Incision Lenticule Extraction
- Micro-Invasive refractive surgery is here
- Paradigm shift is COMING
- Combines femto-second laser technology
 - VisuMax/Zeiss
 - Creates thin disc of tissue inside intact cornea
- Precise lenticule extraction through small incision
- 80,000 eyes worldwide (China, Asia, Europe)
- Single surgery
- No excimer

ReLE_x SMILE Procedure / Zeiss

- Benefits to patients and surgeons
 - Cornea remains intact
 - Cap incision is 80% shorter (20mm now is 4mm)
 - Far less dry eye
 - No flap related complications
 - Single system and no relocation of patient
- USA clinical trials now treated 255 patients
 - 1-8 D / 22-54 yrs / -5.00D average
 - 100% 20/20 or better / no scatter of results
 - 90% within 0.25D at one week / MRSE = +0.02D
 - Look better / See better / feel better than LASIK fellow eye

Argus II / Second Sight Medical/USC

- Creating the bionic eye for retinitis pigmentosa
- Approved by FDA on Feb 14, 2014 as humanitarian use device (affecting <4000/yr)
- US Dept of Energy, National Eye Institute at NIH and National Science Foundation collaborated and provided grant funding over \$100 million to support development of Argus II
- Intended to be implanted in a single eye, worse seeing
- Criteria: >25 yrs, LP or NLP intact inner retina function, past history of useful vision

Argus II / Second Sight Medical/USC

- External hardware of glasses with miniature video camera on nasal bridge transmits images via a wire to battery operated videoprocessing unit worn on the belt
- VPU transforms image into electrical stimulation delivered to a transmitting coil on side of glasses, then sent wirelessly to receiving coil sutured to sclera
- External equipment wirelessly powers the internal implant
- Internal receiving coil and electronics case secured to sclera in a buckle fashion, sent to cable through sclerotomy into eye terminating at epiretinal 60 electrode

Argus II / Second Sight Medical/USC

- Array tacked to retina-choroid-sclera
- Artificially stimulated RGCs transmit signals through axons via functioning optic nerve and tract to LGN, radiations and occipital cortex forming pixelated light images
- General anesthesia with 4 hr duration of surgery
- Post implantation device adjustments done with laptop
- Vision rehabilitation sessions - usually 5-10 for learning to use head, camera etc
- 1st important step in artificial vision for blind patients

Smartlux Portable Electronic Magnifier

- Portable CCTV, 7 oz
- Non-reflective, hard coated 5" LCD screen
- Switch between black on white, white on black, black on yellow, yellow on black
- Magnification is 5X, 7X, 9X, 12X
- 3 screen brightness levels
- Freeze frame function, stores 20 images
- \$595.00
- Eschenbach

CEPHALY / Cephaly Technologies

- Newest treatment for migraine prevention
- Headband uses low dose emission of stimulating electricity
- FDA approved > 18 years age
- Drug free, 20 minute per day
- Portable, battery operated, RX only, \$300
- “counter-irritant” in CNs
- Widely used in Australia, Canada, Europe
- Studies in Belgium finds less use of drugs, significantly fewer HAs, did not eliminate HAs or severity

Corneal Collagen Cross-Linking

- Progressive keratoectasia
 - progressive corneal disease
 - Refractive surgery
 - No treatment
- New treatment, old concept
 - Natural occurrence within cornea and lens
 - 4.5% increase in fibril diameter
 - Dentistry- hardens material for fillings
 - Polymer industry-hardens adhesives
 - Cardiology-glutaraldehyde hardens heart valve
 - Uses UV light & riboflavin

Collagen Cross-Linking (CXL)

- ***Riboflavin*** – photosensitizing agent
 - Excited to triple state by UV
 - Releases radicals
 - Causes hydrogen bonds between AA in collagen chains
 - At the intra & interhelical levels
 - Increases collagen diameters and spacing
- Treatment for keratoconus (1/2000, 20% need PK)
 - Pellucid marginal degeneration
 - Bullous keratopathy
 - Corneal melts/Infectious keratitis
 - LASIK ectasia

Collagen Cross-Linking (CXL)

■ Contraindications

- <400 μ corneal thickness (endothelia damage)
- Incisional refractive surgery

■ Procedure overview

- Epithelial debridement (+/-)
- Ribo 0.1% apply every 2-5 min for 30 mins
- Exposure to UVA irradiation for 30 mins (370nm, 3mW/cm²)
- Add ribo every 2-5 min for shielding
- Treatment diameter 7-9mm
- Post-op treatment same as PRK

■ Results last 2-7 years, may need retreatment

Collagen Cross-Linking (CXL)

- Future applications
 - Keratoconus
 - Poor refractive surgery candidates - can now have surgery
 - Better outcomes - for good candidates for refractive surgery
 - Adjunctively in all laser refractive procedures to provide better structural support of the cornea long-term
- Not FDA cleared here yet but access is available

Myopia Control in Children

- Atropine Treatment of Myopia (ATOM)
- Atropine 0.01% once daily reduces progression of myopia by 50%
- Tried 0.01%, 0.1%, 0.5%, 1.0%
 - Higher concentrations stopped eye growth better but worse when stopped
 - No rebound effect with lower concentrations
 - Treated for 2 years
 - 1 year wash out period
 - 2 year follow-up period
 - Glare 1%

New Ideas in Corneal Surgery

- Top 4 indications for keratoplasty
 - Fuch's
 - Pseudophakic corneal edema
 - Keratoconus
 - Graft failure
- Procedures today are PK, DSEK, DMEK, DPEK
 - DMEK superior to DSEK
 - Now DPEK which includes Dua's layer in donor
 - Allows younger donors
 - Descemet's is 3u at birth and 8-10u in 50 year olds
 - Easier to handle

New Ideas in Corneal Surgery

- 5 Layers of Cornea
 - Epithelium
 - Bowman's – 1800 in England
 - Stroma
 - Descemet's – 1700 in France
 - Endothelium
- 6th layer proposed by Harinder Singh Dua at University of Nottingham in England
 - 15um
 - Denser than stroma
 - Adherent to endothelium

Ocriplasmin / ThromboGenetics, Inc

- Non surgical treatment for vitreomacular adhesions
 - Increased macular thickness
 - CME Diagnosed 8% at slit lamp 30% with OCT
- Vitrectomy vs Vitreolysis?
 - Invasive
 - Anesthesia
 - Face down
 - Retinal breaks
 - Cataract

Ocriplasmin / ThromboGenetics, Inc

- Truncated form of human plasmin produced by bacteria
- Indications: developed for dissolving blood clots in vascular disease
- Single Intravitreal injection
- Results – resolution 30% at 28 days, closure of hole 40% at 28 days
 - better than all other agents tried
- Spin offs – DME, AMD, adjunct to vitrectomy
- New England JourMed 2013
- *Available as Jetrea*

YAG Photoablation-Vitreous Floaters

- Laser photoablation vaporizes opacities into small gas bubbles that dissolve quickly
- Indications – stable floaters x 2 mos, complete PVD, no flashes or pathology
- Strips electrons, creates a plasma, a mini nuclear reaction
- Results – 1/3rd moderate benefit to 100% depending on study; multiple treatments possible
- Wagle AM, et al Am J Ophthal 2011
 - Found symptomatic pts willing to trade 11% of remaining life and take 7% risk of blindness to get rid of floaters
- *Available as Ultra Q Reflex / Ellex Medical Lasers LTD*

Cliradex

- Essential all natural effective cleanser for lashes, face and eyelids
- Indicated in blepharitis and rosacea
- Wash hands and face
- Close eye tightly
- Cool refreshing menthol sensation
- Use one side of towellete per eye
- Keep eye closed for one minute
- Biotissue.com

Cliradex

- Preservative free\essential oil
- 4-terpinol organic compound
- Melaleuca alternifolia – natural tea tree oil
- Box – 24 individually wrapped towelettes per carton
- Cases of 20 cartons
- On-line purchase
- Biotissue.com

Hypochlorous acid 0.01%

- Lid hygiene product
- Rx only
- Excellent broad spectrum microbial coverage for MGD and blepharitis
- Hypochlorous acid is released by PMN white cells (neutrophils) when attacking invading organisms
- Spray a cotton round and clean lids and lashes BID
- Tested against 20 common eyelid organisms
 - Reduced numbers by 99.99% in 60 seconds
- Available as *Avenova* by NovaBay

LipiView[®] Indications for Use

- An ophthalmic imaging device that is intended for use by a physician in adult patients to capture, archive, manipulate and store digital images of specular (interferometric) observations of the tear film, which can be visually monitored and photographically documented.
- No known contraindications

LipiFlow® Indications for Use

The LipiFlow® System is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD), also known as evaporative dry eye or lipid deficiency dry eye.

MiBoThermalFlo

- Ultrathermal Therapeutic Medical Device
- Touch screen / LCD display (12in x 5in)
- Chronic dry eye treatment, 98% patient satisfaction
- Tip temp 108 degrees (manual)
- Heat element is 6w thermoelectric
- Timer is 1-16 minutes (average 12min)
- No pain or down time, warm message
- Painpointmedical.com 855.642.6356

BlephEx by RySurg

- Newest treatment for blepharitis
- In office procedure performed by doctor
- Similar design to Alger brush
 - Hand held, low torque, charger
 - Use topical anesthesia, gloves, eyeprotection/magnification
 - Consent
- Precisely eliminates scurf and bacterial debris
- Not covered by insurance
- Average cost to patient \$120, repeat every 3-6 months
- www.RySurg.com

Sjo Test for Sjogrens Syndrome

- Sjogrens Syndrome is common autoimmune disease affecting exocrine glands
 - 4 million in USA
 - 3 million undiagnosed!!
 - ODs are on the frontline
- Symptoms – DE, dry mouth, nose, joint pain, RA, fatigue, reflux, bronchitis, peripheral neuropathy, liver and kidney dysfunction, 5-10% lymphoma
- Diagnosis – salivary gland biopsy and biomarkers
 - 4.7 years to diagnosis

Sjo Test for Sjogrens Syndrome

Diagnosis – American College of Rheumatology (old way)

SS-A, SS-B, RF, ANA, lip Bx, vital stains of eye

40% sensitivity (changed criteria 12 Xs since 1965)

Diagnosis – Sjo Test (Nicox)

in-office blood panel test, small fingerstick collection

4 traditional markers and 3 proprietary markers

Salivary gland protein / carbonic anhydrase-6

/ parotid secretory protein

90% specificity

Sjo Test for Sjogrens Syndrome

- Sjogrens Syndrome is treated early with drugs that target B-cells and TNF, typical monoclonal antibodies
- Early detection spares organs damage and improves outcomes, lowers cost burden
- Builds relationships between Optometry and primary care and rheumatology
- Sjogrens Syndrome Foundation - www.Sjogrens.org
- Nicox – www.nicox.com

Lifitegrast/SARCode Biosciences Brisbane CA

- T cell modulator similar to cyclosporin but FASTER
 - Starts in 2 weeks!!
 - Phase II
- Lymphocyte function-associated antigen (LFA-1) inhibitor of intracellular adhesion molecules (ICAM-1)
- Prevents binding of T-cell mediated inflammation (LFA-1 to I-CAM-1)
- Works on *active* T lymphocytes
- Cyclosporin works on the *production* of T lymphocytes which takes 100-110 days to complete a cycle of inflammation

InflammaDry (Rapid Pathogen Screening)

- Matrix Metalloproteinase (MMP-9) is the best biomarker for ocular surface disease & dry eye
- Developed as a simple in office test to predict and prevent problems after LASIK and other surface surgery
- Also as a test for dry eye disease
- FDA reviewing now
- Will be available as *InflammaDry*

Tear Lab

- “Lab on a Chip”
 - We have a test!
 - Analogy of treating DM without BG, HA1c etc
 - No longer needs CLIA, COLA, inspection, etc
- Gold cartridge draws nl of fluid and processes
- Osmolarity is the global marker of Dry Eye (DEWS Report)
 - Least variable test for DE
 - Central mechanism in pathogenesis of DED
 - More variable results seen in more advanced disease
 - Large differences between eyes noted, increasing with disease severity
 - 308mosml = Dry Eye
 - Sensitivity 72.8%/Specificity 92%
 - No other clinical sign or test is better than 62%

Tear Lab Severity Scale

- 280-300 Normal
- 300-320 Mild
- 320-340 Moderate
- 340+ Severe

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- 280-300 Normal
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Osmolarity Highest Positive Predictive Value of DED

- Osmolarity 87%
- Schirmer's 31%
- TBUT 25%
- Staining 31%
- Meniscus height 33%
- Dry Eye Workshop Report 2007 OculSurf 2007;5:2 Tomlinson A, et al IOVS. 47(10) 2006

Tear Lab

- Corneal tests and symptoms DO NOT correlate with disease
 - 30% of DE patients are ASYMPTOMATIC
 - Took 7 times for FDA to clear Restasis
 - May not see another drug
- 2007 DEWS Report - MGD most common cause of DE
 - Mucin is everywhere in the three layers of tear film
- Tear Osmolarity in Diagnosis & Management of Dry Eye, Lemp, M AmJ Ophth 2011;151:792-798
- Objective Approach to Dry Eye Disease Severity, Sullivan, B Invest Ophth Vis Science Dec 2010 Vol 51 No 12

Dry Eye Center of Excellence

- Diagnostic Testing Center of Excellence
 - Tear Osmolarity (Tear Lab)
 - MMP-9 for inflammation (InflammaDry / RPS)
 - Meibomian Gland imaging (Tear Science)

Dry Eye Pipeline

- Loteprednol with membrane penetrating vehicle (KalaPharm/Mass)
- Dextenza 0.4mg (OTX/Mass) – Slow release dexamethasone intracanalicular depot
- Cyclosporin Multi-dose PF bottle Restasis
- Mucin-enhancing neurotrophin - (Mimetogen Pharm/Mass) – increases mucin and epithelial healing
- Tru-Tear (Allergan) – Nasal neuro-stimulator increases lacrimal tear production by stimulating trigeminal fibers

TrueTear Neurostimulator (Allergan)

- User controlled Nasal neuro-stimulator increases lacrimal tear production by stimulating trigeminal fibers
- Prescription device, drug free, drop free device, quick
- Well tolerated, mild side effects
- Electric charger, disposable tips (change daily)
- “Dose” – at least twice daily, more if needed, no longer than 3 minutes per application, no retreatment sooner than 1 hr

TrueTear Neurostimulator (Allergan)

- AE – lightheaded, itchy nose, nosebleeds, nasal pain (10%), sore eye, sinus pain, nasal ulcer, chronic nosebleeds
 - most less than 1%
- Contraindications – cardiac pacemaker, defibrillators, cochlear implants, hemophilia, no use in bath/shower, driving, within 3 ft of microwave therapy, flammable anesthetics, not proven in aqueous deficient dry eye
- Results of trials in 2 sites, N=48, F 81%, >22yo, shirmer <10, Staining score 2/4
 - Treated Av Shirmer – 25 / Sham – 9.2

Human Tear Serotonin Correlate with Symptoms and Signs of DE

- Many w DE describe neuropathic pain in absence of any noxious stimuli; phenotypic alterations and sensitization of peripheral nerves could occur
- Free nerve endings interdigitate between epithelial cells and are vulnerable to T cells, MMPs, interleukins, TNF
- Study support peripheral as well as central (pain) sensitization of ocular somatosensory nerves in DE
- Expands new therapeutic biomarkers and target for therapy
- Ophthalmol 2015;122:1675 Chhadva P et al

Amniotic Membrane Transplantation (AMT)

- Ocular surface reconstruction in SJS, severe dry eye, and severe chemical burns
- Human amniotic membrane prepared from placenta of elective cesarean section in seronegative (HIV, HepB & C, syphilis)
- Facilitates epithelialization, reduces inflammation, vascularization and scarring
- Limbal stem cell transplantation is needed in concert with AMT in the most severe chemical burns

Amniotic Membrane Transplantation (AMT)

- Acelagraft (Dehydrated Human Amniotic Membrane Allograft)
 - Highly organized matrix
 - 100% human derived
 - Non-immunogenic
- Cost
 - 1x2 \$315
 - 2x3 \$390
 - 4x4 \$480

Coding for Prokera Ring

- CPT code is 65778
- Description – placement of amniotic membrane on ocular surface for wound healing; self retaining
- Global period – 10 days
- Medicare allowable range - \$1150-1700
- Cost of goods – \$800-950 depending on volume

2Win Binocular Handheld Refractometer & Vision Analyzer

- Fully automated binocular refraction
- Operates at 1 m
- 7 second exam, no drops
- Small portable
- Battery operated
- Ideal for infants, children, disabled or non cooperative patients
- Acoustic and light targets built in
- www.2winforvision.com 408 716 3271

DRS Digital Retinography System

- Fully automated retinal imaging
- Auto-sensing, auto-alignment, auto-focus, auto-flash adjustment
- Both eyes in one minute
- Compact clean design
- Motorized chin rest
- 40-45 degrees field of view
- Embedded PC, ethernet & Wi-Fi connectivity
- www.centerview.com Padova, Italy, Santa Clara CA

Retinoblastoma Advance

- Super-selective Ophthalmic Artery Chemotherapy as Primary Treatment of Retinoblastoma Abrams, D Ophthal 2010;117:1623
- “Chemo-surgery”
- Ophthalmic artery can be safely and repeatedly cannulated in very young children
- Deliver high concentration (low dose) chemotherapy infusion on outpatient basis
- Prevents radiation, enucleation, and systemic chemotherapy

Retinoblastoma Advance

- Ophthalmic Artery Chemosurgery for Retinoblastoma Prevents New Intraocular Tumors Abramson, D Ophthal 2013;120:560-565
- New anterior tumors are found after treatment of primary tumor (XRT or chemo) in 24-48%
- OAC eyes demonstrate fewer new intraocular retinoblastomas; suggests ophthalmoscopically undetectable tumors present at initial diagnosis
- Less EUA, lower costs, higher ocular survival, less anxiety, avoidance of sided effects of repeated focal treatments

New Ideas in OCT

- Ultra-widefield with angiography
 - Extends multi-modality of Spectralis platform
 - Diseases are underestimated for lack of peripheral angiography
 - Can image out to 150 degrees
- Multi-color Imaging – Spectralis
 - High contrast, noise reduction, eye tracking
 - 3 simultaneously acquired selective color laser images
 - Versatility to view individual or multicolor images
 - Identifies pathology unclear on fundus images

Widefield Imaging Technologies

- Optos 200TX – 200 degree view or 80% of retina
 - 2 lasers off ellipsoid mirror and proprietary software
 - Images not affected by media opacities
- Spectralis/Heidelberg – add on ultrawidefield angiography module
 - Lens based system, warpage of image inherent
- Avanti / Optovue – Widefield Enface OCT
 - 40 degree field of view

Peripheral Autofluorescence in AMD

- Colin, et al Ophthal 2013;120:127-1277
- Distinct patterns of peripheral FAF abnormalities were seen in 68.9%
- AMD type correlates with Peripheral FAF changes
 - Neovascular type more common, non-neovascular type, then normals
- Age – any peripheral FAF abnormality was associated with older age
- Female patients had a higher risk of abnormal peripheral FAF compared to males

Widefield Imaging Future

- Significantly higher rate of peripheral autofluorescent abnormalities among eyes with AMD
- Both Granular fluorescent changes and patchy hypofluorescent were common in eyes with advanced AMD
- Patchy hypofluorescence was common among patients with geographic atrophy
- Peripheral pinpoint hyperfluorescent drusen may precede the development of more advanced disease process in the macula
- Tan et al Peripheral autofluorescence in NV AMD *Ophthalmology*. 2013;120(9):1271-77

Multi-Spectral Imaging (MSI)

- “virtual angiography”
- Non-invasive alternative to IVFA
- Valuable adjunct to OCT
- LEDs from 550-950nm
 - Image in pairs
 - Full series is 6 flashes/12 images
 - Shorter wavelengths image inner retina layers (ex VMA)
 - Longer wavelengths image outer retina layers (ex AMD)
- Useful to gauge effects of drugs, neutraceuticals, major benefit in dry AMD

Optos OCT SLO

- Microperimetry assesses retinal sensitivity
 - Monitors course of disease and response to treatments
- Precise correlation between pathologic structure & functional defects
- Only device on market conducts OCT & functional MP testing
- MP testing runs in conjunction with high confocal SLO
 - With tracking of vessels
 - Faster perimetry
 - More accurate change over time assessments compared to SAP

Diabetic Eye Diseases – The Next Wave

■ Three Level Surge

- Baby Boomers – 28% US population

 - AMD & DR

- DM surge

- Affordable Care Act (ACA)

 - Adds 32 million new covered lives

 - Many have not had proper medical care

 - Many have not had proper eye care

■ “Gluttons for Punishment” – Lancet 21 July 2012, 380

- Americans comprise 5% of world population and account for 33% obesity, overfed for first time in history, inactivity results in as many deaths as smoking

Lens Fluorescence Biomicroscope

- ClearPath DS-120 / Freedom Meditech
 - Recently approved
 - Non-invasive, biophotonic quickly detects lens autofluorescence
 - 8 seconds
 - Quantitatively
 - Confocal scanning laser reflectance microscope
 - Pupil tracker
 - Long life blue LEDs
 - Electronic transmission to EHR or other referral sources
- Eliminates fasting, blood draw, waiting time, biohazard burden

Lens Fluorescence Biomicroscope

- Screens for Elevated Advanced Glycolated End products (AGEs)
 - High correlation to uncontrolled glucose
 - Irreversible AGEs in crystalline lens
 - Benefit as a screening tool compared to HgA1c
 - Linear relationship exists between age & autofluorescence
 - Uncontrolled glucose causes deviation in the relationship
- Available in three configurations to fit any office layout

Alcon / Novartis & Google (x)

- Announced collaboration exclusive agreement to license “Smart lens” technology
 - Accommodative CLs
 - Accommodative IOLs – (1.7 Billion presbyopes)
 - Glucose sensing smart CL for Diabetes
 - Wireless connectivity to mobile device
- Google (x) special team designed driverless cars and GoogleGlass
 - “Moonshot” task team

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Promise of Implantable Drug Delivery Systems

- Humans are clumsy, forgetful, imprecise and undependable....high tech drugs are not
- Benefits - longer lasting, highly localized, accurate concentration, fewer side effects
- Reservoir implants – require surgical placement/replacement, simple, longevity, steady state
 - Retisert, Iluvien, I-vation
- Biodegradable implants – no need for removal, less toxicity
 - Ozurdex

Promise of Implantable Drug Delivery Systems

- Vitrasert – 1996 approved for CMV implant of gancyclovir, pars plana insertion
- Retisert – next generation, better target and duration, pars plana insertion and suture, good for uveitis but IOP elevations and cataract are problematic
- Iluvien – fluocinolone intravitreal implant, for AMD (wet & dry) and DME
- Ivation – treatment of DME, implantable titanium screw coated with triamcinolone, self anchors into sclera

Promise of Implantable Drug Delivery Systems – Innovations on Tap

- Biosilicone Technology – pSiividia nano-structured porous silicone, bioerodable, handles any molecule size
- Replenish Media Pump – microelectromechanical device delivers continuous or bolus targeted drugs to ant/post segments via flexible cannula and refillable reservoir system (30 g needle), most of device is outside eye...”reverse-drainage glaucoma device”
- Encapsulated Cell Technology (ECT) – delivers large molecules to retina, stores complex proteins at 37degrees C without degradation

Promise of Implantable Drug Delivery Systems – Innovations on Tap

- Encapsulated Cell Technology (ECT) –
 - Genetic engineering of RPE cells via plasmid transfection
 - Plasmids encode a therapeutic protein, in to cell genome
 - Engineered cells loaded into polymer membrane capsule and inserted into vitreous
 - Continually produce the therapeutic protein
 - No need for long term drug storage
 - “makes the bread fresh daily”
 - Testing now with ciliary neurotrophic factor (CNTF) in retinal disease

Promise of Implantable Drug Delivery Systems – Innovations on Tap

- Envisia – designs and manufactures micro and nanoparticles systems to deliver drugs on nanoscale
- GreyBug – micro and nanoparticle delivery systems for companies with drugs but not delivery vehicles,
- Kala Pharma – mucous penetrating particles (MPPs) to pierce mucosal barriers providing sustain drug concentration only possible before w injection or implant
- pSividia – Durasert delivery system is miniature and injectable; coming w latanoprost, fluocinolone implant, and DME drug, Tethadur system to release avastin

Ozurdex – Dexamethasone Intravitreal Implant 0.07%

- 1st & only injectable dexamethasone implant
- For non-infectious uveitis of the posterior segment
- For macular edema following BRVO or CRVO
- Solid polymer matrix biodegrades to lactic acid and glycolic acid
- Delivered by injection as in office procedure (22-gauge)
 - Ergonomically designed applicator for single use, preloaded
- Contraindicated in advanced glaucoma

Ozurdex – Dexamethasone Intravitreal Implant 0.07%

■ Posterior uveitis results

- 46.8% of treated patients had resolution of vitreous haze at 8wks
- 42.9% gain >15 letters (3 lines) from baseline at week 8

■ BRVO / CRVO

- 9.8 letters gained at day 60

■ IOP data

- 13.9% with >10mmHg increase from baseline IOP at day 60
- 3.2% with >35mmHg increase from baseline IOP at day 60

Iluvien Implant (Alimera)

- Fluocinolone 0.19% injectable implant (intravitreal)
- 3.5mm long x 0.37mm diameter
- Treatment of Diabetic macular edema (DME) in patients previously treated with corticosteroids, that did not have increased IOP
- Single implant delivers steroid for 36 months
- AE
 - cataracts (82%, sham 50%),
 - Increased IOP (34%, Sham 10%)

DME Cost Comparison

- Drug / Cost / No. treatments / 3 yr Total Cost / FDA status
- Iluvien / \$8,800 / 1 / \$8906 / Approved
- Eyelea / \$1,850 / 22 / \$43K / Approved
- Lucentis / \$1,170 / 22-36 / \$28-\$45K / Approved
- Ozurdex / \$1,333 / 5-12 / \$7-17K / Approved
- Avastin / \$50 / 22-36 / \$3-6K / Unapproved

Rifampin as Efficacious Therapy for CSR

- Chronic Central serous chorioretinopathy is sometimes difficult to treat in a small number of patients
- No universally accepted standard exists for this macular disease
- Rifampin (Rifadin/Sanofi) – on forefront as it increases metabolism of endogenous steroids as a consequence of the inductive affect on cytochrome P450
- Promising, cost effective, efficacious therapy for CSC of 6 months duration encroaching on Macula

Improving Prognosis in Melanoma

- Diagnosis / treatment for uveal melanoma has improved
- Cancer related mortality rates remain unchanged
- Gene expression profiling divides uveal melanoma into two molecular subgroups
- Mutations in 2 related genes present in 90% of UM
 - GNAQ & GNA11
- 40% UM develop mutation in BAP1 (BRCA associated protein 1)
 - Confers high risk of metastasis
 - Associated with monosomy 3 (a tumor suppressor gene)
 - Loss of BAP1 causes UM cells to behave like CA stem cells

Improving Prognosis in Melanoma

- DecisionDx-UM / Castle Biosciences
 - PREDICTS accurately which patients will develop metastatic disease
 - Provides foundation for targeted therapies
 - Several investigations underway evaluating potential therapies
 - Earlier intervention would prevent metastasis and improve longevity

Thank you

McGreal Educational Institute

Missouri Eye Associates

Excellence in Optometric Education