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### **Resolvix Pharm/Cambridge Mass**

- 10,000 times more potent than fish oil in anti-inflammatory effect
- Improves corneal disease
- Increases goblet cells
- Safe
- Synthesized form dietary lipids like fish oil
- Finished phase II, starting phase III
- Will be available as *Resolvin Analogues*
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### **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 ICAM-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
- 

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### **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*
- 

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### **Tear Lab (Focus Labs)**

- "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
- 308mosmsl = Dry Eye
- Sensitivity 72.8%/Specificity 92%
  - No other clinical sign or test is better than 62%

#### 7 **Tear Lab (Focus Labs)**

- 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  
AmJOPhth 2011;151:792-798
- Objective Approach to Dry Eye Disease Severity, Sullivan, B  
InvestOphthVisScience Dec 2010 Vol 51 No 12

#### 8 **Rifaximin for DE in Rosacea**

- Semi-synthetic rifampin-based non-systemic antibiotic
  - Very little drug passes GI wall into circulation
- Indications
  - Small intestine overgrowth, IBS, Travelers' diarrhea
    - 98% of papillo-pustular rosacea have SIBO
  - Diagnosis requires GI consult and breath test
    - Lactulose test
  - Different mechanism than doxycycline
  - Interfers with transcription of B subunit of bacterial RNA polymerase
  - Cure for rosacea in one treatment
- Available as *XIFAXAN 550mg tid x 14 days*

#### 9 **DE Pipeline**

- Interleukin (IL-1) blocking agents
  - Different mechanism than cyclosporin
- Steroid subclass – SEGRAs
  - Selective glucocorticoid receptor agonists
  - Mapracorate – compound offers steroids' breath of effects without the cataracts or IOP side effects

#### 10 **Lipiflow Thermal Pulsation System**

- Device for treating dry eye and blepharitis/MGD
- 12 min in office procedure
- Applies heat to posterior eyelids and intermittent pressure to front of eyelids
  - Releases MG obstruction
- FDA approval July 2011
- MG regain function in 4 weeks

- Results last one year
- Tearscience.com

11  **Hyaluronidate Gel Contact Lens**

- Composition
  - Hydrogel component – structural support
  - Hyaluronidate – soluble biopolymer
  - Minerals found in tear film
- Material – methafilcon A
- Water – 55%
- DK/T – 31 (-3.00D)
- BC- 8.6 Diam-14.1 CT-0.08mm
- Front surface – Aspheric
- Power - +4.00 to -8.00

12  **Hyaluronidate Gel Contact Lens**

- Asphericity – masks -1.00D cylinder, adds +0.75 for near
- 1 HA molecule binds 3000 times its weight in water!
- Warmth releases HA on both sides of lens
- Blinking releases HA into tear film
- Only available to ECPs and no on-line channels
- Available as *SAFIGEL 1 day*
- 877.723.4435
- www.safigel.com

13  **Steroids for Corneal Ulcer Trial (SCUT)**

- Multi-centered, double blind, randomized
- N=500
- Ulcers major cause of corneal scarring
- 4<sup>th</sup> leading cause of blindness worldwide
- Treatment goals
  - Elimination of bacterial (now within days)
  - Prevention of scar formation (occurs in “successful” cases)
- Prednisolone 1% not started for 48 hrs pending cultures
- Results – no improvement in BVA at 3 mos, no increase in adverse events either

14  **Ganciclovir ophthalmic gel 0.15%**

- Anti-viral
- Indications
  - HSV keratitis
- Action – inhibits DNA replication
- Side effects – blurred vision, irritation, SPK
- Dose – one drop 5 times per day until dendrite resolved, then TID for one week
- Available as
  - Zirgan/Sirion

15  **Autologous Serum for PED, DES**

- Tears contain EGF, vitamin A, TGF-B, fibronectin and other cytokines.....all found in serum

- 40ml of blood from venipuncture centrifuged for 5 min
  - diluted to 20% by physiologic saline (empiric)/UV bottle
  - Dosed at 6-10 X/D with additional AFTs
- Results
  - 43% healed within 2 wks, all within several months
  - Serum accelerates migration of corneal epithelial cells
  - Serum upregulates mucin expression of corneal epithelium

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### **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

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### **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

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### **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

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### **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
- 

20  **Collagen Cross-Linking (CXL)**

- Contraindications
  - <400u 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/cm<sup>2</sup>)
  - 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
- 

21  **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

22  **Tomorrow's Best IOLs**

- Calhoun Vision, Inc.
  - Next generation "*adjustable*" material, unique, unstable, silicone, foldable
    - Cross-linked silicone polymer matrix - Mechanical and optical properties
    - Macromer - Low molecular weight links to photoreactive group
    - Photoinitiator - Organic molecule dissociates into free radicals, begins polymerization on exposure to special wavelengths, moving macromer down diffusion gradient into radiation area thickening the lens

23  **LAL - IOLs**

- 2 weeks post-operative UV protection required
- Adjust refractive error at 2 week post-op
  - Uses 380nm exposure of light at slit lamp system
- Next perform lock-in
  - Pink tint is commonly reported 1-2 days post lock-in
- Not cleared in US but Canada, Europe etc

24  **Accommodating IOLs**

- Electro-optic diffractive IOL (Elenza)
  - Monofocal IOL with central aspheric modification
    - Far & intermediate vision
  - Smart electro active diffractive liquid crystal
    - Near
    - Microsensors detect physiologic triggers of accommodation (pupil)
    - Onboard processors & algorithms to control power sequence
    - Lithium ion power cells – weekly charge

25  **Implantable Miniature Telescope**

- Indicated in advanced AMD
  - 75 years of age, no previous cataract surgery in one eye
  - Adequate Endothelial cell counts and Anterior chamber depth
- FDA & CMS approved
- Wide angle micro-optics in combination with cornea create telephoto system
- Galilean design
- 2.2-2.7X enlargement of retinal image
- 3.6mm diameter, 4.4mm length (size of pea)

26  **Implantable 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

27  **Cataract Surgery in The Future**

- Biconvex optic of 9mm, injectable copolymer
- Accommodative
- 1 piece design
- Wavefront adjustable
- Power customizable
- Photochromic
- Surface modified or drug impregnated
- Implantable through a 1mm incision

28  **Tafluprost**

- Topical prostaglandin, first preservative-free preparation
- Indications: open angle glaucoma or ocular hypertension
- Supplied: 10 PF ampules per pouch, 3 pouches/box
- Side effects – same as other PGA
- Dosage: once daily at bedtime
- Storage: refrigeration necessary until pouch is opened, then once opened room temperature is fine
- Available as *Zioptan*

- 29  **Glaucoma Evaluation is Transforming**
- In the past, detection & management relied on functional assessment
    - Visual fields (white-on-white)
      - Insensitive for detecting early POAG
      - High degree of variability
  - Recently, structural change over time longitudinal studies have validated the role of structural imaging
    - Are structural defects with normal functional tests false positives or POAG?
- 30  **RAPDX (Konan Medical)**
- Automated pupillographer
  - Assesses differential amplitudes and latencies of pupil responses
  - Far better than human clinical assessments
  - Earlier detection of glaucoma, normal tension glaucoma, MS, infarcts, tumors
- 31  **Salzberg Reading Desk (SRD Vision)**
- Device precisely & automatically measure reading performance parameters under conditions of changeable luminance & contrast
  - Consists of stereo infrared webcams, laptop, high resolution monitor, operating software
    - Subjects read into microphones with progressively smaller type size with software signal processing
  - Advantages – measures at subjects preferred reading distance
  - 2-5 min test time
- 32  **Salzberg Reading Desk (SRD Vision)**
- Applications
    - Pre & post-op reading acuity
    - Compare efficacy of reading devices
    - Acuity measurements for multifocal IOLs & contact lens
    - Real world understandable objective measurement of reading performance
  - Future applications
    - Determine add powers for multifocal IOLs
    - VA measurements at all distances
    - Monitor progression of retinal diseases (AMD)
- 33  **i-Care Tonometer**
- Hand held, portable
  - NO ANESTHESIA
  - Disposable probe
  - Accurate
  - Power – AA batteries
  - Measurement in 0.1 sec
    - Measures motion of cornea
  - Digital display
  - Memory – last 10 results
- 34  **i-Care Tonometer**

- Applications
  - Eye MDs
  - ODs
  - General practitioners
  - Pharmacy
    - Screenings
  - Veterinarians
  - Consumers
    - Self screenings

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**NEW Icare® PRO**

- Professional expertise for glaucoma diagnostics and clinical follow-up
- Rechargeable batteries and docking station with integrated charger & data transmission

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**Icare® Tonovet**

- Useful tool for measuring intraocular pressure on animal patients (dog/cat, horse)
- Painless => creates no anxiety in the animal
- Measurement barely noticed by the animal
- 
- Veterinary ophthalmologists
- 
- Other veterinary medical personnel
- 

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**EyeQuick Digital Ophthalmoscopic Camera**







- Bilateral
- Requires Interpretation
  - separate report form
  - narrative in body of medical record, on date of service
- Hand-held device, portable, bedside, prone
- Can capture anterior segment or posterior segment images, both still or video
- View images on LCD or Transfer to computer
- [www.EyeQuick.com](http://www.EyeQuick.com) 800.596-8335

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**Volk Pictor**

- Bilateral
- Requires Interpretation
  - separate report form
  - narrative in body of medical record, on date of service
- Hand-held device, portable, bedside, prone
- Non mydriatic, automatic focusing, 1920x1440, -20to+20D
- Can capture anterior segment or posterior segment images, otoscopic or dermatologic, still or video
- View images on LCD or Transfer to computer via USB



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  - [www.volk.com](http://www.volk.com) 309.854.1408 Peter Bergstrom
  - **Visual Field 9208x**
  - Bilateral
  - Requires Interpretation
    - separate report form
    - narrative in body of medical record, on date of service
  - Fee \$43.88- (-81) \$57.37+ (-82) \$65.92- (-83)
- 40 
  - **Other Important VF Studies**
  - Paczka (2001) - found FDT better overall performance in detecting damage than RNFL photographs
  - Kondo (1998), Wu (2001) - In patients with SAP VFDs restricted to 1 hemifield, FDT has shown to be able to detect functional losses in the other hemifield
  - Medeiros (2004) – functional defects in FDT predict future defects on SAP
- 41 
  - **Other Important VF Studies**
  - Kim (2007/AAO) – when SAP is normal, some patients with VFD detected by FDT showed decreased NFL thickness (OCT)
    - Provide evidence that coincident FDT & OCT abnormalities may be an early sign of glaucoma
  - Fan, X (2010/Ophthal 117:1530) – FDT detected defects in 2/3rds of study eyes, predicted future defects in SAP
- 42 
  - **Visual Field Testing for Specific Functions**
  - Short wavelength autoperimetry (SWAP)
    - Bistratified ganglion cell (9%) short-wavelength cones
  - Frequency doubling technology (FDT)
    - Magnocellular ganglion cells
  - Motion automated perimetry (MAP)
    - Magnocellular ganglion cells (3%)
  - High pass resolution perimetry (HPRP)
    - Parvocellular ganglion cells
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  - **Opto-Global / Optos**
  - New perimeter
  - AP 100, AP 200
  - Flicker
  - SWAP
  - SAP
  - Screening and threshold testing
  - Network ready
  - Competitive aggressive pricing
- 44 
  - **Octopus 301 Perimeter**
  - 1 ■ Motorized auto eye tracking
  - 100% fixation control
  - Blazing fast speed, testing 30 degree field
  - Ergonomic design patient friendly
  - Blue yellow testing in 3 min/eye
  - Critical fusion testing

- One min screen
- Three min full threshold
- PeriTrend Analysis
- LAN ethernet
- 900 series tests 90 degree field
- 800.787.5426 [www.haag-streit.com](http://www.haag-streit.com)

45  **Current Perimeters are Highly** **Variable**

- 1 ■ After *one* abnormal visual field test:
  - 86% of patients test within normal limits on next exam
  - 
  - After *two* consecutive abnormal test results:
    - 66% of patient test within normal limits on next exam<sup>1</sup>

46  **Closing Statements**

- Advances in perimetry are continuing
  - Faster third generation algorithms reduce test time by 50%
- Customization for specific needs
  - Early detection / established glaucoma / screening
- Early VF loss is often selective, with specific types of axons disturbed
  - SWAP allows early recognition, HPRP follows progression
- SAP perimetry will continue to be preferred for established glaucoma with VFDs
  - Considerably improved methods of computer-assisted interpretations of serial VFs
- Screening methods will sacrifice sensitivity for specificity and ease of use to detect the half of glaucoma patients who have undiagnosed disease
  - Deployed in non-professional environments
  -

47  **Ophthalmic Genetics**

- Researchers have identified genes for OAG
  - TIGR/Myocilin = juvenile OAG
  - OPTN (optineurin) = Primary OAG (NTG)
    - Optineurin may provide neuroprotection to optic N
  - CYP1B1 = Congenital glaucoma
- Genetic testing will allow clinicians to determine if Pt is predisposed to or affected with specific type of glaucoma, even before symptoms appear
- OcuGene (InSite Vision/Alimeda) – simple, in office test, 99% accurate detection of TIGR (trabecular meshwork inducible glucocorticoid response gene)
  - Positives may be treated more aggressively, earlier
  -

48  **Surgical Glaucoma Therapy**

- Future directions
  - Newer antifibrinolytics
    - CAT-12, a monoclonal antibody to TGF-B2

- Photodynamic therapy
- Novel drug delivery systems
  - Collagen implants, bioerodable polymers, liposomes & microspheres
- Glaucoma drainage implants instead of filtering surgery
  - Shunts aqueous from AC tube through an episcleral plate
- Ocular genetics
  - Discover genes, gene therapy, primary prevention of glaucoma may become a reality



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## **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



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## **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

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## **Visual Evoked Potential**

- Nova-DN VEP Vision Testing System (Diopsys)
  - Not new technology, but clinically useful and affordable is
    - Improves sensitivity & specificity in glaucoma diagnosis
  - Short duration transient VEOP (SD-tVEP) to record electrical responses of the entire visual system
  - Objective test, 4-6 minutes
  - Low contrast testing – health of magnocellular pathways
  - High contrast testing – health of parvocellular pathways
  - Serial tracking of disease progression
  - Useful in MS, TBI, Stroke and other CNS disorders

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## **Visual Evoked Potential - Coding**

- Nova-DN VEP Vision Testing System (Diopsys)

- CPT: 95930
  - Bilateral
  - No CCI bundling edits in office setting
- ICD – includes many optic nerve and retina disorders, visual disturbances (amblyopia, SVD, night blindness, sudden vision loss, et al), neurological (aphasia, MS, Lyme, TBI, intrcranial diseases, conversion, gait abn, coordination, etc
- Fee: \$133.19 (range \$60-\$180 commercial)
  - 
  -

55 

### **Nova-VEP**

- Device - \$35,000
- Patches - \$80
- Skin gel - \$23
- Wires - \$22/set
- CPT code – 95930 VEP
- Fee - \$159
- 5 Year financing requires 5 pts/month to break even
- Available as *Nova-VEP*
- 

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### **Neuroprotection in Glaucoma**

- Tsai Curr Eye Res 2005
- EPO (erythropoetin) found to have protective effect on RGCs
  - Currently approved and well understood for anemias, post chemo-therapy, and renal diseases
- Others under study include brimonidine, memantine, BDNF
- Future will be neuroprotection to improve environment and neuroregeneration with stem cells

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### **Vitrectomy Causes Cataract & Glaucoma**

- Chang, S AJO 2006
- Vitrectomy well known to result in cataract within 2 years
  - O<sub>2</sub> now discovered to be responsible
  - After cataract and vitrectomy angle oxygen changed from 12mmHg to 32mmHg
- Study found increased IOP in operated eye compared to fellow eyes
  - 68% of OAG developed in operated eye
  - Presence of natural lens at time of vitrectomy associated with 28 month delay in OAG

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### **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
- The patient can download the results on an auxiliary device
- 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
- The sensor is not only suitable for use in the eye it can also help patients with chronic hypertension with implantation into a blood vessel

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### **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 will begin testing the implant in animals by December

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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

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### **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
- I-vation – treatment of DME, implantable titanium screw coated with triamcinolone, self anchors into sclera
- 

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### **Promise of Implantable Drug Delivery Systems – Innovations on Tap**

- Biosilicone Technology – pSividia 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

63  **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 (CNF) in retinal disease
  - 
  -

64  **Ozurdex – Dexamethasone Intravitreal Implant 0.07%**

- 1<sup>st</sup> & 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
- 

65  **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
- 

66  **Biologics in Recalcitrant Uveitis**

- Standard treatment - includes topical steroids & cycloplegics, oral steroids, injectable steroids, sustained release formulations of steroids
- Steroid sparing agents – methotrexate, azathioprine are antimetabolite treatments

- Biologics – developed in the 1990s, targeted proteins for inflammatory mediators (cytokines or surface receptors)
  - Off label in US

67  **Biologics in Recalcitrant Uveitis**

- Anti-cytokines – the proinflammatory cytokine tumor necrosis factor-alpha (TNF-a) plays a role in pathogenesis of uveitis
  - Infliximab (Remicade) – most commonly used in uveitis (Behcet's, sarcoid, intermediate, birdshot, sympathetic ophthalmia)
  - Adalimumab (Humira)
  - Etanercept (Enbrel)
- Interferons – IFN-a is a cytokine responsible for autoimmune disease
  - 83-94% of uveitis with Behchets recovered within 2-4 weeks

68  **AMD Risk Factors**

- Age > 60
- Race W>B, Sex F>M
- HTN/Smoking
- Nutrition
- Family History
- Fair complexion
- Cardiovascular disease/CRP/obesity/high saturated fat diet
  - AmJEpidem Mar2011 abdominal obesity in men each 0.1 increase in waist/hip ratio increases odds of early AMD by 13%, late AMD by 75%

■

69  **Forecasting ARMD Through 2050**

- Arch Ophthal 2009; 127 (4):533-540
- Early AMD 9.1mil in 2010 to 17.8mil in 2050
- CNV & GA 1.7mil in 2010 to 3.8mil in 2050
- Visual Impairment from AMD is 620,000 in 2010 to 1.6mil in 2050

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**Nutritionals**

- First degree relatives of ARM pts 2-4 times greater risk of ARM compared to controls
- Twin studies show high levels of concordance of the disease among monozygotic sibs
- Vitamin E may cause bleeding
- Vitamin D may be of benefit
- Diets high in omega-3 FAs are of benefit
- Control of weight, HTN & cholesterol is important
- Diet of green leafy vegetables increase lutein, zeaxanthin which increase optical density of macular pigment providing protective role

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**Nutritionals**

- EyePromise (ZeaVision)

- Zeaxanthin 6mg
  - in the same 1:1 ratio as found in healthy macula
- Lutein 6mg
- Beta carotene – none
- Vitamin C – 120mg
- Vitamin E – 60 IU
- Zinc – 15mg
- Copper – none
- Fish oil (omega-3) – 250mg
- Alpha Lipoic acid – 10mg
- 

75  **Nutritionals**

- EyePromise Vizual Edge (ZeaVision)
  - Zeaxanthin 26mg
  - Lutein 8mg
  - Vitamin C – 240mg
  - Vitamin D3 – 2000 IU
  - Vitamin E – 120 IU
  - Zinc – 30mg
  - Fish oil (omega-3) – 380mg, total fish oil 500mg
  - Alpha Lipoic acid – 20mg
- New NSF certified product to enhance & improve visual performance (glare recovery, contrast, temporal processing speed, light sensitivity)

76  **Nutritionals**

- Zeaxanthin & Visual Function Trial (ZVF) Richer, S Optom Nov 2011
  - Randomized, controlled trial from 2007-2010
  - Zeaxanthin 8mg/day + Lutein 8mg
  - Visual improvement in elderly AMD pts of 2 lines
- Macular Re-pigmentation Enhances Driving Vision in Elderly Adult Males with AMD Richer, S JClinExpOphthal
  - Zeaxanthin 8mg/day for one year
- Pearls – enhanced functional vision with higher doses of ZX

77  **Why Is Early Diagnosis Important?**

78  **Average CNV Presentation**

- Average size:
  - 3300μ
- Location:
  - 80% Subfoveal
  - 20% Extrafoveal
- Initial Vision:
  - 20%  $\geq$  20/40
  - 40% 20/50 – 20/200
  - 40% < 20/200

79  **Inherent Faults of the Amsler Grid**



- Completion
  - The Amsler Grid does not overcome cortical completion
- Fixation
  - The Amsler Grid does not force fixation
- Crowding
  - Inhibition by neighboring peripheral lines reduces detection

80 

81 

## **Hyperacuity**

- Snellen 20/15 Resolution
  - 1 minute of arc
  - 0.017 degrees
- Vernier Resolution
  - Two seconds of arc
  - 0.03 minutes of arc
  - 0.00051 degrees
  - The width of a pencil viewed at 300 m !

82 

## ***The Future of AMD Monitoring*** **Foresee PHP™**

83 

## **Graduated Height of Artificial Distortions**

84 

85 

86 

## **BlueLaser Autofluorescence Track Dry AMD**

- Functional indication of retinal health
  - Measures metabolic activity of RPE
- Geographic Atrophy Progression Study (GAP)
  - Use autofluorescence to track progression
  - 10 new therapies for dry AMD
    - Combine BluePeak & OCT
    - May change the world like ranibizumab & OCT changed wet AMD
- Spectralis multimodality design platforms
  - 7 models available

87 

## **Dry AMD is the Next "Wet Degeneration"**

- Drusen Volume & Area "Map"
  - G. Hagemen of University of Utah
    - Drusen are toxic waste of RPE cells react to light = GA = cell death
- Highly reproducible
- Fundus image does not correlate to volume analysis
- "Life cycle" of drusen
  - Clinically always look the same
  - Drusen "die"
- New OCT applications to identify, count and monitor drusen for change over time

88 

## **Emerging Treatments for Dry AMD**

- Fenretinide in Geographic Atrophy (GA)
  - Phase II oral capsules of Vit A derivative
  - Binds retinol

- Stimulates photoreceptors & RPE
- Downregulates Vit A
- Downregulates lipofusin
- Side Effects: poor night vision

89

### **Emerging Treatments for Dry AMD**

- MacuClear's MC-1101
  - G. Choiu, PhD – AMD pathogenesis may begin with decreased choroidal blood flow
- Topical (tid), vasodilating, anti-inflammatory, anti-oxidant
- Favorable safety profile
- Significant increase in choroidal blood flow in phase I
  - 500%!
- Fast track approval granted and moving into phase IIIa
- Potential for glaucoma being investigated

90

### **AMD Research on Genetics**

- Age related macular degeneration gene located
- Encodes for a protein called Complement Factor H
  - Increases inflammatory proteins
  - Increases C-reactive protein
- We now know a genetic component of the disease exists!

91

### **New Wet AMD Clinical Concepts**

- Defining AMD Risks will become routine
- Complement Factor H + Loc387715 + CFB/C2 gene mutation
  - 285 times risk of AMD
  - <1% risk of AMD without these genes!!
- Useful clinical test available by end 2011
  - Swab of mouth

92

### **SequenomCMM**

- RetnaGeneAMD
  - Simple in-office DNA cheek swab
  - Tested in 1132 CNV cases and 822 controls in Caucasians
    - Multi center (Boston, Utah, Australia)
  - Results in 8-10 days
  - Genetic counseling for doctors and patients
  - Impact of 13 genetic variants (SNPs) of 8 genes on 4 chromosomes (1,6,10,19)
    - 3 SNPs increase risk
    - 10 SNPs decrease risk
- SequenomCMM – prenatal & ophthalmic
- 877.821.7266 [www.sequenomCMM.com](http://www.sequenomCMM.com)

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### **SequenomCMM – Calculating Risk Score**

- Gene
 

– ARMS2	+1.45
– CFH	+0.81
– C3	+0.42
– F13B	-0.01
– CFHR5	-0.13
– CFHR4	-0.15

- CFH	-0.19
- F13B	-0.45
- CFHR5	-0.60
- CFH	-0.76
- CFH	-0.79
- CFB	-0.82
- C2	-0.95
-	

94  **SequenomCMM – Calculating Risk Score**

- Impact on disease
  - ARMS2 = 3.39x's increased risk
  - CFH = 2.5x's increased risk
  - C3 = 1.25x's increased risk
  - C2/FB = 0.3 protective
- Log odds established for each SNP in multiplex panel and risk scores calculated based on individual genotype assignment yielding wide spectrum of disease risk (reflective of case controlled population)
- Low risk <25% CNV probability
- High risk >75% CNV probability

95  **What is Macula Risk Gene Test?**

- Macula Risk® is a prognostic DNA test intended for patients who have a diagnosis of early or intermediate AMD.
- Using the complete combination of AMD genes, and smoking history, Macula Risk® identifies those most likely to progress to advanced AMD with vision loss.
- Macula Risk® allows you to stratify patients for appropriate monitoring as recommended by the AOA and the AAO Preferred Practice Patterns - "*in an effort to detect asymptomatic CNV at a treatable stage.*"
- The patient sample is a cheek swab taken in the doctor's office. Macula Risk® is reimbursed by most providers including Medicare.

96  **AMD – A Genetic Disease**

- Macula Risk
- 
- A test that identifies AMD
- patients who will progress
- to vision loss.
- Samples DNA
- 
- 
- Cheek Swab

97  **Dry AMD / GA & Genetics**

- Progression of GA & Genotype in ARMD, Klein, M Ophthal 2010;117:1554-1559
- Growth rates of geographic atrophy NOT associated with variants in CFH, C2, C3, APOE, TLR3 genes
- Nominal association in LOC387715, ARMS2, HTRA-1 genotypes

98  **Importance of Multivitamins in AMD**

- ArchInternMed 2009; 169(4):235-341 Christen et al
  - Folic Acid, Pyridoxine and Cobalamin Combination Treatment & ARMD in Women: The Women’s Antioxidant & Folic Acid Cardiovascular Study
    - Trial data from large cohort (N =5442) of Women at High risk of cardiovascular disease
    - Homocystein concentration in blood increases risk AMD
    - Daily supplements reduce homocysteine in blood and risk of AMD

99  **Importance of Multivitamins in AMD**

- ArchInternMed 2005; 165(4):854-7 Reeves et al
  - Healthy Lifestyle Characteristics among adults in US
    - Trial data suggests importance of getting people to stop smoking, start proper diet, and exercise
    - Only 3% of Americans do
    - Once we understand a person’s dietary & lifestyle status we can better “prescribe” nutritional therapy
  - Leading antioxidant in US is \_\_\_\_\_?
  - Leading vegetable in US is \_\_\_\_\_?

100  **Omega-3s Beneficial in AMD**

- Arch Ophthal 2008 Chong et al
  - Australian meta-analysis of many studies (N=88,000)
  - High O-3s associated with 38% reduction in risk late AMD
- IOVS 2008 Nguyen et al
  - Australians fed rats O-3s, tested with ERG
  - Conclude beneficial across all retina layers, especially GC
- Arch Ophthal 2009 Tan JSL; 127(5):656-665
  - Dietary Fatty acids and 10 year incidence of ARMD/Blue Mountain Eye Study
  - Protection against early AMD demonstrated with regular consumption of fish, omega-3 polyunsaturated fats and low intake of linoleic acid. Benefit of regular consumption of nuts

101  **Omega-3s & Vitamin D Beneficial in AMD**

- Arch Ophthal Christen WG 2011;129(7):921
  - N=39,870 female health professional
  - Regular consumption of DHA & EPA & fish significantly decrease risk of AMD
- ArchOphthal, MillerAD 2011;129(4):481-489
  - CAREDS study of postmenopausal women
  - N=1330
  - High 25(-OH) D concentrations protect against early AMD in women less than 75 years old

102  **Macular Pigment Studies in Cataracts**

- ArchOphthal 2008; Mueller et al
  - CAREDS/WHI
  - N=1802 women with highest levels of L/Zx had 32% lower incidence of NSC

- Ophthal 2008 115(8) Sperduto et al
  - NEI Trial of Centrum Silver
  - N=1020 18% less lens events
- AmJClinNut 2008; Tan et al Blue Mountain Group
  - N=2464 Vit C and dietary antioxidants decreased NSC 50%
  -

103  **Macular Pigment Studies in Diabetes**

- IOVS 2008; Gierhardt et al
  - Proved Zx mechanism of protection in early DR
    - Anti-inflammatory & VEGF regulation
- CAREDS 2007 Diabetic women have 30% lower MPOD
- Graetes 2008 Spanish Group
  - Fed diabetic rats lutein and found it to be as effective as insulin at preventing cataract
  -

104  **Ranibizumab / Lucentis**

- for injection
- Dose – 0.5mg/monthly
- Administration – 27g needle intravitreal injection
- Indication – neovascular “wet” macular degeneration
- Contraindications – ocular infection
- Warnings – risk of endophthalmitis, increased IOP
- Dose – may decrease to q3m after 4 monthly injections
  - Less effective
- Studies – ANCHOR, SAILOR, PIER, MARINA, FOCUS

105  **Bevacizumab / Avastin**


- for injection, twice the half life of Lucentis, fraction cost for AMD
- Effect – Anti VEGF for CA of lung and colorectal CA
- Dose – 0.5mg/monthly
- Administration – 27g needle intravitreal injection
- Indication – neovascular “wet” macular degeneration
- Contraindications – ocular infection
- Warnings – risk of endophthalmitis, increased IOP
- Dose – may decrease to q3m after 4 monthly injections
  - Less effective

106  **Avastin for EVERYTHING ocular**

- AMD
- PDR
- PDR with vitreous hemorrhage
- DME
- Vein occlusions
- ROP
- Choroidal melanoma
- NVG
- The future is topical eyedrops, oral formulations

107  **Aflibercept / Eylea**

- for injection,
- Effect – Anti VEGF
- Dose – monthly for 3 months, then every other month
- Administration – 27g needle intravitreal injection
- Indication – neovascular “wet” macular degeneration
- Contraindications – ocular infection
- Warnings – risk of endophthalmitis, increased IOP
- Benefit – less injections, less cost

108  **Pazopanib / GlaxoSmithKline**

- TOPICAL
- Effect – Anti VEGF-A, targets receptor tyrosine kinase so inhibition is after VEGF binds to receptor
- Dose – 5mg/ml TID
- Accumulates in high concentration in posterior retina through trans-scleral route (end around on anterior segment)
- Indication – neovascular “wet” macular degeneration
- Approved now for renal cell cancer
- Benefit – no injections, less cost, 4.3 letters at day 29 trend toward improvement at day 8

109  **New Wet AMD Clinical Concepts**

- Ciliary Neurotrophic Factor (CNTF)
  - Immuno-isolation
  - Implanted pars plana releasing drug for over one year
  - Outer nuclear layer & photoreceptor layer thickens
    - No correlation with VA improvement
- Anti-Platelet Derived Growth Factor (PDGF)
- POT-4 / PotentiaPharma, Inc
  - Binds to C3 – Potent inhibitor of C3
  - SMALL cyclic peptide (not large 3-D protein)
    - Lasts for MONTHS!!
  - Studies using depo form combination with VEGF drugs

110  **New Wet AMD Clinical Concepts**

- Complement is MOST IMPORTANT
- Human Genome Project – completed in 2005
  - Chromosome 1 is location of complement factor H (CFH)
  - 1<sup>st</sup> to be mapped!
  - C3, C3a, C5, C5a are all pathways of activation of VEGF
- *VEGF expression is result of complement activation!!*
  - Complement is the bomb of inflammatory system
    - Requires detonator – 30 proteins in blood for triggers
    - Membrane Attack Complex (MAC) & Fc-Fragment

111  **Comparative Clinical Trials**

- Avastin vs Lucentis
- CATT Comparative ARMD Treatment Trial
- IVAN
- LIBERA Trial – OCT guided (high dose)
- LUCAS Trial – OCT guided (trial & extended)

- MANTA Trial – 3 Rxs & treat as needed
- PrONTO – 3 Rxs, Monthly OCTs & +/-injections
- RADICAL – Triple therapy
  - Reduced fluence PDT / dexamethasone / ranibizumab
- All results will come in 2011

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### **Comparative Clinical Trials**

- RADICAL – Triple therapy
  - Reduced fluence PDT / dexamethasone / ranibizumab
- Anti-VEGF & Radiation
  - NeoVista – Strontium-90 applicator (stainless steel 20-ga tube) via core vitrectomy channel
  - Positive results in CNV in AMD
  - Better results when used in combination with two injections of bevacizumab
- CABERNET (CNV secondary to AMD treated with BEta Radiation Epiretinal Therapy)
  - Brachytherapy/ranibizumab vs ranibizumab alone

113 

### **Nanotechnology Vision Chip**

- NASA developing the Nanotechnology Vision Chip
  - Technology for stimulating retinal neural cells using an array of carbon nanotubes (CNTs)
  - NASA Ames Research Center, in conjunction with Stanford University School of Medicine
- Use: to restore vision in patients suffering from age-related macular degeneration
- An array of electrically conductive CNT towers grown directly on the surface of a silicon chip
- Each CNT tower in the array is connected to its own electrical circuit, so that electrical signals generated by the pixels of a light detector can be transmitted to the CNT towers

114 

### **Nanotechnology Vision Chip**

- Thousands of CNT towers are closely spaced in an array, to match the spacing of the neurons within the retina
- Implanted into the retina, so that the CNT towers come in direct contact with the retinal neurons
- Electrical signals generated by a CCD camera are delivered to the implanted device via telemetry
- Prototypes have used towers that are 100 microns in diameter and approximately 150 microns tall

115 

### **Nanotechnology Vision Chip**

- An alternate version of this technology, the CNT towers are coated with special growth factors to stimulate growth of retinal neurons toward the CNT towers
- CNT can be coated with a variety of growth factors and cytokines to stimulate attachment of neural cells to the CNT towers
- With this enhancement, only minimal penetration of the retinal

tissue (25–50 microns) may be needed to promote neural cell/CNT tower connections and may restore vision

■

#### 116 **Nanotechnology Vision Chip**

- Short-term in vitro tests of the implant materials with retinal ganglion cells suggest excellent biocompatibility
- Optimization of dimensions and spacing serves to maximize retinal layer stimulation
- Small, nano-sized components allow an image resolution density similar to that of native retinal photoreceptors

■

#### 117 **Retinal Tissues Templates**

- Researchers at Purdue University have created scaffold-like patterns on the surface of a pig's retina
  - Make templates out of molecular peptides
  - Each of the lines was less than 100 nanometers wide
- Biomedical engineers used an atomic force microscope to lay down lines of peptides in a process known as dip-pen nanolithography
  - Analogous to the lithography, or patterning, process used for semiconductor
- Hypothesized that placing templates on the retina could enable transplanted cells to take hold and grow
  - Implant retinal pigment epithelial cells, could be guided or organized if a template or scaffold were present
  - Could promote the growth of transplanted healthy cells
    - To treat age-related macular degeneration

#### 118 **Virus Modification for AMD**

- Virus Vector for treatment of CNVM
  - Using Adenovirus model
  - Genetically modified to contain DNA strand to stop the production of VEGF
  - Injected intra-vitreally
  - Virus infects retina
  - DNA incorporated into the cell matrix
  - Inhibits the production of VEGF
  - Even with direct laser damage no neovascularization occurs
  - One year post injection the protection remains
  - Animal model only at this time

#### 119 **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



