Proteomics Sheds New Light on Mechanisms of Primary Open-Angle Glaucoma

Researchers at Cleveland Clinic Cole Eye Institute have applied emerging technology to better understand the molecular mechanisms of primary open-angle glaucoma.

Using liquid chromatography mass spectrometry iTRAQ technology to gain insight into the underlying pathology, they published their findings in the October 2011 issue of Investigative Ophthalmology & Visual Science.

GROWTH FACTOR IMPLICATED

A growing body of evidence implicates transforming growth factor beta 2 (TGFβ2) in primary open-angle glaucoma pathology. TGFβ2, an immunosuppressive factor in normal human aqueous humor that helps maintain the immune privilege of the eye, is often elevated in the aqueous humor and trabecular meshwork of primary open-angle glaucoma patients.

The molecular mechanisms elevating TGFβ2 in glaucoma patients are not known. To better understand the molecular consequences of elevated TGFβ2 in the anterior segment, the researchers quantified proteomic changes induced by TGFβ2 in cells cultured from human trabecular meshwork.

Cole Eye Institute scientist John W. Crabb, PhD, Professor of Ophthalmology and Molecular Medicine at Cleveland Clinic Lerner College of Medicine, led the study. Human trabecular meshwork cell cultures were provided by the University of North Texas Health Science Center in Fort Worth.

Continued on next page
**Expanded repertoire of proteins**

In the most extensive quantitative proteomic analysis of TGFβ2 signaling in trabecular meshwork cells to date, the team quantified 853 proteins.

Proteins significantly altered by TGFβ2, namely those present in amounts at least one standard deviation above or below the mean amount, were identified. Forty-seven of the 853 proteins were found to be significantly altered by TGFβ2 treatment, including 30 that were elevated and 17 that were decreased. Forty proteins had not previously been associated with TGFβ2 signaling in the trabecular meshwork.

Bioinformatics analyses revealed key information about the biological functions of the altered proteins. The results support previous findings that TGFβ2 induces extracellular matrix remodeling and abnormal cytoskeletal interactions in the trabecular meshwork. They also suggest elevated TGFβ2 disrupts other physiological processes in the trabecular meshwork such as transcription, translation, steroid metabolism and the glutamate/glutamine cycle.

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**Key points**

1. A new approach to studying primary open-angle glaucoma is presented. The molecular mechanisms of this disorder are not well understood.

2. Quantitative proteomic technology was used to measure protein changes induced by transforming growth factor beta 2 (TGFβ2) in human trabecular meshwork cells.

3. The findings dramatically expand the repertoire of proteins known to function in TGFβ2 signaling, provide new insights into primary open-angle glaucoma, and establish a quantitative proteomic database for the trabecular meshwork that includes biomarker candidates.

**New insights for future research**

Eight TGFβ2-altered mitochondrial proteins were identified, strongly implicating mitochondrial dysfunction in the trabecular meshwork as a contributor to damage in the aqueous humor outflow pathway, cellular senescence and elevated intraocular pressure.

“Our main goal has been to determine primary open-angle glaucoma mechanisms and to identify biomarker candidates,” says Dr. Crabb. “The present findings also establish a quantitative proteomics database for the trabecular meshwork that includes candidate glaucoma biomarkers for future studies.”

Dr. Crabb worked on the study with glaucoma clinician Kathryn E. Bollinger, MD, now of the Medical College of Georgia in Augusta. Co-authors involved in proteomic analyses at Cole Eye Institute included Xianglin Yuan, PhD, and Jack S. Crabb. Cell cultures were provided by Abbot F. Clark, PhD, and graduate student Tasneem Putliwala, of the University of North Texas Health Science Center.

*For more information, please contact Dr. Crabb at ophthalmologyupdate@ccf.org.*
ENDOWED CHAIRS NAMED

DANIEL F. MARTIN, MD, APPOINTED BARBARA AND A. MALACHI MIXON III INSTITUTE CHAIR IN OPHTHALMOLOGY

A $3 million gift to Cleveland Clinic’s Cole Eye Institute has endowed The Barbara and A. Malachi Mixon III Institute Chair in Ophthalmology. The gift recognizes the sight-saving care that Mr. Mixon received here.

Cole Eye Institute Chairman Daniel F. Martin, MD, is the first chair holder. Dr. Martin has designed and developed many clinical trials and has served as principal investigator for seminal studies on age-related macular degeneration, diabetes, uveitis and CMV retinitis.

Dr. Martin was Study Chairman of trials that led to FDA approval for both the ganciclovir implant and valganciclovir. He is currently Study Chairman for the NIH-sponsored Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) to compare the efficacy, safety and dosing of Lucentis® and Avastin®.

Dr. Martin believes the Mixons’ gift will serve as a catalyst for further cutting-edge research and will allow for increased involvement in clinical trials.

Mr. Mixon, Chair Emeritus of Cleveland Clinic’s Board of Directors and Board of Trustees, chaired the Board of Directors from 2003 to 2010 and chaired the Board of Trustees in 1997. He also heads the Cole Eye Institute Leadership Board.

Dr. Martin graduated from The Johns Hopkins University School of Medicine and completed an ophthalmology residency at Emory University School of Medicine, a vitreoretinal surgery and diseases fellowship at Duke University Medical Center, and an ocular immunology and uveitis fellowship at the National Eye Institute, NIH.

PETER K. KAISER, MD, APPOINTED CHANEY CHAIR FOR OPHTHALMIC RESEARCH

Peter K. Kaiser, MD, has been appointed the Chaney Family Endowed Chair for Ophthalmology Research at Cole Eye Institute. A clinical trials specialist, he has chaired five major multicenter international retina trials. Dr. Kaiser serves on numerous study executive committees and was first to treat any patient with a modified small RNA-interfering molecule.

Dr. Kaiser is a pioneer in sutureless micro-incision vitrectomy surgery and has helped to develop the latest vitrectomy systems. An expert in optical coherence tomography (OCT), he is the founding director of Cole Eye Institute’s Digital OCT Reading Center. This center is involved in almost all retinal clinical trials currently being performed.

Bruce and Virginia Chaney endowed the chair more than a decade ago in gratitude for their care at Cole Eye Institute. With the passing of the Chaneyes, their son Jim, his wife, Jeannie, and their children continue the family’s support of vision research here.

In addition to his research and clinical activities, Dr. Kaiser serves as Editor-in-Chief of Retinal Physician magazine. He is also on the Editorial Boards of the American Journal of Ophthalmology, Ocular Surgery News, International Ophthalmology Clinics, Retina Times, OSN Retina and Retina.

Dr. Kaiser is also a member of the Board of Directors of the American Society of Retina Specialists. He is the team ophthalmologist for the Cleveland Browns and Cleveland Cavaliers as well.
New Gene Implicated in Complete Congenital Stationary Night Blindness

A large group of investigators, including members of Cleveland Clinic Cole Eye Institute, has identified a new gene involved in a form of congenital stationary night blindness (CSNB). The group published its study in the February 2012 issue of The American Journal of Human Genetics. The research team discovered mutations in GPR179, a previously uncharacterized G-protein receptor, in patients with complete CSNB. This finding brings to four the number of genes that have been linked to this uncommon condition. The previously identified genes are NYX, GRM6 and TRPM1.

NEW MOUSE MODEL DEVELOPED

The project began with the discovery of a new mouse model (nob5) of complete CSNB, identified through electroretinogram recording. The normal electroretinogram has two major components: the a- and b-waves (see Figure 1). These reflect the activity, respectively, of photoreceptors that capture light and of bipolar cells that transmit photoreceptors centrally toward the brain. The b-wave is missing in nob5 mice, a feature shared with human patients. The identification of a mutation in the mouse GPR179 gene led to the evaluation of GPR179 in 44 human patients and the discovery of inactivating mutations in two probands (see Figure 2).

CSNB DIAGNOSIS A CHALLENGE

Neal Peachey, PhD, who led the Cole Eye Institute’s work on this project, says that even more genes could be involved in complete CSNB, which is a diagnostic challenge. “It is purely a functional loss. The retina looks perfect; it just doesn’t work,” he says. “The only way to diagnose it definitively is using the electroretinogram to confirm there is no b-wave. Without this test, it is likely to be misdiagnosed or missed altogether.”

As the name implies, CSNB is an inherited condition in which affected individuals have difficulty seeing at night. But many CSNB patients also have abnormal day vision, including reduced visual acuity, as well as nystagmus.

Figure 1. In a normal electroretinogram, a-waves reflect the activity of photoreceptors and b-waves reflect the activity of bipolar cells that transmit photoreceptors centrally toward the brain.

Figure 2. In CSNB and in nob5 mice, the b-wave is missing. This electroretinogram is from one of the patients who, like the mice, was found to have an inactivating mutation in the GPR179 gene.
Gene therapy looks promising

Complete CSNB has several features that make it amenable to gene therapy, Dr. Peachey explains. “First, we have animal models for all of the genes for complete CSNB. This is critical,” he says.

Second, since the retina does not degenerate in CSNB, there is greater potential for restoring function. In fact, restoration of visual function has already been achieved by delivering a normal copy of the NYX gene to a mouse model for that form of complete CSNB. “We hope to have even more luck with GPR179,” says Dr. Peachey.

Broader implications

A critical challenge is to deliver genes to bipolar cells. “If we can show that we can rescue the vision of CSNB patients with gene therapy, it could open the door to treating other inner retinal diseases,” he adds.

Extensive collaboration

This work was a collaborative effort with many groups. The mouse studies also involved the University of Louisville, The Jackson Laboratory, the Cleveland VA Medical Center, Morehouse School of Medicine, Oakland University and Emory University. Human studies involved contributions from the Royal Netherlands Academy of Arts and Sciences, the Netherlands Institute for Neuroscience, Erasmus University, the Retina Foundation of the Southwest, and McGill University.

For more information, please contact Dr. Neal Peachey at ophthalmologyupdate@ccf.org.

Key points

1. Congenital stationary night blindness (CSNB) is a genetically and clinically heterogeneous retinal disorder characterized by loss of night vision and varying degrees of daytime vision impairment.

2. A mutation in GPR179 was identified in patients with complete CSNB by a collaborative team involving Cole Eye Institute researchers. GPR179 is the fourth gene to be implicated in this disorder.

3. Gene replacement therapy has potential to restore normal visual function in patients with CSNB. The functional defects in a GPR179 mouse model closely resemble those seen in humans. However, as in other models for complete CSNB, retinal structure is normal.
Acanthamoeba Keratitis: A Rare Vision-Threatening Infection Associated With Contact Lens Wear

Contact lens-related microbial keratitis affects approximately 1 in 500 soft contact lens wearers annually in the United States. Most infections are bacterial in origin and can be managed empirically, often resolving without significant visual sequelae. In some cases, unusual organisms infect the cornea that are resistant to standard broad-spectrum antibiotics. One such genus of protozoa, Acanthamoeba, is a rare but important cause of infectious keratitis.

Infections caused by Acanthamoeba spp. are often misdiagnosed initially, resulting in a delay in definitive treatment. However, early diagnosis and institution of appropriate treatment are necessary to limit long-term ocular morbidity. The following three cases presented within a one-month span at Cole Eye Institute, in September 2011.
**CASE 1: TEEN WITH SYMPTOMS FOR ONE MONTH**

**Presentation.** A 15-year-old female soft contact lens wearer was referred for a one-month history of severe pain, photophobia and mildly blurred vision, left eye. She reported good contact lens hygiene and had no history of exposure to fresh water. Medications included prednisolone acetate 1% four times daily and tobramycin 0.3% twice daily OS.

Her vision was 20/20 OD and 20/40 OS. Her left eye was remarkable for mild generalized conjunctival injection with punctate epithelial keratitis in a ringlike distribution. Multiple areas of perineural infiltration were visible in the peripheral corneal stroma. The anterior chamber was quiet.

**Evaluation and treatment.** The epithelium was scraped and cultured for bacteria, fungi and Acanthamoeba. Confocal microscopy performed the following day revealed multiple double-walled cysts in the corneal stroma, diagnostic of Acanthamoeba keratitis (Figure 1). Combination treatment was initiated with chlorhexidine gluconate 0.02% and propamidine isethionate 0.1% (Brolene®) every two hours OS.

One week later, the Acanthamoeba culture was positive. The patient reported significantly reduced pain at this time. Over the next four weeks, her symptoms waxed and waned, and repeat epithelial debridements were performed for any superficial recurrence of the ring infiltrate.

Eight weeks after starting anti-amoebic treatment, the patient’s cornea was clear. Topical prednisolone acetate was started four times daily to decrease photophobia.

Four weeks later, the patient’s vision was 20/20 OS, and her pain and photophobia resolved. The steroids were tapered to once daily, and the Brolene was discontinued to reduce epithelial toxicity. The patient is being followed monthly to monitor for signs of recurrent infection.

**CASE 2: TEEN WITH SYMPTOMS FOR THREE MONTHS**

**Presentation.** An 18-year-old soft contact lens wearer presented for a second opinion after being diagnosed with contact lens-related keratitis at another center. Her symptoms began three months previously with intermittent episodes of sharp left eye pain lasting seconds. A topical fluoroquinolone prescribed at that time provided no improvement. Topical corticosteroids were subsequently added for worsening photophobia.

The patient had had one month of topical steroid treatment when she presented to Cole Eye Institute. She reported 10/10 constant pain, severe photophobia and mildly blurred vision of her left eye. Current medications were besifloxacin (Besivance®) 0.6% four times daily and difluprednate (Durezol®) 0.05% every hour while awake OS. Vision was 20/20 OD and 20/40 OS. Her exam was remarkable for moderate diffuse conjunctival injection and punctate epithelial keratitis in a ringlike distribution. No infiltrates or perineural inflammation were present. The anterior chamber was quiet.

**Evaluation and treatment.** Confocal microscopy was nondiagnostic. Corneal scraping and cultures for bacteria, fungus and Acanthamoeba were performed. The patient was started empirically on polyhexamethylene biguanide (PHMB) 0.02%, chlorhexidine gluconate 0.02% and natamycin 2.5% drops hourly. The Durezol was tapered over the following week.

All cultures were negative at one week. Meanwhile, a ring-shaped stromal infiltrate developed (Figure 2). The epithelium was debrided, and repeat cultures were performed. The ring infiltrate gradually became more pronounced. Three weeks after presentation, a corneal biopsy was performed via anterior lamellar resection of a 2.5-mm segment of superior stroma, approximately 150 µ thick. The epithelium was again debrided, and sent for fungal and Acanthamoeba culture.

Pathologic examination identified rare structures suggestive, but not diagnostic, of Acanthamoeba. The epithelial culture grew Acanthamoeba eight days later. At this time, the epithelium was closed and the corneal infiltrate was improving, with subjective...
improvement of pain. Several keratitic precipitates were located posterior to the infiltrate, accompanied by a mild anterior chamber reaction. PHMB and chlorhexidine were decreased to every two hours while awake, and the natamycin was discontinued. Two weeks later (six weeks after initiating anti-Acanthamoeba treatment), prednisolone acetate was added four times daily.

One week after that, the patient reported almost complete resolution of her pain and photophobia. The infiltrate became significantly less opaque, with resolution of the keratic precipitates (Figure 3). Two weeks later, the prednisolone was decreased to three times daily, and the disinfectant drops were continued every two hours while awake. Spectacle-corrected vision improved to 20/40, and the patient is being monitored on a monthly basis for recurrence.

CASE 3: MIDDLE-AGED MALE WITH SYMPTOMS FOR TWO WEEKS

Presentation. A 52-year-old soft contact lens wearer was referred for evaluation of a two-week history of photophobia, intermittent pain and blurred vision affecting his right eye. He reported good contact lens hygiene but noted frequent hot tub use. At the time of referral, medications included prednisolone acetate 1% and moxifloxacin (Vigamox®) 0.3% four times daily.

Vision was 20/60 OD and 20/20 OS. Slit-lamp examination was remarkable for diffuse punctate epithelial erosions OD without an obvious pattern. One area of perineural infiltration was visible in the inferotemporal corneal stroma.

Evaluation and treatment. Diagnostic scraping was performed, with cultures sent for bacteria, fungi and Acanthamoeba. Empiric treatment was initiated with chlorhexidine gluconate 0.02%, PHMB 0.02% and natamycin 2.5%. Two days later, the patient returned with multifocal areas of epithelial opacification. Repeat epithelial debridement was performed, with cultures for Acanthamoeba and fungus.

The initial culture was positive for Acanthamoeba after three days. The second culture (taken after two days of hourly combination anti-Acanthamoeba treatment) also grew Acanthamoeba five days after it was plated. The patient was continued on chlorhexidine and PHMB hourly (while awake) for three weeks.

Vision improved to 20/25 over this time, and the patient reported significantly reduced pain and photophobia. Several repeat epithelial debridements were performed for signs of early epithelial recurrence. The cornea is currently clear, and the patient is being monitored on a monthly basis.

DIAGNOSTIC AND THERAPEUTIC TIPS

- **Confocal microscopy** is a useful diagnostic tool when positive, but a negative study is insufficient to exclude the diagnosis.

- **Combination epithelial debridement and culture** has diagnostic and therapeutic benefit, especially in the setting of superficial corneal involvement. Repeat cultures may yield positive results days or weeks after initiation of appropriate therapy and are indicated when the diagnosis remains uncertain.

- **First-line treatment** should consist of hourly biguanides. For advanced or poorly responsive cases, we recommend combination therapy with multiple agents, including a diamidine.

- **Cautious use of topical corticosteroids** may be beneficial after completing one to two months of anti-infective treatment to reduce symptoms and corneal scarring.

For more information, contact author Dr. Jeffrey Goshe at ophthalmologyupdate@ccf.org.
A 31-year-old woman presented to Cole Eye Institute because of decreased vision in both eyes. She had a history of dermatomyositis managed by rheumatologist Brian Mandell, MD, PhD, of Cleveland Clinic’s Orthopaedic & Rheumatologic Institute. He recently started her on azathioprine.

**Emergency presentations.** On Oct. 3, 2011, the patient was seen in the Emergency Department because of headache, fever and generalized myalgias. She was diagnosed with a nonspecific viral infection and sent home. Two days later, she returned to the Emergency Department with intense muscle pain, fever, nausea, vomiting, and vision loss. She was seen by Dr. Mandell, who referred her to Cole Eye Institute.

**Uveitis/retina service consults.** Vitreoretinal fellow Matthew Ohr, MD, arranged a consult with the uveitis/retina service. Cole Eye Institute has three uveitis specialists who jointly participate in the care of challenging cases: Careen Y. Lowder, MD, PhD, and uveitis and vitreoretinal specialists Daniel F. Martin, MD (Cole Eye Institute Chairman), and Sunil Srivastava, MD.

The patient’s initial exam was significant for violaceous macular rash present on the upper eyelids of both eyes, consistent with the heliotrope rash characteristic of dermatomyositis. Her best corrected vision was 20/400 in each eye. The anterior chambers had 1+ cells.

Dilated fundus examination revealed bilateral severe retinal vasculitis and diffuse intraretinal hemorrhages with numerous paravascular white lesions presumed to be extravasated leukocytes (see photos next page). The patient was diagnosed with retinal vasculitis secondary to dermatomyositis.

**Multidisciplinary treatment.** This patient’s vision-threatening condition was associated with systemic symptoms that required multidisciplinary management. Dr. Mandell was contacted to develop a treatment plan.
That evening, the patient received 1 gram of intravenous Solu-Medrol® (methylprednisolone) at Cole Eye Institute’s ambulatory surgical center. She was admitted for further evaluation and treatment by Dr. Mandell.

Follow-up. The patient continued under the care of Drs. Lowder and Mandell. She responded very well to intravenous steroids, as her fundus exam revealed (see photos below). The patient was then transitioned to oral prednisone and cyclophosphamide. At her last exam on Nov. 23, 2011, her best corrected vision had improved to 20/80 in her right eye and 20/50 in her left eye.

Authors Dr. Matthew Ohr and Dr. Careen Lowder may be contacted at ophthalmologyupdate@ccf.org.
COLE EYE INSTITUTE CME

Mark your calendars for continuing medical education symposia hosted by the Cole Eye Institute. You’ll gain insights into state-of-the-art diagnostic, medical and surgical techniques, as well as the promise that research holds for patients with ophthalmic conditions.

Innovations in Glaucoma
For glaucoma specialists and comprehensive ophthalmologists
Saturday, April 21, 2012 (Cole Eye Institute)
Activity Directors: Edward Rockwood, MD; Jonathan Eisengart, MD

North Coast Retina Symposium III
For retina specialists only
Friday-Saturday, May 18-19, 2012 (Cole Eye Institute)
Activity Directors: Daniel Martin, MD; Sunil Srivastava, MD

Ocular Coherence Tomography and Imaging Course
For ophthalmologists, optometrists, nurses, technicians, photographers and others
Friday, Aug. 24, 2012 (Las Vegas, Nev.)
Activity Director: Peter Kaiser, MD

Ophthalmic Ultrasonography: Practical Aspects
For ophthalmologists, optometrists, nurses, technicians, photographers and others
Friday-Saturday, Sept. 14-15, 2012
(InterContinental Hotel, Cleveland, Ohio)
Activity Directors: Arun Singh, MD; Brandy Hayden

Most CME courses will be held at the Cole Eye Institute’s James P. Storer Conference Center. For details about any of our 2012 CME courses, please contact Jane Sardelle at sardelj@ccf.org.

COLE EYE INSTITUTE GRAND ROUNDS

Ophthalmologists from other institutions are welcome to attend Cole Eye Institute Grand Rounds, held Mondays from 7 to 8 a.m. throughout the academic year, except during holidays and major meetings.

Each session features two or more cases that represent outstanding teaching examples, followed by extensive discussion. Cases may feature rare or difficult-to-manage conditions, unusual presentations of common disorders, and/or state-of-the-art diagnosis and management. Three to four M&M cases are presented each year.

Category 1 continuing education credits are offered. Grand Rounds, held in the James P. Storer Conference Center at Cole Eye Institute, are video-conferenced weekly. No registration is required. For details, please contact Jane Sardelle at sardelj@ccf.org.
DISTINGUISHED LECTURE SERIES

Cleveland Clinic’s Cole Eye Institute is proud to present the 2012 Distinguished Lecture Series, which provides a forum for internationally renowned researchers in the visual sciences to present their latest findings on basic and clinical ophthalmic research. Ample opportunity for questions and answers is provided after lectures.

March 15, 2012
The Challenge and Benefits of Identifying Genes and Mutations Causing Retinitis Pigmentosa
Stephen P. Daiger, PhD
The Thomas Stull Matney, PhD, Professor of Environmental and Genetic Sciences
Human Genetics Center, School of Public Health
The University of Texas Health Science Center
Houston, Texas

May 17, 2012
Paracrine Mechanisms of Neuroprotection in the Retina: How Photoreceptors Survive for Decades in Progressive Retinal Degenerations
John D. Ash, PhD
Associate Professor
Willard M. Bullard Eminent Scholar Chair in Ophthalmic Sciences
Department of Ophthalmology
University of Florida
Gainesville, Fl.

April 19, 2012
Monocarboxylate Transporters (MCTs) in RPE: Insight Into Mechanisms Regulating Cell Differentiation and Polarity
Nancy J. Philip, PhD
Associate Professor
Department of Pathology, Anatomy and Cell Biology
Thomas Jefferson University

Sept. 20, 2012
What Happens When the Macula Fails to Protect Itself From Oxidative Stress?
James T. Handa, MD
Robert Bond Welch Professor
The Wilmer Eye Institute at Johns Hopkins
The Johns Hopkins Hospital
Baltimore, Md.

Oct. 18, 2012
Time to Branch? Pattern Generation in Vascular Networks
Holger Gerhardt, PhD
Head, Vascular Biology Laboratory
London Research Institute – Cancer Research UK
Lincoln’s Inn Laboratories
London, UK
Head, Vascular Patterning Laboratory
VIB Vesalius Research Center
University of Leuven
Leuven, Belgium

Nov. 15, 2012
Updates on the Long-Term Progression of Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS)
Emily Chew, MD, PhD
Deputy Director, Division of Epidemiology and Clinical Applications Sciences (DECA)
National Eye Institute, National Institutes of Health
Bethesda, Md.

The Distinguished Lecture Series is held from 7 to 8 a.m. in the James P. Storer Conference Center on the first floor of Cole Eye Institute. No registration is required, and we will validate your parking ticket. Call Laura Hogan at 216.444.5832 for details.

CLEVELAND CLINIC EXECUTIVE EDUCATION

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**Retinal Diseases**

**Fluocinolone Acetonide Intravitreal Inserts for Vein Occlusion in Retina (FAVOR)**

**Objective:** This study will assess the safety and efficacy of fluocinolone acetonide intravitreal inserts in subjects with macular edema secondary to RVO.

**Contact:** Peter K. Kaiser, MD, 216.444.6702, or Gail Kolin, RN, 216.445.4086

**A One-Month, Multicenter, Observational Study to Evaluate the Degree of Ocular Inflammation Associated with Pars Plana Vitrectomy (Pyramid)**

**Objective:** The purpose of this study is to evaluate the degree of ocular inflammation, retinal thickening and ocular pain in subjects who are undergoing a pars plana vitrectomy.

**Contact:** Rishi P. Singh, MD, 216.445.9497, or Gail Kolin, RN, 216.445.4086

**A 12-Week Patient Study in Neovascular Age-related Macular Degeneration (GSK)**

**Objective:** This study is designed to determine whether pazopanib eye drops have the potential to reduce retinal edema and maintain or improve visual acuity in cases of previously untreated subfoveal choroidal neovascularization (CNV) lesion secondary to age-related macular degeneration (AMD) and to further characterize the safety and tolerability of pazopanib eye drops administered over a 12-week period.

**Contact:** Rishi P. Singh, MD, 216.445.9497, or Gail Kolin, RN, 216.445.4086

**Home Vision Monitoring Using the ForeseeHome Device Following Treatment of Neovascular Age-Related Macular Degeneration (CNV)**

**Objective:** The purpose of the current study is to evaluate if, in post-treatment patients, parameters as measured with the ForeseeHome are in agreement with clinical decisions and retinal characteristics as measured with optical coherence tomography (OCT).

**Contact:** Rishi P. Singh, MD, 216.445.9497, or Sonal Uppal, PhD, 216.444.7137

**Uveitis**

**Safety and Efficacy of AIN457 in Noninfectious Uveitis**

**Objective:** This study will test the efficacy and safety of AIN457 for patients with active uveitis that requires systemic immunosuppression.

**Contact:** Careen Lowder, MD, 216.444.3642, or Laura Holody, 216.445.2264

**Study Assessing Double-Masked Uveitis Treatment (SAKURA)**

**Objective:** The purpose of this study is to evaluate the safety and efficacy of intravitreal injections of DE-109 ophthalmic suspension for uveitis treatment.

**Contact:** Careen Lowder, MD, 216.444.3642, or Laura Holody, 216.445.2264

**Glaucoma**

**Comparing the Effectiveness of Treatment Strategies for Primary Open-Angle Glaucoma**

**Objective:** The purpose of this study is to compare standard treatment strategies for glaucoma, including therapeutics, lasers and other types of surgery.

**Contact:** Edward Rockwood, MD, 216.444.1995, or Gail Kolin, RN, 216.445.4086

**Pediatric Eye Disease**

**Bilateral Lateral Rectus Recession versus Unilateral Recess-Resect for Intermittent Exotropia (IXT1)**

**Objective:** The purpose of this study is to evaluate the effectiveness of bilateral lateral rectus muscle recession versus unilateral lateral rectus recession with medial rectus resection procedures for the treatment of strabismus.

**Contact:** Elias Traboulsi, MD, 216.444.4363, or Sue Crowe, RN, 216.445.3840

**Increasing Patching for Amblyopia in Children 3 to <8 Years Old (ATS15)**

**Objective:** This study is designed to evaluate the effectiveness of increasing prescribed patching treatment after visual acuity has stabilized with initial treatment and amblyopia is still present.

**Contact:** Elias Traboulsi, MD, 216.444.4363, or Sue Crowe, RN, 216.445.3840

**Genetics**

**Molecular Genetics of Eye Diseases**

**Objective:** The objective of this project is to study the molecular genetics of ophthalmic disorders through the compilation of a collection of DNA, plasma and eye tissue samples from patients and from families with a broad range of eye diseases and malformations.

**Contact:** Elias Traboulsi, MD, 216.444.4363, or Sonal Uppal, PhD, 216.444.7137

**Cornea/Refractive Surgery**

**Donor Preparation Pressure and Refractive Shift in Descemet-Stripping Automated Endothelial Keratoplasty (DSEK)**

**Objective:** The purpose of the study is to determine if the infusion pressure used during DSEK (Descemet-stripping automated endothelial keratoplasty) donor tissue preparation affects postoperative graft morphology, refractive outcome and graft endothelial cell count in the recipient.

**Contact:** William J. Dupps, MD, PhD, 216.444.8396, or Laura Holody, 216.445.2264

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**Continued on next page**
Other Open Studies

Safety Study of a Single IVT Injection of QPI-1007 in Chronic Optic Nerve Atrophy and Recent Onset NAION Patients (NAION)

Objective: This is an open-label, dose escalation, safety, tolerability and pharmacokinetic study, where active study drug (QPI-1007) will be given to all patients who participate. This study will determine whether QPI-1007 is safe when it is injected into the eye. The study will also reveal if there are any side effects of the drug and how long it takes for the body to clear the drug.

Contact: Rishi P. Singh, MD, 216.445.9497, or Laura Holody, 216.445.2264

The following studies have completed patient enrollment in the last year at Cole Eye Institute and are in follow-up:

Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ACU-4429 in Subjects with Geographic Atrophy (Acucela)

A 16-week evaluation of Novartis Health Management Tool in Assessing Self-test Visual Function in Patients with AMD Treated with Lucentis

A Phase II Multicenter, Prospective, Randomized, Comparator-Controlled, Dose-Ranging Study Evaluating PF-04523655 Versus Ranibizumab in the Treatment of Subjects with Choroidal Neovascularization (MONE)

A Phase II Dose-Ranging Study of Pazopanib to Treat Neovascular Age-Related Macular Degeneration (GSK AMD)

Infant Aphakia Treatment Study (IATS)

An Open-Label, Multicenter, Phase II Trial of Adalimumab (Humira) in the Treatment of Refractory Non-infectious Uveitis

A Clinical Safety and Efficacy Comparison of Nevanac® 0.1% to Vehicle Following Cataract Surgery in Diabetic Retinopathy Patients

A Randomized, Double-masked, Sham-controlled Phase III Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)

A Randomized, Double-Blinded, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration (VEGF Trap)

A Phase I Open-Label, Dose-Escalation Trial of REDD14NP Delivered by a Single Intravitreal Injection to Patients with Choroidal Neovascularization Secondary to Exudative Age-Related Macular Degeneration (QUARK)
# COLE EYE INSTITUTE STAFF

**Chairman, Cole Eye Institute**

- Daniel F. Martin, MD ........................................... 216.444.0430

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- John Costin, MD ........................................... 440.988.4040
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- Philip N. Goldberg, MD ................................ 216.831.0120
- Michael Gressel, MD ....................................... 440.988.4040
- Mohinder Gupta, MD ....................................... 419.289.6466
- Martin A. Markowitz, MD ................................ 440.461.4733
- Shari Martyn, MD ........................................... 216.831.0120
- Peter McGannon, MD ...................................... 440.988.4040
- Michael E. Millstein, MD .................................. 216.831.0120
- Wynne Morley, MD ......................................... 440.366.9444
- Sheldon M. Oberfeld, MD ................................ 440.461.4733
- Allen S. Roth, MD .......................................... 216.831.0120
- David B. Sholiton, MD .................................... 216.831.0120
- Scott A. Wagenberg, MD .................................. 440.461.4733

**Cornea and External Disease**

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- Jeffrey M. Goshe, MD ...................................... 216.444.0845
- Roger H.S. Langston, MD ................................ 216.444.5898
- Martin A. Markowitz, MD ................................ 440.461.4733
- Peter McGannon, MD ...................................... 440.988.4040
- David M. Meisler, MD ...................................... 216.444.8102
- Wynne Morley, MD ......................................... 440.366.9444
- Sheldon M. Oberfeld, MD ................................ 440.461.4733
- Allen S. Roth, MD .......................................... 216.831.0120
- Scott A. Wagenberg, MD .................................. 440.461.4733
- Steven E. Wilson, MD ...................................... 216.444.5887

**Glaucma**

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- Edward J. Rockwood, MD ................................ 216.444.1995
- Shalini Sood-Mendiratta, MD ............................ 216.445.5277

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- Michael E. Millstein, MD .................................. 216.831.0120
- Allen S. Roth, MD .......................................... 216.831.0120
- Steven E. Wilson, MD ...................................... 216.444.5887

**Neuro-Ophthalmology**

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- Lisa D. Lystad, MD ......................................... 216.445.2530

**Oculoplastics and Orbital Surgery**

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- Julian D. Perry, MD ........................................ 216.444.3635

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- Maria Inton-Santos, MD ................................ 216.445.1016
- J. Victor Ryckman, MD .................................. 216.444.6330
- Sara Spagnuolo, MD ...................................... 216.444.6324

**Ophthalmic Oncology**

- Arun D. Singh, MD ........................................ 216.445.9479

**Ophthalmic Research**

- Bela Anand-Apte, MBBS, PhD ......................... 216.445.9739
- John W. Crabb, PhD ...................................... 216.445.0425
- Stephanie Hagstrom, PhD ............................... 216.445.4133
- Joe G. Hollyfield, PhD .................................. 216.445.3252
- Neal S. Peachey, PhD .................................... 216.445.1942

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- Paul Rychwalski, MD ...................................... 216.444.4821
- Elias I. Traboulsi, MD .................................... 216.444.2030

**Retina**

- Amy Babiuch, MD ......................................... 440.988.4040
- Ryan Deasy, MD .......................................... 440.988.4040
- Justis P. Ehlers, MD .................................... 216.636.0183
- Peter K. Kaiser, MD ...................................... 216.444.6702
- Daniel F. Martin, MD .................................... 216.444.0430
- Andrew P. Schachat, MD ............................... 216.444.7963
- Jonathon E. Sears, MD ................................ 216.444.8157
- Rishi P. Singh, MD ........................................ 216.445.9497
- Sunil K. Srivastava, MD .................................. 216.636.2286
- Richard Wyszynski, MD ................................ 440.988.4040

**Uveitis**

- Careen Y. Lowder, MD, PhD .......................... 216.444.3642
- Sunil K. Srivastava, MD .................................. 216.636.2286

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REFERRALS
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