Ohio’s Aging Eye Summit

State of Vision Research for the Aging Eye at CWRU and University Hospitals

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- 19 MDs
- 1 MD, PhD
- 5 ODs
- 2 OD, PhDs
- 5 PhDs with primary appointment
- 4 PhDs with secondary appointments
- 1 CRA, MA photographer and Professor
- Comprehensive
- Cornea/External Disease/Refractive
- Electrophysiology
- Glaucoma
- Neuro-ophthalmology
- Oculoplastics
- Ophthalmic pathology
- Optometry/Contact lens/low vision
- Pediatric ophthalmology and adult strabismus
- Retina-vitreous
- Uveitis
The CWRU Visual Sciences Research Center (VSRC)
36 PIs in 13 Departments and 3 Schools

**Visual Sciences Research Center**
- NEI P30 Core Grant
- NEI T32 Training Grant
- VSRC Speaker Series
- Annual Symposium
- Pharm 432 Course

**NEI grants**
- 14 R01s
- 3 R21s
- 1 UG1

*College of Arts and Sciences
**School of Engineering
The CWRU Visual Sciences Research Center (VSRC)
Thematic Areas

• Age-related macular degeneration and retinal degenerations
• Cataract
• Contact-lens-induced inflammation
• Corneal Diseases
• Diabetic retinopathy
• Eye imaging
• Genetics of eye diseases
• Glaucoma
• Ocular toxoplasmosis
Thematic research areas related to the aging eye in the CWRU Ophthalmology

• Glaucoma: Dr. Rhee
  – Understanding the trabecular meshwork, the drain of the eye, to develop new treatments—studies on the SPARC protein

• Diabetic retinopathy: Patricia Taylor, PhD
  – Relation of inflammation in diabetic retinopathy. Role of IL-17A
Thematic research areas related to the aging eye in the Department

- ARMD, Alzheimer’s disease, and diabetic retinopathy: Irina Pikuleva, PhD
  - Understanding role of cholesterol homeostasis in ARMD, diabetic retinopathy, and Alzheimer’s disease
Research in the Pikuleva Laboratory

R01 EY018383, years 19-24 (Pikuleva): Cholesterol homeostasis in the retina

- Evaluate hamsters as a model for studies of retinal cholesterol
- Assess HPCD treatment for mitigation of retinal manifestations of AMD in Apoe\(^{-/-}\), Cyp27a1\(^{-/-}\)-Cyp46a1\(^{-/-}\) and hAPOB100-Tg mice
- Establish retinal significance of APOJ for the pathway of retinal cholesterol transport

R01 EY025383, years 5-9 (Pikuleva, multiPI): Cholesterol homeostasis in pathogenesis of diabetic retinopathy

- Determine whether type 2 diabetes induces changes in retinal cholesterol homeostasis leading to retinal cholesterol accumulation and formation in the retina of cholesterol crystals

R01 AG067552, years 19-23 (Pikuleva): Cholesterol-metabolizing P450s - structure and function

- Identify a general mechanism underlying the multiple brain effects of CYP46A1 activity modulation
- Begin to develop the next generation of CYP46A1 activators
Why Study Cholesterol in the Retina?

- Chorioretinal cholesterol is linked to AMD:
  - Cholesterol is a significant component of drusen (>40% of druse volume) and subretinal drusenoid deposits
  - GWAS identified several cholesterol-related genes (CETP, ABCA1, LIPC, and APOE) as risk factors for wet AMD

- Statin treatment may retard AMD progression reducing cholesterol levels systemically and in the retina with effect on cholesterol-laden drusen with early disease
CYP46A1:

- Enzyme initiating the major pathway of cholesterol removal from the brain

- Expressed in specific neurons of the brain and retina; protein levels in the brain are ~6-fold higher than those in the retina

- Involved in cognition:
  - *Cyp46a1*−/− mice show severe deficits in spatial, associative, and motor learning
  - Conversely, old transgenic *CYP46A1* female mice have improved spatial memory and an increased NMDAR expression

- Potential target for Alzheimer’s and Huntington’s diseases, Niemann-Pick disease type C, spinocerebellar ataxia, glioblastoma as well as conditions accompanied with seizures; being tested in clinical trials for inhibition (2 trials) and activation (1 trial)

- Potential target for AMD at early stages before advanced drusen and neovascularization
Efavirenz

- Sustiva (Bristol-Myers Squibb) or from Cipla (generic)
- Approved by the FDA in the US as an anti-HIV medication to keep the viral load low
- Represents a non-nucleoside reverse-transcriptase inhibitor
- Given orally at the 600 mg/day dose or ~10 mg/kg of body weight
- Exhibits off target interaction and activation with cytochrome P450 46A1 (CYP46A1), the major enzyme, which controls cholesterol elimination from the brain
Efavirenz Effect of Retinal Abnormalities in 5XFAD mice
(6 month of TX with 0.1 mg/kg of BW)
A Proof-of-Concept Clinical Research Study of Efavirenz in Patients with Alzheimer's disease  
(NCT03706885)

Irina A. Pikuleva, PhD, Case Western Reserve U, Cleveland, OH  
Site 1 PI: Alan Lerner, MD, University Hospitals, Cleveland, OH  
Site 2 PI: Steven Arnold, MD, Massachusetts General Hospital, Boston, MA

Endpoints:

1º: CYP46A1 engagement  
(≥30% change in plasma 24-hydroxycholesterol)

1º: serious adverse effects  
in the geriatric population

2º: the ²H₂O study—  
preliminary work  
has already shown clearance  
of excess cholesterol from  
the brain

3º: the effect of the APOE,  
CYP46A1, and CYP2B6  
genotypes; decreases in  
the CSF phosphotau,  
amyloid β protein, and  
total tau
Thematic research areas related to the aging eye in the Department

- Fuchs Dystrophy: Dr. Jonathan Lass
- Genetics studies: 3 new genes reported associated with Fuchs dystrophy*
  - KANK4, LAMC1, and ATP1B1
- RCT: Cornea Preservation Time Study with 95% of patients undergoing DSAEK for Fuchs dystrophy. Provides insights into best surgical practices for the disease. 

*Afshari et al Nature Communications 2017
+Lass et al Cornea 2015
& Rosenwasser et al JAMA Ophthalmology 2017

FECD case post DSAEK
FECD guttae seen on specular microscopy

*Afshari et al Nature Communications 2017
+Lass et al Cornea 2015
& Rosenwasser et al JAMA Ophthalmology 2017
Thematic research areas related to the aging eye in the Department

- Diabetes and Fuchs Dystrophy: Dr. Jonathan Lass
  - Effect of donor and recipient diabetes on DMEK outcomes by one year

![FECD](image1)

![Pseudophakic cornea edema](image2)

![FECD case post DMEK](image3)

![Post DMEK ECD determination](image4)
Diabetes Endothelial Keratoplasty Study Support

Cooperative Agreement with the National Eye Institute UG1 EY30030 and UG1 EY30039


* As of 6/1/2021
Diabetes Endothelial Keratoplasty Study (DEKS) Background

- Diabetes epidemic worldwide and the United States
  - 23.1 million diagnosed in US (7.2% of the population)
  - 7.2 million adults undiagnosed
  - 30.3 million total with diabetes (9.4% of the population)
- Cornea donor pool approaching 40% with diabetes at most eye banks
  - Compared to <10 - 20% a decade ago
- 2014 first report diabetes increases risk of Descemet membrane endothelial keratoplasty (DMEK) prep failure*
- DMEK is fastest growing transplant procedure
  - Eye banks increasingly avoid diabetic donors for DMEK
  - Causing constraints limiting DMEK tissue allocation to non-diabetic donors with high cell counts

*Greiner et al Cornea 2014;33:1129-33
Our Cornea Preservation Time Study (CPTS) Results in 2018 Support Diabetes Endothelial Keratoplasty Study Funding This Year

- Higher DSAEK graft failure rate at 1 and 3 years with donors with diabetes*
- Higher endothelial cell loss following DSAEK at 1 and 3 years with donors with diabetes+
- Higher graft detachment rate following DSAEK#

*Terry et al Ophthalmology 2018;125:1700-1709
**Diabetes Endothelial Keratoplasty Study**

**Multicenter, randomized, masked, clinical trial examining graft success and cell loss 1 year post DMEK**

- **Major Participants and Eligibility Criteria**
  - DMEK cases; no DSAEK cases
  - Exclude eyes with failed PKP, tube shunts, uncontrolled
  - 30-<91 years old undergoing DMEK for FECD, PCE, or failed DSAEK or DMEK
  - All glaucoma, AC IOL, or anterior synechiae >3 clock hours

**Minimization**
Participants could enroll both eyes – first eye in a 2:1 minimization procedure non-diabetic vs diabetic, second eye assigned alternative group

- **Non-diabetic Group**
  N = 947 eyes

- **Diabetic Group**
  N = 473 eyes

Majority of recipients with Fuchs dystrophy
Diabetes Endothelial Keratoplasty Study
Goals

- Determine definitively whether there is an association between donor and recipient diabetes with DMEK graft success and endothelial cell loss at one year
- Determine if donor and recipient diabetes severity impact DMEK graft success and endothelial cell loss
Donor and Recipient diabetes severity measures

• Determine definitively presence of diabetes in the donor
  – Detailed review of history
  – Post-mortem HbA1c testing—detect undiagnosed diabetes with HgbA1c > 6.5 and uncontrolled diabetes with high HgbA1c

• Hgb A1c testing on all recipients at baseline and 1 year

• Lions Vision Gift donor severity scale on both donor and recipient
  • Duration of diabetes for 10 years or more
  • Body mass index
  • Hypertension
  • Treatment of diabetes (diet, oral agent, insulin)
  • History of micro- and/or macrovascular complications: renal failure and/or dialysis; stroke; myocardial infarction; leg ulcers or amputations; diabetic retinopathy with proliferative disease including vitreous hemorrhage; history of retinal laser; history of vitrectomy; history of intravitreal anti-VEGF therapy

    Each gets a point up to 5 points: Scale 0 (no diabetes) to 5 (severe diabetes)

• AGE and oxidative markers testing on donor: Measurement of post-mortem advanced glycation endproducts and oxidative markers from skin biopsy on the donor as more sensitive measure of tissue damage
Diabetes Endothelial Keratoplasty Study
Learn about Other Factors impacting DMEK outcomes

- Tracking not only donor and recipient diabetes but over 60 other donor, recipient, operative and postoperative factors impacting DMEK outcomes
- Will help determine best practices for DMEK success for the management of Fuchs dystrophy
Diabetes Endothelial Keratoplasty Study Impact

- Targeted use of corneas from well characterized diabetic donors whose tissues will be more widely utilized for keratoplasty in the US and worldwide
- Sort out other donor, recipient, operative and postoperative factors that could improve DMEK outcomes, and lower primary and early failures
Future for Aging Eye Diseases Management

• Fuchs dystrophy
  – Medical: growth factors, ROCK inhibitors
  – Surgical: EK improvements, cell-based therapy

• Glaucoma
  – New class of agents with further understanding of the trabecular meshwork and optic nerve protection
  – Longer acting delivery systems

• Macular degeneration
  – Improvement in anti-VEGF treatment—activity, frequency
  – Novel treatments—cholesterol modification, apoptosis inhibition