Ophthalmology Update
From Cole Eye Institute
Welcome to the latest issue of Ophthalmology Update.

It is an exciting time at the Cole Eye Institute. After years of planning and with the philanthropic support of almost $100 million in generous contributions, we will break ground in 2020 for an expansion that will more than double the size of our existing building on Cleveland Clinic’s main campus.

In the past decade, the number of patients who have sought ophthalmology care with us has dramatically increased. Our clinical volume has risen by 146% and our surgical volume by 240%. The expanded Cole Eye Institute will accommodate our continued growth and, more importantly, will drive the transformation of the care we deliver, emphasizing innovation, value, patient satisfaction and optimal outcomes. It truly will be a next-generation facility. You can learn more about our expansion plans on P. 22.

We are honored to have been ranked among the nation’s Top 10 ophthalmology programs for eight years in a row, including in 2019-20, by U.S. News & World Report’s Best Hospitals survey. A successful ophthalmology program is defined not only by high-quality care, but by impactful research, comprehensive training and meaningful community service.

We are laser focused on all of these areas. As you will see in this issue:

- Our physician-researchers are making remarkable progress in some of ophthalmology’s most critical areas, from discovering a key corneal immunoprotective mechanism to developing a novel retinal toxicity indicator and deciphering the molecular pathways by which hypoxia-inducible factor stabilization works to prevent retinopathy of prematurity. More than a dozen of our investigators are supported by at least one of the National Institutes of Health’s R01, R21, K08, K23 and UG1 grants.

- Our ophthalmology residency program has earned recognition as one of the nation’s 12 best, according to a 2019 Ophthalmology Times survey of our peers.

- Our Cole Eye Institute practitioners are expanding their efforts to identify vision problems in at-risk populations in Northeast Ohio with the help of an upgraded mobile screening van. The Cleveland Clinic & KOHL’S Vision First program, now in its 19th year, is a national model.

We welcomed four new staff members to the Cole Eye Institute team in 2019: J. Bradley Randleman, MD; Bryan M. Roth, MD; Kristie Stalker, OD; and Claudia Perez-Straziota, MD. As you will read on P. 11, Dr. Randleman brings a wealth of expertise in corneal surgery and research, particularly regarding the identification and management of corneal ectatic diseases.

I am proud to share the accomplishments of our ophthalmologists, optometrists, researchers, nurses, technicians and others who are dedicated to advancing the care of Cole Eye Institute’s patients. Their collaborative spirit and quest for excellence are what make Cleveland Clinic a premier destination for ophthalmology care.

Daniel F. Martin, MD | THE BARBARA AND A. MALACHI MIXON III INSTITUTE CHAIR IN OPHTHALMOLOGY
CHAIR, COLE EYE INSTITUTE
Cole Eye Institute | By the Numbers

110 +
Ophthalmologists, optometrists and researchers

25
Residents and fellows

320,000 +
Clinical visits annually

17,000 +
Surgeries annually

1,477 +
Refractive cases annually

27
Locations

29
Clinical trials underway
Influenced by the results of the Infant Aphakia Treatment Study (IATS), the management of infantile cataracts has undergone significant changes in the past two decades. A new study of surgical outcomes suggests unilateral cataract surgery appears relatively safe for children between the ages of 7 and 24 months.

Before the IATS, which involved investigators from 13 academic institutions in the United States and enrolled patients between 2004 and 2010,¹ there was no agreement on the benefits of implantation of intraocular lenses (IOL) in infants under the age of 7 months, nor were there any prospective studies that analyzed possible complications thereof.

The IATS demonstrated no visual benefits of IOL implantation compared with using contact lenses to replace the natural lens of the eye after its removal. Unfortunately, infants undergoing IOL implantation had high rates of additional intraocular surgery (72%), as well as adverse events such as lens proliferation into visual axis (44%), pupillary membrane (28%), corectopia (28%), glaucoma (19%) and glaucoma suspect (9%).²

We believe the findings of the IATS have influenced most pediatric ophthalmologists to prefer contact lens care instead of IOL insertion in infants under 6 months of age.

**Toddler Aphakia and Pseudophakia Study Results**

The recent Toddler Aphakia and Pseudophakia Study (TAPS) was designed to evaluate the outcomes of cataract surgery in children prior to 24 months of age and was conducted at 10 of the 13 IATS sites. It is the largest cohort of cataract outcomes in this age group.

Despite limitations of retrospective data including the use of nonrandomized patients and nonstandardized documentation, the close parallels between the care provided to TAPS and IATS patients allow for comparison in determining the effect of age on outcomes.

In this first report of TAPS,³ children who underwent unilateral cataract surgery with or without IOL placement during the IATS enrollment years of 2004 to 2010 were followed up, and intraoperative complications, adverse events, long-term visual acuity outcomes and incidence of strabismus were analyzed.
Fifty-six children were included, with a mean postoperative follow-up of 47.6 months. Median age at cataract surgery was 13.9 months (range 7.2-22.9). Of patients in the study, 92% received a primary IOL. The only intraoperative complication was inadvertent capsular disruption in five patients (9%).

At 5 years of age, visual acuity of treated eyes was very good (> 20/40) in 11% and poor (< 20/200) in 44%. Adverse events were identified in 24%, with a 4% incidence of a glaucoma suspect status. An additional unplanned intraocular surgery occurred in 14% of children. Neither adverse events nor intraocular reoperations were more frequent in children who were operated between 7 and 12 months of age than those who had surgery at 13 to 24 months.

Although most children had IOL implantation concurrent with unilateral cataract removal, the incidence of complications, reoperations and glaucoma was low in children older than 7 months, and compared favorably to same-site IATS data for infants operated before 7 months of age.

THE BOTTOM LINE ON SAFETY

Unilateral cataract surgery in infants older than 7 months appears to have a less complicated course than in patients younger than 7 months, with fewer intraoperative complications, adverse events and reoperations and smaller myopic refractive shift.

The TAPS results suggest that there are no deleterious consequences of implanting intraocular lenses over the age of 7 months compared with leaving the child aphakic and wearing a contact lens.

Dr. Traboulsi is Head of the Department of Pediatric Ophthalmology and Director of the Center for Genetic Eye Diseases at Cleveland Clinic's Cole Eye Institute. Dr. Bothun is an ophthalmologist in Mayo Clinic's Department of Pediatric and Adolescent Medicine.

References


High-Tech Advances in Low-Vision Care

AN INCREASING VARIETY OF OPTIONS CAN HELP MORE PATIENTS

By Kristi Stalker, OD

Low vision — visual impairment that cannot be corrected by medical or surgical treatment or conventional eyeglasses — affects almost 4 million people in the U.S. It is important for these patients to know about and have access to rehabilitative aids that can improve their ability to perform activities of daily living.

Many advances in low-vision care are related to general technological advances and are helping patients achieve their vision goals.

SMARTPHONES AND TABLETS

Smartphones and tablets have greatly improved quality of life for visually impaired patients who are willing and able to adopt new technology. Accessibility settings on these devices can be changed to enlarge text, increase contrast, control brightness and invert color. The device’s camera can be used to zoom in on distant objects or magnify close objects.

Voice-activated digital assistants such as Siri, Google Assistant and Alexa can accomplish various tasks, including reading or sending a text, checking a calendar, making a list or looking up a phone number. In a smartphone’s “accessibility” menu, patients can find the TalkBack (Android™) or VoiceOver (iPhone®) function that will read aloud words on the phone screen.

Useful apps available for download include:

Seeing AI. This app can read text, identify currency, scan bar codes and identify people.

TapTapSee. The user photographs an object by double-tapping the phone screen. The app announces a description of the image.

Be My Eyes. Through a live video call, a volunteer network of sighted people provides task assistance and navigation and answers questions about what users are “seeing.”

Blindfold Games. This entertainment app provides people with visual impairments more than 80 games, such as puzzles and card, video and board games.

HEADBORNE ELECTRONIC GLASSES

While wearable magnifiers have progressed significantly, they are still bulky and costly and, therefore, have had limited use in my practice thus far. Headborne electronic glasses such as seeBOOST and OrCam project images from a video camera, allowing for enhanced contrast and magnification. Some models can read text aloud, as well as identify items by bar code and people by facial recognition.

NAVIGATION AIDS

Technology also is making transportation easier for people with visual impairments. Ride-sharing services such as Uber and Lyft and navigation services with GPS can help people reach their destinations.

PORTABLE VIDEO MAGNIFIERS

The primary goal of most low-vision patients is to read standard print. Sometimes this can be accomplished with a stronger add at a closer working distance or with an optical magnifier. But patients often need more magnification or a larger field of view than these devices allow.

Portable video magnifiers such as Smartlux® Digital by Eschenbach Optik have become quite affordable and allow patients to read fine print comfortably due to multiple magnification and color settings.

Some video magnifiers also have optical character recognition. This feature allows users to switch between listening mode and scrolling text, which can be beneficial for patients with eccentric fixation.
“Smart canes” are equipped with ultrasound sensors that can detect nearby obstacles above chest level and warn users with a tactile vibration. They can be linked with a smartphone to provide navigation assistance.

“Smart paint” infused with light-converting oxides is being tested on the edges of crosswalks in some locations. When smart canes come in contact with the paint, they vibrate. The vibration helps pedestrians with low vision stay inside crosswalk lines. Researchers hope to use this paint to interact with GPS to identify the location of bus stops and businesses.

**RETINAL PROSTHESES**

Surgically implanted devices such as the Argus® II Retinal Prosthesis System have shown promise for patients who are profoundly blind. Cole Eye Institute has been a leader in Argus II bionic eye implantation in North America.

The Cole Eye Institute team is led by retina surgeons Aleksandra Rachitskaya, MD, and Alex Yuan, MD, PhD, and genetic counselor Meghan DeBenedictis, MS, LGC, MEd. Together they are advancing the field of retinal prostheses by developing virtual reality platforms for visual rehabilitation of patients learning to use their new vision. In the pilot study, patients reported having more confidence in moving around and improved balance.

The team also is studying changes in patients’ brains as a result of the new visual input.

**PATIENT ACCESS**

Currently, low-vision exam services are covered by most private and government insurance plans. However, low-vision devices typically are not. Patients must pay out of pocket, despite advocacy efforts to classify these devices as durable medical equipment. Surgically implanted devices are classified as prosthetics and are covered by Medicare.

Medical providers should not reserve low-vision care recommendations only for patients who are profoundly blind. They should offer care options to patients with all levels of visual impairment.

A high-tech low-vision aid, nonstandard glasses, tinted lenses, specialized lighting or simply a refined refraction may improve patients’ functioning and satisfaction.

*Dr. Stalker is a staff member of Cleveland Clinic’s Cole Eye Institute.*
How Does the Cornea Guard Against Infection and Regulate Inflammation?

RESEARCH UNCOVERS NEW COMPONENT AND CAPABILITIES IN THE EYE’S IMMUNE SYSTEM

The human cornea is a remarkable structure, and not just for its refractive capabilities. Though constantly exposed to opportunistic and potentially pathogenic microbes in the environment, it rarely becomes inflamed or infected, indicating the presence of a formidable, highly effective protection system.

In 2012, then University of California, Berkeley, ophthalmic researcher Connie Tam, PhD, led a team that discovered a previously unknown component of that complex protection system — a structural protein called cytokeratin 6a (K6a), expressed by corneal epithelium, that also possesses novel antimicrobial properties.

Short phosphorylated fragments of K6a are potent, broad-spectrum bactericides, capable of binding to and killing a variety of ocular pathogens, including *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*.

Since Dr. Tam joined Cleveland Clinic’s Cole Eye Institute in 2014, her ongoing research has been focused on better understanding the surprising corneal protective role of K6a and its peptide fragments. For instance, Dr. Tam is exploring how and where the protein fragments are generated, how they rapidly mobilize to a potential infection site, whether fragments can differentially target microbes, and whether K6a’s capabilities might be harnessed in new human antimicrobial agents.

Her latest findings, presented at the 2019 Association for Research in Vision and Ophthalmology annual meeting, reveal K6a’s ability to control local inflammation in the cornea, whether from infectious or noninfectious causes.

“We would never have thought that a keratin protein, which is shifting back and forth between its polymerized and subunit forms in the epithelial cell, could be an active player in the host defense and immunoregulatory mechanisms,” Dr. Tam says. “Perhaps understanding more about how it works can help us develop new therapies for infectious and inflammatory diseases.”

A FORMIDABLE BARRIER

The healthy cornea’s ability to resist epithelial penetration by virtually all microbes and to constantly clear pathogenic bacteria from its surface points to the existence of a unique constitutive function distinct from the adaptive immune system. Ocular immune homeostasis is crucial, since corneal inflammation, if not prevented or constrained, could reduce optical clarity, alter refractive shape and ultimately result in permanent vision impairment or blindness.

Some elements of the cornea’s constitutive patho-protective capacity previously have been identified, including antimicrobial proteins in tears and antimicrobial peptides (AMPs).
of the β-defensin and cathelicidin classes produced by ocular surface epithelial cells. AMPs are the eukaryotic equivalents of antibiotics and work by binding to and lethally disrupting the permeability of microbial membranes. They also have a cell-signaling and mobilization capacity, serving to link the innate and adaptive immune systems. Comprehension of AMPs’ functionality and interactions is still evolving.

Dr. Tam suspected that additional ocular antimicrobial elements exist, helping to maintain immune homeostasis. She investigated, mining an immortalized cell line derived from human corneal epithelium for evidence of constitutively expressed AMPs.

Fractionation and mass spectrometry revealed AMPs derived from K6a, a subtype of one of the more than 50 known human keratin proteins.

Structurally, keratin subtype K6a forms the cytoskeleton of epithelial cells, including those in the cornea.

Synthetic analogs of the natural K6a-derived AMPs (KAMPs) that Dr. Tam tested showed bactericidal activity against several potential ocular pathogens, including P. aeruginosa, S. aureus and S. pyogenes. Dr. Tam confirmed KAMPs’ in vitro antimicrobial capabilities in vivo; mouse corneas with deficient K6a production or topically treated with a proteasome inhibitor showed impaired bacterial clearance efficiency in vivo and increased bacterial adherence on the surface ex vivo.

Tagged KAMPs tracked with fluorescence microscopy and high-resolution transmission electron microscopy revealed that when the peptide bonded with P. aeruginosa bacterial cells, it caused them to become permeable, lose motility and die within hours, although the precise mechanism is unknown.

In subsequent research, Dr. Tam showed that the human cornea’s exposure to bacterial ligands prompts remodeling of the cornea’s K6a filamentous network, via depolymerization of the keratin cytoskeleton and production of KAMPs in the cytosol. That remodeling is a host defense response involving direct upregulation of KAMP production by the ubiquitin-proteasome system, without an appreciable increase in K6a gene expression or proteasome activity — a new role for proteasome-mediated proteolysis in innate immunity defense.

![Figure](image-url) A depiction of KAMPs’ patho-protective role in the cornea.
A ROLE IN INFLAMMATION CONTROL

Dr. Tam’s newest findings shed more light on K6a’s immunoregulatory capabilities. Using human cells and mouse models, she found another important role of cytosolic K6a — controlling local inflammation driven by both infectious and noninfectious causes.

Specifically, when Dr. Tam used CRISPR-Cas9 genome-editing technology to delete K6a proteins in human corneal epithelial cells, and then stimulated the epithelial cells with bacterial outer-membrane molecules called lipopolysaccharides (LPS), the result was increased production of proinflammatory and chemotactic cytokines.

In mouse models of P. aeruginosa- or LPS-induced keratitis and sterile corneal epithelial wound healing, increased cytokine and chemokine levels in the K6a-deficient corneas worsened clinical outcomes. The negative manifestations included extensive neutrophil infiltration, irreversible tissue damage, impaired wound healing and, in the case of infectious keratitis, increased bacterial load.

Although inflammation is the body’s natural immune reaction to injury and microbial insults, unconstrained inflammatory responses can irreversibly damage tissue structure and, in the case of the cornea, pose a great risk of vision loss and blindness.

Common risk factors for corneal inflammation (keratitis) include contact lens use, corneal trauma, tear deficiency and diabetes. The Centers for Disease Control and Prevention estimates that at least 1 million clinical visits for keratitis occur annually in the United States, causing significant medical and socioeconomic burdens.

In clinical practice, topical corticosteroids are the current standard of care for corneal inflammation. Although powerful, corticosteroids function nonspecifically to inhibit the host immune response and are associated with serious side effects, such as elevated intraocular pressure, corneal thinning, cataracts and secondary infection. Therefore, new and more targeted therapeutic options for controlling inflammation are necessary to improve patient care and clinical outcomes.

Building on her newest findings, Dr. Tam will investigate the immunoregulatory mechanisms of cytosolic K6a, as she believes increased understanding of K6a’s molecular role will aid development of tissue-specific anti-inflammatory drugs with fewer side effects than corticosteroids.

Figure. Confocal image of immunofluorescence-labeled K6a filaments (green) in cultured human epithelial cells. Cell nuclei are counterstained with propidium iodide (red).
BRILLOUIN IMAGING, CORNEAL CROSS-LINKING COULD AID IDENTIFICATION AND MANAGEMENT OF KERATOCONUS AND POSTOPERATIVE ECTASIA

When internationally recognized eye surgeon and researcher Ronald Krueger, MD, left Cleveland Clinic Cole Eye Institute in 2018 to lead the University of Nebraska Medical Center’s ophthalmology program, Institute Chair Daniel F. Martin, MD, knew he would have a tough time finding someone with comparable credentials.

Dr. Krueger is a talented surgeon and a pioneer in characterizing refractive surgery’s impact on corneal tissue. “Only a handful of people could come in and fill his shoes,” Dr. Martin says.

continued next page
One who came to mind was Dr. Martin’s friend, colleague and former student J. Bradley Randleman, MD. They knew each other from their time at Emory University, where Dr. Randleman had been the chief ophthalmology resident and later an endowed professor and Director of the Cornea Service, and where Dr. Martin was an endowed professor and Director of the Retina Service before leaving to take the reins at Cole Eye Institute.

Dr. Randleman went on to become a widely respected cornea specialist, holding the Hughes Professorship at Emory University followed by becoming professor of ophthalmology at the University of Southern California’s Keck School of Medicine and Director of the Cornea & Refractive Surgery Service at USC’s Roski Eye Institute. He is editor-in-chief of the Journal of Refractive Surgery and has written four textbooks and more than 150 peer-reviewed publications.

In 2019, after months of conversations with Dr. Randleman about joining the Cole Eye Institute faculty, Dr. Martin clicked on a photo in his email inbox and learned he’d succeeded. It was an image of Dr. Randleman and his family, all wearing Cleveland Clinic T-shirts.

Dr. Randleman’s research focus is the identification and management of corneal ectatic diseases, including keratoconus and postoperative ectasia after LASIK, and the therapeutic potential of corneal cross-linking (CXL). He is the co-principal investigator of a five-year, $2 million National Institutes of Health Research Project Grant (R01) to develop an optical technology that could improve keratoconus diagnosis and treatment.

With the combination of Dr. Randleman, Ocular Biomechanics and Imaging Laboratory Director William J. Dupps, MD, PhD, and Director of Corneal Research Steven Wilson, MD, Dr. Martin predicts that Cole Eye Institute will become a major center of expertise in corneal research.

In this interview, Dr. Randleman speaks about his work and his plans.
Q: Why did you choose keratoconus as a research focus?

Dr. Randleman: I just found it fascinating. It was a bit of a mystery. You can’t physically see the anatomical changes that patients are having until they’re pretty far down the road, diagnostically. The more I learned about it, the more I realized how little we truly understand keratoconus at the basic physiologic, anatomic level, and even causally, why certain people get keratoconus and others don’t; why it progresses so far, so fast, in some patients and barely changes in others. It’s tied in nicely with the other side of my clinical practice, which is refractive surgery, because that’s the major thing we’re screening for — any subtle signs of an ectatic cornea.

Q: How has refractive surgery changed with the realization that keratoconus can be an unintended result?

Dr. Randleman: The indications for surgery have shrunk a bit since the 1990s. We don’t treat myopia at levels as high as we initially did. We certainly screen much more diligently than we did in the early period.

Q: What’s the prevalence of keratoconus, both spontaneous and surgery-induced?

Dr. Randleman: For disease-based keratoconus, the best estimate is about 1 in 2,000, but that’s for fairly late-stage disease. It varies tremendously by region. We did a study of prevalence in pediatric patients in Riyadh, Saudi Arabia, and it was 1 in 21. A study in the Netherlands found 1 in 375 in the general population. It’s not unreasonable to think that as many as 1 in 500 people have some evidence of disease, and maybe as many as 1 in 200 have some subtle, abnormal findings. For post-refractory surgery prevalence, 1 in 2,500 to 3,000 is a ballpark figure — maybe as few as 1 in 5,000, depending on the surgical center.

Q: You were involved in developing an early method of quantitatively assessing patients’ risk for ectasia after LASIK surgery. How did that come about, and what’s the status now?

Dr. Randleman: When LASIK was introduced in the U.S. in the late 1990s, there were some initial reports of postsurgical ectasia. People wondered whether it was an anomaly or could it happen to anyone, and was it predictable based on risk.
Dr. Randleman: First, we want to look at a wide range of patients in their baseline state — normal patients and those with various stages of keratoconus, from subclinical to advanced — to see what information Brillouin imaging can give us. Our hope is that we can find some biomechanical metrics that identify these eyes as being different than normal in places where our current imaging does not. The second focus of our study is using Brillouin to assess individual refractive procedures that we know weaken the cornea, to determine the amount of weakening, where it happens and to what extent it differs in various procedures. How different, biomechanically, is LASIK versus PRK versus SMILE [small-incision lenticule extraction]? And finally, with cross-linking, which we know strengthens the cornea in keratoconus, we’ll use Brillouin to see how quantifiable the change in stiffness is before and after cross-linking and where it occurs anatomically.

Q: How would you use that information?

Dr. Randleman: If we’re able to answer those questions, it allows us to start looking at individualizing refractive surgery protocols or cross-linking protocols. If we can tell a patient coming in what their corneal biomechanical profile is, we can better match them with a specific treatment protocol.

Q: How would you do that? Are you hoping the research results in a diagnostic device?

Dr. Randleman: I think the outcome will be a clinically available device. That’s certainly where we’re headed. Ultimately, the hope is that we can find something that will give us a sense of the cornea’s inherent strength, so that we know if we can modify it with refractive surgery or if we need to be thinking about doing a strengthening procedure before the patient has had any real anatomic changes and lost any vision. And, ideally, we’ll even be able to determine how much treatment needs to be done to give an exact outcome. We’re many steps away from that. First we need to characterize what’s happening en masse to the cornea.
Q: Corneal cross-linking, or CXL, is a relatively new approach to strengthen the cornea, approved by the U.S. Food and Drug Administration in 2016 to treat progressive keratoconus and post-LASIK ectasia. Are there still outstanding questions about it?

Dr. Randleman: Certainly one thing we don’t know is how long the effect lasts. The earliest treatments were around 2000, in Dresden, Germany. We’re getting reasonably good 10-year data. We’ll be happier when we have 30-year data. The biggest thing that confounds us right now is trying to predict what type of outcome an individual patient will have. The vast majority of patients are stabilized with CXL, meaning their corneas do not continue to get steeper or thinner, but not everyone is. Who are those outliers? Did they need more treatment? A higher intensity? Longer treatment? Those things we don’t know.

Q: Is that outcome variability due to individual variation in patients, possibly in corneal biomechanical properties? Or to variation in the CXL protocol, such as whether it’s done with the epithelial layer intact or removed?

Dr. Randleman: My first guess is that it’s something different about the individual patient. Any epithelial-on protocol is doing something to supposedly enhance riboflavin penetration, and that’s poorly studied to date. Even in the 96% of patients who have stabilization with CXL after epithelial-off treatment, some have significant flattening, some have no flattening, some have an induction of astigmatism and some have a reduction of astigmatism. So all of those are things we would like to understand better and, ideally, to treat individually, which we just don’t have the ability to do right now.

Q: Does CXL have potential uses beyond treating ectasia?

Dr. Randleman: The big one is in infectious keratitis. That’s really exciting, because a single treatment may be as effective as weeks of antibiotics. And it takes out that guesswork of whether it’s Gram positive, Gram negative or an early fungal infection. We also don’t have to worry whether a particular patient is going to be resistant to one medicine versus another. Once infections become deeper and later stage, cross-linking is less effective. It probably would be best as a front-line treatment. There have been some other potential CXL uses discussed. Later-stage treatment for patients with corneal edema who are not good surgical candidates — it may have some limited role there. Another is cross-linking for refractive outcomes and/or corneal regularization. Those are quite exciting.

Q: What do you mean by regularization?

Dr. Randleman: For instance, maybe you have a patient who is coming in for cataract evaluation and has some irregular astigmatism. You don’t need to stabilize their cornea, but if you could reduce their irregularity by selectively applying cross-linking, that would be a great minimally invasive procedure that may improve their vision as well. CXL also has been looked at as a less-invasive option for low myopia and low hyperopia. The jury is still way, way out on that. But if we became a bit more refined in those, then people with half a diopter of refractive error who don’t really generally go for surgery may become refractive surgery candidates using this selective CXL treatment. And for people who have a good but not perfect refractive outcome after cataract surgery, CXL may be a minimally invasive treatment we could do to fine-tune their vision. Another area that’s in desperate need of improvement is primary keratoprostheses. These devices are a mix of plastic or some type of nonorganic material combined with a corneal graft. One of the big issues is that the corneal rim is subject to melting. Some doctors have cross-linked those. It hasn’t been done very often, but making keratoprostheses more robust would be a real game changer.

Q: Why did you decide to join Cole Eye Institute’s staff?

Dr. Randleman: It’s a phenomenal place. I had the good fortune of working with Dr. Martin when he was at Emory University School of Medicine. He was on faculty when I started my residency training. He’s always been a friend and mentor. I’ve collaborated with Steve Wilson and B.J. Dupps numerous times on studies, panels and course designs. Dr. Dupps and I are looking at the same thing — corneal biomechanics — from different directions. Dr. Wilson is predominantly looking at wound healing — corneal microstructure, if you will — which is intimately important in what we’re doing with cross-linking, in how we may modify refractive procedures based on what we’re trying to do biomechanically. So these things all fit really well together. There’s really no place in the United States that is this well funded from a research standpoint and has this many individuals working on refractive surgery, keratoconus and the continuum of corneal biomechanics. I’m very excited to be here.
Researchers at Cleveland Clinic’s Cole Eye Institute are pioneering the use of novel image analysis systems to evaluate optical coherence tomography (OCT) for early detection of retinal disease and unique characterization of disease features.

Conventionally, OCT is used in clinical practice to visualize the retina, vitreoretinal interface and choroid. OCT provides outstanding visualization of retinal anatomy and is a critical piece to the evaluation of most retinal diseases.

Now, a new Cole Eye Institute study suggests that ellipsoid zone (EZ) mapping, a new image visualization/analysis platform on OCT, may be an effective screening tool to identify subtle retinal changes indicative of toxicity from hydroxychloroquine treatment. The research was presented at the American Academy of Ophthalmology’s (AAO) 2019 annual meeting by Katherine E. Talcott, MD.

**LOOKING FOR SUBTLE RETINAL CHANGES**

Hydroxychloroquine is commonly used to treat autoimmune inflammatory diseases such as rheumatoid arthritis. A rare side effect is retinal toxicity, which can cause irreversible and progressive vision loss. Detecting early signs of toxicity is critical to avoid more severe vision complications. However, the early changes on OCT can be subtle and difficult to detect.

Cleveland Clinic Cole Eye Institute retina specialists Justis P. Ehlers, MD, who holds the Norman C. and Donna L. Harbert Endowed Chair for Ophthalmic Research, and Sunil K. Srivastava, MD, have developed an OCT analysis platform that integrates EZ mapping technology with OCT images to quantify metrics of various layers of the retina to better understand changes in disease.

Dr. Ehlers and his team have used the technology to detect alterations in the ellipsoid zone and outer retina in patients...
known to have hydroxychloroquine toxicity, but it has not been used to examine patients on hydroxychloroquine without known toxicity.

In the image analysis study described at AAO, a team led by Drs. Ehlers and Talcott through the Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research, examined the OCT scans of 401 patients who had been treated with hydroxychloroquine over a seven-year period and who also had OCT scans performed at different time points. The researchers applied the ellipsoid zone mapping software to the patients’ OCT images to determine whether detectable longitudinal changes in the outer retinal bands were present.

The study’s goal was to assess whether subclinical changes in ellipsoid zone integrity occurred and whether this software tool was helpful in identifying these changes. “We actually were surprised that we were able to identify, in select patients, clear quantitative changes over time, even when the physician taking care of the patient didn’t recognize signs of toxicity,” Dr. Talcott says. “We found that this tool was able to pick up those changes.”

When evaluating the group overall, the researchers detected a significant increase in en face EZ attenuation from the first to the second OCT scan that correlated with the hydroxychloroquine-treated patients’ age ($p = 0.01$), daily dose ($p = 0.01$) and adjusted body-weight dose ($p = 0.04$). These findings suggest a progressive loss over time of EZ integrity. Of note, the features identified that correlate with increased attenuation are all risk factors for hydroxychloroquine toxicity.

The goal is to better determine how to use this technology as a screening tool. “We need to home in on what would be our cutoff for toxicity screening, and how we would better examine those patients who had had a change,” Dr. Talcott says.

“This tool could represent an important asset for clinicians to use in the screening for outer retinal diseases and retinal toxicity,” Dr. Ehlers says. “This could potentially be used to augment identification for patients at risk and/or patients with early toxicity. Optimized identification of those patients could reduce their risk of progression and additional visual loss.”

In addition to identifying OCT as a potential method for identifying hydroxychloroquine toxicity, the current study has other clinical implications, Dr. Talcott notes.

“More patients are probably having changes from this medication than we would expect,” she says. The researchers found that the mean dose being taken by patients in the study was only slightly less than the recommended dose. That means that nearly half of patients were taking more hydroxychloroquine than recommended. “The number of patients at risk could be higher than we anticipated,” she says. “We need better tools to screen for these patients.”


**Figure.** A case example of a 52-year-old patient with hydroxychloroquine toxicity as seen on en face ellipsoid zone mapping. At baseline, the patient had evidence of ellipsoid zone attenuation (pink areas) seen on en face ellipsoid zone mapping (A), three-dimensional macular cube reconstruction (B) and OCT images (C). The patient continued on hydroxychloroquine for 26 months after baseline. At follow-up, the patient had progressive ellipsoid zone attenuation (pink areas) seen on en face ellipsoid zone mapping (D), three-dimensional macular cube reconstruction (E) and OCT images (F), signifying progressive toxicity.
The transcription factors known as hypoxia-inducible factors (HIFs) are oxygen sensors in the cellular environment. In a hypoxic setting, such as the womb during embryogenesis, HIFs mediate the adaptive response to reduced oxygen availability. They direct the expression of genes vital to survival and development, including those promoting erythrocyte production and regulating fetal retinovasculature formation.

In hyperoxic conditions, such as the high-oxygen concentration needed to support premature infants’ breathing, HIF activity is downregulated and normal blood vessel growth is inhibited, leading to the vasoproliferation of retinopathy of prematurity (ROP) and potential blindness.

The class of drugs called HIF stabilizers prevent HIF degradation and thus have shown promise in preventing ROP and treating anemia secondary to chronic kidney disease (CKD). But HIF stabilizers’ mechanism of action has raised concerns that they might exacerbate pathologic retinal angiogenesis (neovascularization) associated with ROP or diabetic retinopathy in CKD.

Cleveland Clinic Cole Eye Institute researchers tested that premise, using the HIF stabilizer roxadustat in a mouse model. In results presented at the 2019 Association for Research in Vision and Ophthalmology annual meeting, George Hoppe, MD, PhD, and colleagues reported that administration of roxadustat during hyperoxia does not result in pathologic angiogenesis, and instead effectively prevents oxygen-induced retinopathy (OIR).

The research also revealed more about the molecular pathways by which HIF stabilization works and how it should be therapeutically used.

THE ROLE OF HIFS
When premature babies are placed in high-oxygen environments, their still-developing retinas are protected by choroidal circulation. However, when infants leave this environment, hypoxia causes their retinal tissue to become ischemic. The central element of the body’s response to hypoxia is upregulation of HIFs.
“HIFs are responsible for transcription of hundreds of genes. They stimulate blood vessel growth, affect cytoprotection and cytostability, and reduce mitochondrial restoration.” – George Hoppe, MD, PhD

“HIFs are responsible for transcription of hundreds of genes,” Dr. Hoppe says. “They stimulate blood vessel growth, affect cytoprotection and cytostability, and reduce mitochondrial restoration.”

Abnormal HIF upregulation leads to preretinal neovascularization, he explains. These disorganized, pathological blood vessels are extremely fragile and can lead to fibrovascular scarring on the retina, a major cause of retinal detachments and retinal hemorrhaging in infants.

The most common treatment for neovascularization is laser surgery to obliterate the tissue, he says. However, this also destroys peripheral tissue, often leaving only central vision. Dr. Hoppe and his collaborator, Cole Eye Institute ophthalmologist Jonathan Sears, MD, have worked for more than a decade to find ways to intervene during the hyperoxic phase and prevent neovascularization. Their work has repeatedly pointed them to HIFs.

HIF STABILIZERS

HIFs’ alpha subunits are critical to the transcription factors’ oxygen-dependent regulatory capabilities. The alpha units are hydroxylated at conserved proline residues by HIF prolyl-hydroxylases, allowing for recognition and targeting for rapid degradation in normoxic or hyperoxic conditions. Degradation of subunit HIF-1α results in halted downstream angiogenic pathways, including the reduction of vascular endothelial growth factor (VEGF) secretion associated with oxygen-induced vascular obliteration. HIF-2α regulates a variety of hypoxia-inducible genes during embryonic development, including those involved in erythropoiesis and angiogenesis.

HIF stabilizers such as roxadustat act by inhibiting prolyl-hydroxylase enzymes, preventing HIF degradation.

In the retina, pathologic angiogenesis is mediated by Müller cell macroglia. Dr. Hoppe and his colleagues tested whether Müller cell HIF-2α activation was necessary for HIF stabilization-induced prevention of OIR, so that they could determine whether roxadustat activates pathologic angiogenesis.

To carry out the investigation, the Cole Eye Institute researchers used mice with a knockout of HIF-2α in their Müller cells. The researchers subjected the knockout mice to 75 percent oxygen from day 7 to day 12 of their lives and intraperitoneally injected them three times with either phosphate-buffered saline or roxadustat at days 6, 8 and 10. At day 17 their retinas were stained and areas of vaso-oblitration and neovascular tufting were measured; retinal HIF protein and gene expression levels also were assessed.

WHAT THE STUDY FOUND

The results showed that systemic roxadustat administration during hyperoxia prevented OIR. The drug primarily upregulated HIF-1α in mouse retinal tissue. Retinal HIF-2α levels increased by 50%, but retinal expression of HIF-2α targets that are known to promote angiogenesis and endothelia cell migration did not increase. When wild-type non-HIF-2α-knockout mice were treated with HIF stabilization after ischemia developed, vascular loss and neovascularization increased.

Dr. Hoppe and his colleagues had hypothesized that elimination of the HIF-2α subunit from the mice retina would prevent roxadustat from blocking neovascularization, demonstrating that the HIF-2α pathway is important for the drug’s action.

“We actually saw quite the opposite,” Dr. Hoppe says. “We didn’t see exaggerated angiogenesis. We didn’t see the drug stop working. In fact, it worked even better.

“That was kind of a defeat, because we couldn’t implicate HIF-2α in the action of the drug,” he says. “But it was good news for the pharmaceutical company that is now conducting clinical trials, and good news for patients overall.”

Roxadustat is currently in phase 3 clinical trials for the treatment of chronic anemia related to kidney disease.

While the Cole Eye Institute research showed that roxadustat administration does not lead to pathological angiogenesis, and that HIF-2α stabilization isn’t required for vasoprotection and OIR prevention, HIF-2α upregulation could exacerbate existing neovascularization and vaso-oblitervation. That reinforces the need to use HIF stabilization to prevent ischemia, not react to it, Dr. Hoppe says. ●
Anti-VEGF Therapy Effective in Treating High-Risk Nonproliferative Diabetic Retinopathy Without Diabetic Macular Edema

SIGNIFICANT REDUCTION IN RISK FOR VISION LOSS AND DISEASE PROGRESSION

Intravitreal injections of the anti-vascular endothelial growth factor (VEGF) drug aflibercept induce regression of disease in patients with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) and without diabetic macular edema (DME), according to new results of the PANORAMA trial.

Retina specialist Rishi Singh, MD, of Cleveland Clinic’s Cole Eye Institute, presented the results of the phase 3 randomized, double-blind trial, the first large, prospective trial of its kind since the Early Treatment Diabetic Retinopathy Study, at the American Academy of Ophthalmology’s 2019 annual meeting.

VEGF, a signal protein, stimulates blood vessel formation. Its overexpression is believed to drive the process of vascular proliferation in diabetic retinopathy. The previously published VISTA and VIVID studies showed that VEGF inhibitors decrease the rate of disease progression in patients with NPDR and DME, but anti-VEGF efficacy and safety had not been studied in patients with NPDR without concurrent DME.

“The last time we studied these patients, laser treatment was the only option,” says Dr. Singh, a retina. “Now we have evidence that a treatment regimen achievable in the real world works in these high-risk patients.”
HIGH-RISK, HIGH REWARD

The PANORAMA study randomized 135 participants with moderately severe to severe NPDR (Diabetic Retinopathy Severity Scale [DRSS] scores from 47 to 53) and without DME to receive intravitreal aflibercept injections every 16 weeks after four loading doses, 134 participants to receive the same injections every eight weeks after five loading doses, and 133 participants to a sham control. Noncontrols had Type 1 or 2 diabetes mellitus and a baseline best-corrected visual acuity (BCVA) score of ≥ 69 letters. The mean age was 55.7 years, and 44% of patients were women.

The primary endpoint was the proportion of patients whose DRSS scores improved two or more steps in one year. Researchers also sought to determine whether aflibercept reduced vision-threatening events and impacted visual acuity.

At week 52, 65.2% of the 16-week injection group and 79.9% of the eight-week group had a two-step or more improvement in their DRSS scores versus 15% of the sham group ($p < 0.0001$ for both). During the study, 20% of control patients developed a vision-threatening complication or DME, compared with only 4% of the 16-week treatment group and 3% of the eight-week group ($p < 0.0001$ for both).

“These are excellent outcomes for patients who are at risk for vision loss,” says Dr. Singh. “An 80% to 90% reduction in risk for threats to vision is great news for patients and may result in a new treatment paradigm. However, these treatments come at a cost and potential risk, and DME can be very effectively managed if it develops. More information on the long-term importance of improving DRSS scores is needed before this paradigm is likely to be widely adopted in clinical practice.” The Diabetic Retinopathy Clinical Research Retina Network is conducting a four-year study (Protocol W) that should help answer this question.

TREATING RETINAL DISEASE AT CLEVELAND CLINIC

Diabetic retinal disease is the leading cause of blindness in working-age adults in the United States. Dr. Singh’s work to establish effective treatments for DME and diabetic retinopathy earned him the 2018 early career investigator award from the president of the American Society of Retina Specialists. Dr. Singh is President of the Retina World Congress and leads the Cole Eye Institute Center for Ophthalmic Bioinformatics, which addresses leading causes of blindness.

“Understanding presentations of these ophthalmic diseases, their risk factors, their prognosis for progression and their optimal response to treatment through bioinformatics processes is an important step in improving the lives of our patients,” says Dr. Singh.

“PANORAMA results are very encouraging,” he notes. “But there is always more work to do. We hope that harnessing the power of bioinformatics will allow further insight into many ophthalmic diseases, including diabetic retinal disease.”
Creating the First Animal Model of Brachytherapy-Induced Radiation Retinopathy

FIRST STEP TOWARD TESTING THERAPEUTICS

By Michael Ramos; Alex Yuan, MD, PhD; and Arun Singh, MD

A patient is diagnosed with uveal melanoma. Thanks to therapeutic advances, enucleation is now a last resort. A multidisciplinary team of ophthalmologists and radiation oncologists develops a plan to treat the patient with targeted radiotherapy. They elect to use a radioactive plaque, a treatment known as brachytherapy, to deliver high-dose radiation to the tumor.

The tumor shrinks significantly. However, the patient develops the serious vision-impairing complication of radiation retinopathy.

UNDERSTANDING THE DISEASE: WHY WE NEED AN ANIMAL MODEL

Radiation retinopathy is a broad term describing a spectrum of retinal changes following radiation exposure.

Classically defined by its vasculopathy, radiation retinopathy typically develops six months to three years following irradiation. It begins with preferential loss of endothelial cells, leading to vessel occlusion, leakage and retinal nonperfusion. As the disease progresses, retinal layers are compromised, further impairing vision. Late-stage radiation retinopathy is characterized by ischemia-induced ocular neovascularization.

Despite an established disease progression, the underlying pathophysiological mechanisms of radiation retinopathy remain unclear.

Treatments include risk-factor modification, such as:

- Limiting the total dose of radiation delivered to the tissue.
- Intravitreal injection of anti-vascular endothelial growth factor (VEGF) and/or corticosteroids.
- Laser photocoagulation to limit neovascularization.

Modest success has been achieved with these therapies. However, they fail to address the cellular and molecular events leading to radiation retinopathy, and prevention strategies remain limited.

The lack of elucidated mechanisms and dedicated treatment options demonstrates a clear need for more robust research. Similar to the research on other retinal vasculopathies such as diabetic retinopathy, radiation retinopathy research can benefit from the mindful use of an appropriate animal model — a useful tool in the quest to understand disease pathologies.

MAKING THE MODEL

Despite its near 95% effectiveness and use as a first-line treatment in many cancers, episcleral plaque brachytherapy is commonly associated with radiation retinopathy.

Because no brachytherapy-induced radiation retinopathy animal model exists, we sought to establish one. It is our goal to set the stage for more mechanistic studies and eventually test promising therapeutics in a model closest to clinical experience.

Several factors need to be considered when establishing a radiation retinopathy model:

1. Mode of radiation administration. Though technically challenging, we decided on a radioactive episcleral plaque, as one had not yet been described. Most of the previous models used external beam radiation in the form of X-rays.

2. Type of ionizing radiation. The emitter used determines the penetrating power and the energy delivered to the tumor and surrounding tissue.

3. Dose of radiation. Higher doses, measured in gray (Gy), result in greater retinal damage sooner after treatment.

4. Differences in ocular anatomy among species (Figure 1). Factors such as lens size and vascular architecture may impact the development of retinopathy in different models.

Figure 1. Animal eye schematics: Gross anatomical differences are significant when considering radiation field and size of the eye. Each schematic is drawn to scale.
To create our model, a 1 mm by 4 mm radioactive iodine-125 seed was surgically implanted posterior to the limbus of the left eye of Lewis rats (Figure 2). The initial dose of radiation treatment lasted six hours, after which the seed was removed. A total dose of 45 Gy at a distance of 1 mm from the seed was delivered. Escalating dosages of radiation will be administered to find the optimal range.

For 12 months, rats will be followed using optical coherence tomography (OCT) and wide-field fluorescein angiography (FA) to monitor the appearance of retinopathy (Figure 3). Based on previous reports using external beam radiation, most animals show signs of retinopathy (i.e., dot hemorrhages, cotton wool spots or retinal thinning) approximately six months after treatment.

**MOVING FORWARD**

This pilot study is the first attempt at episcleral plaque brachytherapy-induced radiation retinopathy in an animal model. In conjunction with the appropriate model, clinically relevant imaging modalities, such as OCT and wide-field fluorescein angiogram, will allow for easier in vivo comparative anatomical assessment and classification of radiation-induced retinopathic changes.

Future investigations can dive deeper into potential pathophysiological mechanisms, such as those involving inflammatory pathways, leukocytes, microglia and apoptosis. These studies will allow for a better understanding of radiation retinopathy and the development of more effective therapies for this disease.

*Michael Ramos is a research technician at Cole Eye Institute. Dr. Yuan is a retina specialist. Dr. Singh is Director of the Department of Ophthalmic Oncology.*
Cleveland Clinic’s Cole Eye Institute will more than double its size with a building expansion scheduled to begin construction in 2020.
The expansion involves adding more than 150,000 square feet to the existing 130,000-square-foot building to accommodate the Cole Eye Institute’s rapidly growing clinical, surgical, educational and research needs. The existing building (shown at right in the rendering above) will be renovated and connected to the addition via a large glass atrium to create an integrated, next-generation eye center. The project is expected to be completed by 2023.

continued next page
“Our new, highly advanced facility is designed to provide exceptional clinical, diagnostic and surgical services for the entire range of eye diseases, from the most simple to the most complex, as well as to facilitate research and discovery of the next generation of therapies.”

– Daniel F. Martin, MD

The addition will feature 60 new exam rooms and an ophthalmic surgical center that will increase the number of operating rooms from five to 12. It will also house:

• A new Center of Excellence in Ophthalmic Imaging.
• An expanded simulation center for the education and training of residents and fellows.
• A significantly enlarged Ophthalmic Research Center to facilitate growth of eye research and to consolidate ophthalmology research labs currently housed in multiple locations across Cleveland Clinic’s main campus.
The Cole Eye Institute has grown dramatically during the past decade and has one of the highest ophthalmology patient volumes in the United States. Patient visits have increased from 130,000 annual visits in 2008 to more than 320,000 in 2019. In the same period, annual surgical procedures increased from 5,000 to more than 17,000.

“The current building has served us well, but we have surpassed its capacity,” says Cole Eye Institute Chairman Daniel F. Martin, MD, who holds the Barbara and A. Malachi Mixon III Institute Chair of Ophthalmology. “Our new, highly advanced facility is designed to provide exceptional clinical, diagnostic and surgical services for the entire range of eye diseases, from the most simple to the most complex, as well as to facilitate research and discovery of the next generation of therapies.”

The expansion of Cole Eye Institute will create new space for clinical and surgical care, education and research.
Clinical Trials

The following studies are either currently enrolling new patients or are pending approval by the Institutional Review Board and should be enrolling shortly.

RETINAL DISEASES

› A Phase III, Multi-Center, Randomized, Double-Masked, Sham-Controlled Study to Compare the Efficacy and Safety of Intravitreal APL-2 Therapy with Sham Injections in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD) (DERBY)

Objective: To determine if intravitreally injected APL-2 reduces the progression of GA compared to sham injections in patients with GA secondary to AMD.

Contact: Rishi Singh, MD, 216.445.9497
or Pam Donati, 216.444.3735

› A Multicenter, Double-Masked, Randomized, Dose-Ranging Trial to Evaluate the Efficacy and Safety of Conbercept Intravitreal Injection in Subjects with Neovascular Age-related Macular Degeneration (PANDA)

Objective: To evaluate the efficacy and safety of 0.5 mg and 1.0 mg conbercept IVT injected compared with the VEGF antagonist drive control, aflibercept IVT injections in subjects with neovascular age-related macular degeneration.

Contact: Katherine Talcott, MD, 440.998.4040
or Tyler Mullen, 216.445.3840

› Prospective Intraoperative and Perioperative Ophthalmic Imaging with Optical Coherence Tomography (PIONEER Study)

Objective: To assess the feasibility and utility of intraoperative OCT and perioperative OCT in optimizing the management of surgical ophthalmic diseases.

Contact: Justis Ehlers, MD, 216.636.0183
or Jamie Reese, RN, 216.636.0183

› An Eighteen-Month, Two-Arm, Randomized, Double-Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema Secondary to Central Retinal Vein Occlusion (RAVEN)

Objective: To determine if intravitreally injected brolucizumab reduces macular edema when compared to aflibercept (EYLEA®) in treating patients with visual impairment due to macular edema secondary to central retinal vein occlusion.

Contact: Katherine Talcott, MD, 440.998.4040
or Pam Donati, 216.444.3735

› A Phase II, Multicenter, Randomized, Single-Masked, Sham-Controlled Study to Assess Safety, Tolerability, and Efficacy of Intravitreal Injections of FHTR2163 in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration (GALLEGO)

Objective: To compare the effects of FHTR2163 versus a simulated injection on patients with geographic atrophy secondary to AMD.

Contact: Sumit Sharma, MD, 216.445.4904
or Pam Donati, 216.444.3735

› A Phase 2b Multicenter Dose-Ranging Study Evaluating the Safety and Efficacy of a Long-acting Intravitreal Sunitinib Malate Depot Formulation (GB-102) Compared to Intravitreal Aflibercept in Subjects with Neovascular (Wet) Age-related Macular Degeneration (GRAYBUG Study)

Objective: To find out how long and how well GB-102 works in treating people with wet AMD compared to standard-of-care intravitreal injections of Eylea (also called aflibercept).

Contact: Rishi Singh, MD, 216.445.9497
or Angela Meador, 216.445.7176
A Phase 2, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (KODIAK)

Objective: To determine whether a drug called KSI-301 is safe and effective in the treatment of wet AMD, compared with the standard treatment aflibercept (also called EYLEA).

Contact: Sumit Sharma, MD, 216.445.4904 or Angela Meador, 216.445.7176

First-in-Human Study of the Safety of AR-13503 Sustained Release Intravitreal Implant in Subjects with Neovascular Age-Related Macular Degeneration (nAMD) and Subjects with Diabetic Macular Edema (DME)

Objective: To investigate the safety and preliminary effectiveness of AR-13503 SR Implant alone and in combination with aflibercept (Eylea) in the treatment of nAMD or DME.

Contact: Rishi Singh, MD, 216.445.9497 or Pam Donati, 216.444.3735

A Multi-Center, Non-Randomized, Open-Label, Multiple Ascending Dose Study To Investigate The Safety, Tolerability, Pharmacokinetics And Pharmacodynamics Of RO7200220 In Monotherapy And In Combination With Ranibizumab Following Intravitreal Administration In Patients With Diabetic Macular Edema (DOVETAIL)

Objective: To learn about the safety of RO7200220 at different dose levels and how well RO7200220 is tolerated when given alone or in combination with ranibizumab.

Contact: Sumit Sharma, MD, 216.445.4904 or Tyler Mullen, 216.445.3840

A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab Every 4 Weeks versus Aflibercept Every 4 Weeks in Adult Patients with Visual Impairment Due to Diabetic Macular Edema (KINGFISHER)

Objective: To evaluate the effectiveness (efficacy) and safety of brolucizumab in the treatment of subjects with visual impairment caused by DME.

Contact: Aleksandra Rachitskaya, MD, 216.444.2200 or Pam Donati, 216.444.3735

A Phase III, Multicenter, Randomized, Visual Assessor Masked, Active-Comparator Study of the Efficacy, Safety, and Pharmacokinetics of the Port Delivery System with Ranibizumab in Patients with Diabetic Macular Edema (PAGODA)

Objective: To test an eye implant that releases a drug called ranibizumab over a prolonged period of time versus ranibizumab delivered by injections into the eye to treat DME.

Contact: Aleksandra Rachitskaya, MD, 216.444.2200 or Tyler Mullen, 216.445.3840

A Phase 2, Randomized, Placebo-Controlled, Double-Masked Study to Assess Safety and Efficacy of Multiple Doses of IONIS-FB-LRX, an Antisense Inhibitor of Complement Factor B, in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration (IONIS)

Objective: To test an experimental drug called IONIS-FB-LRX (also known as ISIS 696844) for GA secondary to AMD.

Contact: Sumit Sharma, MD, 216.445.4904 or Angela Meador, 216.445.7176
CORNEA

› Corneal Elastography and Patient-Specific Modeling

Objective: To obtain static corneal volume measurements with standard-of-care imaging (Scheimpflug-based tomography) and OCT to provide the shape data for a 3D model of each cornea.

Contact: William Dupps, MD, 216.444.8396 or Angela Meador, 216.445.7176

› A Phase 2 Open Label Trial of ST266 Eye Drops In the Treatment of Persistent Corneal Epithelial Defects (NOVEOME)

Objective: To determine if ST266 works and is safe and effective at closing holes in corneal epithelial tissue.

Contact: William Dupps, MD, 216.444.8396 or Angela Meador, 216.445.7176

UVEITIS

› A Phase III, Multicenter, Sham-Controlled, Randomized, Double-Masked Study Assessing the Efficacy and Safety of Intravitreal Injections of 440 μg DE-109 for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye

Objective: To see how safely and effectively an investigational study drug (DE-109) will work to treat active non-infectious uveitis of the posterior segment of the eye.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

› Automated Analysis of Anterior Chamber Inflammation by Optical Coherence Tomography

Objective: A prospective, observational case series investigating the feasibility of utilizing optical coherence tomography (OCT) scans of inflammation in the anterior chamber, vitreous and sclera of patients with uveitis.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

› Automated Analysis of Anterior Chamber Cell Surrounding Cataract Surgery with Aqueous Fluid Analysis

Objective: To quantify the number of anterior chamber cells identified using OCT and compare the results to clinical exam, and to collect fluid obtained during cataract surgery and analyze the aqueous fluid using a hemocytometer to measure the actual number of cells in the anterior chamber.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

› A Phase 2, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Filgotinib in Subjects with Active Non-Infectious Uveitis

Objective: To evaluate the efficacy of filgotinib versus placebo to treat the signs and symptoms of non-infectious uveitis.

Contact: Sumit Sharma, MD, 216.636.2286 or Emily Fisher, 216.445.1649

› International Collaborative Study of Susac Syndrome

Objective: To prospectively, retrospectively and efficiently collect scientifically sound clinical information on at least 50 current, 50 past and 50 future patients with Susac syndrome (SS), from around the world, so that we can learn more about the immunopathogenesis, clinical features, clinical spectrum, clinical assessment, natural history, treatment, clinical course and long-term outcome of SS.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

› Swept-Source Optical Coherence Tomography (OCT) Imaging in Ophthalmic Diseases (SWORD)

Objective: To assess the use of swept-source OCT in patients evaluated for ophthalmic disease.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566
Imaging Quantification of Inflammation (IQI)

Objective: To perform an observational study utilizing real-time quantification of ocular inflammation to determine minimal important change.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

Vitreous and Blood Sampling of Patients with Uveitis and Birdshot Choroidopathy

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

Prospective Imaging of the Intravitreal Fluocinolone Acetonide Implant Using Fluorescein Angiography and Optical Coherence Tomography in Uveitis Patients

Objective: To identify imaging changes in uveitis patients receiving the injectable fluocinolone acetonide implant.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

GENETICS

Molecular Genetics of Eye Diseases

Objective: To study molecular ophthalmic disorders through the compilation of a collection of DNA, plasma and eye tissue samples from patients and families with a broad range of eye diseases and malformations.

Contact: Elias Traboulsi, MD, 216.444.4363 or Meghan J. DeBenedictis, 216.445.7671

Genetics in Uveitis

Objective: To identify changes in genes that may lead to uveitis.

Contact: Sunil Srivastava, MD, 216.636.2286 or Kim Baynes, BSN, RN, COA, 216.444.2566

An Observational, Multicenter Study of the Prevalence of Cerebrotendinous Xanthomatosis (CTX) in a Patient Population Diagnosed with Early-Onset Idiopathic Bilateral Cataracts

Objective: To assess other manifestations of CTX within patients presenting with idiopathic bilateral cataracts.

Contact: Marina Eisenberg, MD, 216.444.4363 or Pam Donati, 216.444.3735

An Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of AGTC-501 (rAAV2tYF-GRK1-RPGR) in Subjects with X-linked Retinitis Pigmentosa Caused by RPGR Mutations

Objective: To test whether a study drug called AGTC-501 (rAAV2tYF-GRK1-RPGR) is safe and to see if it can improve vision and symptoms of XLRP.

Contact: Elias Traboulsi, MD, 216.444.4363 or Meghan J. DeBenedictis, 216.445.7671

A Multiple-Site, Phase 1/2, Safety and Efficacy Trial of a Recombinant Adeno-associated Virus Vector Expressing CNGB3 (rAAV2tYF-PR1.7-hCNGB3) in Patients with Congenital Achromatopsia Caused by Mutations in the CNGB3 Gene

Objective: To test whether a study drug called rAAV2tYF-PR1.7-hCNGB3 is safe and to see if it can improve vision and symptoms of achromatopsia.

Contact: Elias Traboulsi, MD, 216.444.4363 or Meghan J. DeBenedictis, 216.445.7671

Luminopia One: A Novel Therapeutic Option for Amblyopia

Objective: To learn more about Luminopia One and determine whether it is a safe and effective treatment for amblyopia.

Contact: Fatema Ghasia, MD, 216.444.0999 or Pam Donati, 216.444.3735
News Briefs

New Vision First Van

The Cleveland Clinic & KOHL’S Vision First program, which provides free vision screening for children in Northeast Ohio, has received a new van to support its community outreach efforts.

The customized van’s purchase and outfitting was made possible by contributions from Kohl’s Cares and the Chaney Family. It has two exam stations and is equipped with ophthalmoscopes, retinoscopes, a portable slit lamp, autorefractor, phoropter, lensmeter and an electronic medical record computer terminal. The new van replaces one that had been in service since the program began in 2002.

The Vision First program provides free eye exams for every 4- to 6-year-old child in the Cleveland Metropolitan School District, as well as several other area school systems. Staffed by a Cole Eye Institute ophthalmic technician, the Vision First van screens for a variety of eye diseases and conditions, especially amblyopia and strabismus. For children who fail this initial screening, a Cole Eye Institute optometrist performs complete ocular exams, writes prescriptions for corrective lenses and provides referrals to a pediatric ophthalmologist as needed.

Almost 15% of students who receive an exam require vision correction. Kohl’s Cares provides free glasses to children identified with vision impairment.

Supporting Delly’s Vision Day

One hundred fifty children from Cleveland’s Slavic Village neighborhood received free vision screenings and, if needed, free glasses through the efforts of Cleveland Cavaliers guard Matthew “Delly” Dellavedova and his wife, Anna; Cole Eye Institute; the Essilor Vision Foundation Changing Life Through Lenses program; and the Cavaliers.

Delly’s Vision Day took place on Oct. 17, 2019, at the Cavaliers’ Rocket Mortgage FieldHouse. The event provided the opportunity for children served by social service provider University Settlement to undergo vision exams conducted by Cole Eye Institute practitioners. Those who needed glasses met with an ophthalmologist or optometrist on-site to determine their prescription, and were able to pick their new frames courtesy of Essilor.

Delly’s Vision Day is an outgrowth of the Dellavedovas’ work to improve childhood literacy and encourage reading. Matthew Dellavedova, the son of a teacher, and Anna Dellavedova, herself a teacher, noticed that some of the children they encountered had poor eyesight, which led to the vision screening program.

American Academy of Ophthalmology Lifetime Honorees

Three prominent Cole Eye Institute ophthalmologists have earned the American Academy of Ophthalmology’s 2019 Life Achievement Honor Award for their significant contributions to the organization’s scientific and educational programs and to the field of ophthalmology.

The recipients are:

Daniel F. Martin, MD, Chairman of Cole Eye Institute and holder of the Barbara and A. Malachi Mixon III Institute Chair in Ophthalmology.

Arun D. Singh, MD, Director of the Department of Ophthalmic Oncology.

Elias I. Traboulsi, MD, Head of the Department of Pediatric Ophthalmology and Director of the Center for Genetic Eye Diseases.
Grant Bolsters Vision Research

Cole Eye Institute recently received a $300,000 grant from the Cleveland Eye Bank Foundation to support breakthrough vision research.

The funding, which will be distributed in $100,000 increments over the next three years, is intended to accelerate local research projects aimed at improving the prevention, treatment and reversal of vision loss due to eye disease or aging.

“We’ve made significant advancements in discovering treatments to help slow or stop vision loss, but more research is needed,” said Cole Eye Institute Chairman Daniel F. Martin, MD. “We’re grateful for this generous gift, which will help us discover better treatments to reduce vision loss for years to come.”

Residency Program Recognized for Excellence

Cole Eye Institute’s ophthalmology residency program is among the 12 best in the nation, according to a 2019 survey conducted by Ophthalmology Times.

The multimedia platform’s annual poll asks the chairs and residency directors of major U.S. ophthalmology departments to determine the best performers in four categories: residency, clinical care, research and overall ophthalmology program.

Under the leadership of Director Jeffrey M. Goshe, MD, participants in Cole Eye Institute’s residency program receive training intended to equip them with near-fellowship-level competency across all subspecialties. They are given a combination of apprenticeship and graduated autonomy, including providing the primary medical and surgical care in resident-run ophthalmology services at two affiliated medical centers during their second year.

Dr. Goshe has instituted a yearlong presurgical training program and prioritized resident surgical experience, which has resulted in resident surgical volumes reaching the top 10% of programs nationally. The residency program consistently produces graduates who qualify for top academic fellowships or secure competitive positions in private practice.
News Briefs

Foundation Supports Ophthalmology Advancements

The rate of serious eye conditions requiring specialized care is steadily increasing in the U.S., due largely to a growing elderly population.

To address this concern, the Timken Foundation of Canton has made significant commitments to advance patient care, medical education and research at Cole Eye Institute.

In 2013, the foundation funded the construction of the Louise Timken Microsurgical Education Lab to honor the aviation pioneer credited with being the first nonmilitary female pilot to own and fly a jet aircraft. Macular degeneration forced her to end her flying career in 1992.

The 600-square-foot ophthalmic surgical education lab employs the latest advancements in synthetic models and computer simulation technology. It is the centerpiece of the Cole Eye Institute residency program.

In 2017, another Timken Foundation grant established the Louise Timken Ophthalmic Education Center to encompass all Cole Eye Institute educational activities. The funding also supports Cole Eye Institute’s upcoming expansion.

“This most recent gift has moved forward our ability to plan for the future,” says Cole Eye Institute Chairman Daniel F. Martin, MD. “We are very thankful to the Timken family for their support in helping us accelerate our expansion plans.”

Chaney Family Endowment Helps Advance Ophthalmology Research

The generous gifts that endow physician and research positions at Cleveland Clinic enable the chair holders to start new projects, support additional staff, and pay for equipment and experiments. They also support preliminary data collection, an important step in obtaining outside funding for their work.

Cole Eye Institute ophthalmologist Peter Kaiser, MD, holds the Chaney Family Endowed Chair for Ophthalmology Research. “Through the Chaney family’s generous support, I am able to engage in innovative research to make advancements in the way eye diseases are cared for and treated,” he says.

Dr. Kaiser is the Founding Director of Cole Eye Institute’s Digital Optical Coherence Tomography Reading Center, one of the largest coordinating centers for analysis of images from worldwide retinal clinical trials. He also is the Director of the Ophthalmic Imaging Center, which is developing improved imaging techniques for diagnosis and treatment.

He pioneered the use of the three-dimensional heads-up video display, an optical innovation that improves ophthalmic surgeries. He conducts collaborative research using swept-source optical coherence tomography, which provides real-time, non-invasive cross-sectional images at microscopic resolution.

Dr. Kaiser’s recent accomplishments include:

- Receiving the American Academy of Ophthalmology’s Lifetime Achievement Award.
- Serving as the worldwide study chairman for the phase 3 PANDA trial evaluating the anti-vascular endothelial growth factor (VEGF) agent conbercept for treatment of age-related macular degeneration (AMD).
- Delivering the Krill Lecture to the Chicago Ophthalmological Society on “The Future of Wet AMD Treatment.”
- Serving as the key retina doctor for the U.S. Food and Drug Administration submission of brolucizumab, Novartis’ new anti-VEGF agent.
Upcoming Ophthalmology Continuing Medical Education Events

Uveitis Update
April 4, 2020
James P. Storer Conference Center
Cole Eye Institute | Cleveland, OH
To register: ccfcme.org/uveitis2020

Complicated Cataract Surgical Symposium
April 18, 2020
James P. Storer Conference Center
Cole Eye Institute | Cleveland, OH
To register: ccfcme.org/complicatedcataract2020

North Coast Retina Symposium XI
May 30, 2020
James P. Storer Conference Center
Cole Eye Institute | Cleveland, OH
To register: ccfcme.org/northcoastretina2020

Stay Connected with Cleveland Clinic’s Cole Eye Institute

Consult QD — Ophthalmology
News, research and perspectives from Cleveland Clinic experts:
consultqd.clevelandclinic.org/ophthalmology

facebook.com/CMEClevelandClinic
@CleClinicMD
clevelandclinic.org/MDlinkedin
clevelandclinic.org/cqdssubscribe

24/7 Referrals
855.REFER.123
clevelandclinic.org/refer123

Outcomes Data
View Outcomes books at clevelandclinic.org/outcomes

CME Opportunities
Visit ccfcme.org for live and online offerings from Cleveland Clinic’s Center for Continuing Education.