Cleveland Clinic

COLE EYE INSTITUTE

OPHTHALMOLOGY**UPDATE**

WINTER 2023

MESSAGE FROM THE **CHAIR**

Construction of the Jeffrey and Patricia Cole Building at Cole Eye Institute is well underway! We are excited by the wonderful opportunities this new space will allow for all aspects of our mission: clinical and surgical care of patients, research, and education. The new addition will more than double the size of our Cleveland Clinic main campus facility and will be followed by significant renovation of the original building to create a seamlessly integrated eye institute.

One of the features that I am most excited about is the centralization and expansion of multiple ophthalmology research labs. Research is the backbone of academic centers like the Cole Eye Institute. Bringing together research teams in leading-edge lab spaces will enable more bold and collaborative efforts by our scientists and clinicians.

In this issue of *Ophthalmology Update*, we highlight some of the latest research advances emerging from our laboratories and clinics. Our lead story features an exciting discovery from Cleveland Clinic in corneal research — the revelation that losartan, a drug commonly used to treat hypertension, can reverse corneal scarring and restore vision when used topically. This discovery could benefit millions of patients, even those who sustained eye injury or developed significant corneal disease many years ago. In the article, Steven E. Wilson, MD, our director of corneal research, explains what led to this noteworthy discovery and the promising early results in patients.

Other important research advances covered in this issue include:

- A "second generation" of Brillouin microscopy that may help ophthalmologists screen patients for refractive surgery, select surgical technique and identify patients who need corneal cross-linking
- A novel machine learning-based model that can distinguish between a benign choroidal nevus and melanoma of the eye with 86% accuracy
- The use of eye movement recordings to better understand visual function deficits in patients with amblyopia
- An understanding of the way zebrafish regenerate photoreceptors in a disease model of progressive retinal dystrophy

Also in this issue is an article highlighting Justis P. Ehlers, MD, who was awarded Young Investigator Awards from both ASRS and the Macula Society in 2022. Dr. Ehlers has assembled a lab of more than 30 people investigating imaging biomarkers that may one day lead to enhanced diagnostics and precision medicine for retinal diseases.

While not analyzed in a lab or measured quantitatively, empathy and listening are paramount in patient care. These factors are masterfully demonstrated in the enclosed case study, where the sensitivity of a Cole Eye Institute ophthalmologist helped detect an impending stroke.

Patient care, research and education are tightly interwoven in this publication, just as they will be in our new Cole Eye Institute. I hope you enjoy this issue of *Ophthalmology Update*.

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**

330,000
OUTPATIENT VISITS ANNUALLY

18,000
SURGERIES ANNUALLY

3,000
REFRACTIVE SURGERIES ANNUALLY

125
OPHTHALMOLOGISTS, OPTOMETRISTS AND RESEARCHERS

53
RESIDENTS, FELLOWS AND RESEARCH GRADUATE STUDENTS

44
CLINICAL TRIALS

26
LOCATIONS

HYPERTENSION DRUG LOSARTAN REVERSES SCARRING AND RESTORES VISION AFTER CORNEA DAMAGE

STUDIES INDICATE DRAMATIC RESULTS WHEN USED TOPICALLY WITH OR WITHOUT CORTICOSTEROIDS

Steven E. Wilson, MD

One of the most common medications for hypertension also may treat corneal damage, able to reverse corneal scarring and restore vision — potentially even in patients with eye injuries and diseases that occurred years ago. Losartan, taken orally by patients to control blood pressure, has shown dramatic results when tested in topical form on rabbit corneas and, most recently, as eye drops in humans.

Refractive and corneal surgeon Steven E. Wilson, MD, Director of Corneal Research at Cleveland Clinic Cole Eye Institute, says his work with losartan is the most significant discovery of his 30-year career. Cole Eye Institute Chair Daniel F. Martin, MD, calls it one of the great achievements in corneal research at Cleveland Clinic, research that is currently funded by nine National Institutes of Health (NIH) R01 or U.S. Department of Defense grants.

"The first major finding to come out of my lab was our 1996 publication[1] showing that injury to the corneal epithelium causes apoptosis in underlying keratocytes," says Dr. Wilson. "That is still our No. 1 cited paper. Then, in many studies, with the first being in 2013,[2] we showed that basement membrane regeneration helps prevent corneal scarring. Those studies were important, but the potential clinical impact of losartan — the benefit it could offer to millions of patients worldwide — makes our latest work the most significant."

Research recently published by Dr. Wilson's team has led Cleveland Clinic to pursue a patent (currently pending) on "topical drug treatment to prevent or reduce corneal scarring." The patent will cover losartan as well as other drugs in the same class that also may prevent or treat myofibroblast-related scarring in the cornea.

MAKING CORNEAL SCARRING DISAPPEAR

For three decades, Dr. Wilson's lab has been funded by the NIH and/or Department of Defense to study corneal wound healing and explore drugs that inhibit corneal scarring after injury, refractive surgery or infection. Part of the work has involved studying how scar-causing myofibroblasts develop, a process driven by transforming growth factor (TGF) beta-1 and TGF beta-2. The TGF beta connection led Dr. Wilson to consider the hypertension drug losartan, an angiotensin-converting enzyme (ACE) II receptor antagonist, which is known to inhibit TGF beta signaling.

To perform the first study of losartan's effects on corneal scarring fibrosis, Dr. Wilson's team applied for funding from the Department of Defense.

"The Department of Defense was interested in our work because wartime injuries to the corneal endothelium, due to chemical agents or trauma, are not uncommon," says Dr. Wilson.

The three-year grant resulted in two landmark studies.

In the first one, published in *Experimental Eye Research* in early 2022, researchers tested the use of losartan in rabbits after descemetorhexis, the surgical removal of an 8 mm patch of Descemet's membrane and corneal endothelium. Rabbits received topical losartan (0.4 mg/mL, six times per day) or oral losartan (a dose far greater in mg/kg than humans take for hypertension treatment, three times per day). After one month, corneas treated with the topical drug were clearer. Scarring had begun to disappear in the periphery, and the clearing effects were moving toward the center

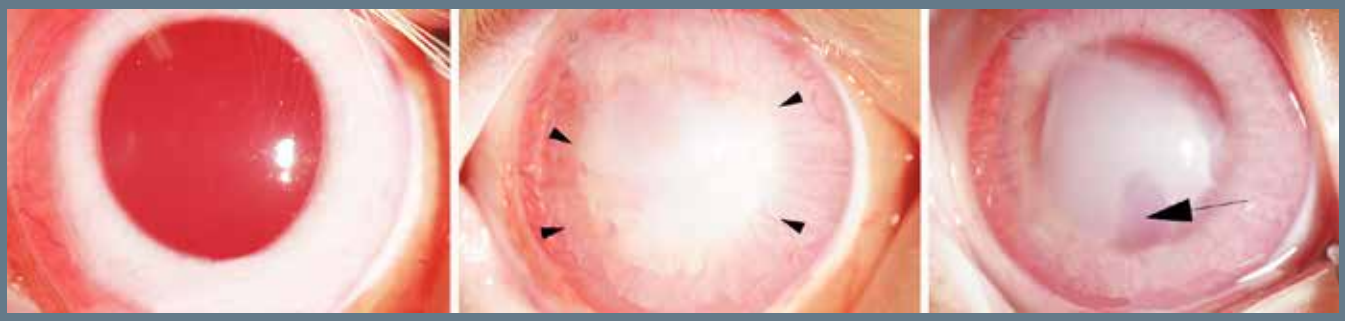

Figure. The first successful trial of topical losartan after removal of an 8 mm circle of Descemet's membrane and endothelium (descemetorhexis). **Left panel.** An unwounded cornea treated topically six times per day with 0.4 mg/mL losartan for one month showed no signs of toxicity. **Middle panel.** A cornea that had descemetorhexis and then received topical vehicle six times per day for one month shows severe corneal scarring fibrosis extending into the periphery of the cornea and also corneal neovascularization (arrowheads). **Right panel.** A cornea that had descemetorhexis and then received topical 0.4 mg/mL losartan six times per day for only one month shows a markedly clearer peripheral cornea, along with a significant decrease in corneal neovascularization. An area of significant central stromal clearing (lacunae) is indicated by the arrow.

of the cornea (Figure).[3] The development of myofibroblasts had been stunted. These effects of topical losartan on scarring were expected to be even greater after several months of treatment.

"The oral dose was far higher than what a human would use for hypertension, yet it had no effect on the cornea," says Dr. Wilson. "Using oral and topical doses together also did not increase the effect of the topical dose. We think it's because losartan's oral route does not penetrate the cornea as the topical route does."

This first study showed that even with epithelium at the front of the cornea intact, topical losartan can affect the entire cornea, all the way to the endothelium at the back. This is a critical finding, notes Dr. Wilson. While previous studies have suggested the scar-healing effects of antibodies to TGF beta, those and other substances will not penetrate a closed (healed) epithelium. As a result, their overall effect on scarring fibrosis is limited.

"It likely will take weeks to months of a continuous anti-TGF beta effect to see any meaningful reduction of fibrosis in humans," says Dr. Wilson.

In the second study, published this summer in *Translational Vision Science & Technology,* the team evaluated the use of topical losartan and corticosteroid to heal rabbit corneas from alkali burn injuries to the epithelium, stroma and endothelium. Compared with corneas treated with losartan (0.8 mg/mL, six times per day) or corticosteroid alone, those treated with both medications had significantly decreased opacity and fewer myofibroblasts in the stroma after one month of treatment.[4]

A third study (publication pending), supported by Research to Prevent Blindness funding, evaluated the use of topical losartan (0.8 mg/mL, six times per day) to treat late haze after photorefractive keratectomy. Again, the team found decreased corneal opacity and fewer myofibroblasts in the stroma after one month.

WHY LOSARTAN COULD WORK IN LONG-STANDING CONDITIONS

All three of these recent studies showed that topical losartan decreased the production of myofibroblasts, the main type of cell responsible for corneal opacity after injury or infection. While all three studies involved applying losartan preventively, at the same time as the model injury, Dr. Wilson believes topical losartan can have similar success on any scarring caused by myofibroblasts, no matter how long-standing.

"The development of myofibroblasts is a dynamic process," he says. "The cells are constantly dying and dividing, relying on a continuous supply of TGF beta-1 or -2 or both. If we interfere with TGF beta signaling, even if the corneal injury occurred months or years ago, myofibroblasts will likely undergo apoptosis. In their place, normal corneal cells — keratocytes and corneal fibroblasts — will move into the damaged tissue and restore the cornea's transparency."

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"TOPICAL LOSARTAN LIKELY CAN PREVENT OR REVERSE SCARRING ANYWHERE IN THE ANTERIOR SEGMENT OF THE EYE, ANYWHERE THERE ARE MYOFIBROBLASTS, WHICH CAUSE THE MOST SEVERE, PERSISTENT TYPES OF SCARRING."

– STEVEN E. WILSON, MD

PROMISING RESULTS IN PATIENTS

In 2022, in Brazil, physicians who trained as Dr. Wilson's fellows at Cleveland Clinic and University of Washington put that theory to the test. They created a topical losartan solution for off-label use in patients (which is allowed in Brazil if the medication is approved for oral use).

One patient with a free cap after LASIK surgery had developed severe diffuse lamellar keratitis, resulting in severe scarring fibrosis that limited vision to 20/200. Within five months of treatment with the losartan eye drops at 0.8 mg/mL six times per day, the patient's cornea had returned to total transparency and the patient's vision was 20/30.

A second patient with scarring and neovascularization developing years after radial keratotomy saw a dramatic decrease in fibrosis just 15 days after beginning use of losartan eye drops. The patient is continuing use of losartan, and physicians are noting further improvement.

Most recently, the physicians have begun using topical losartan in patients with recurrent herpes simplex keratitis.

While none of these cases have been published to date, early results are promising.

"The first two patients are far enough along that we know they have had dramatic clearing," says Dr. Wilson. "In my experience, no other drug treatment has performed like this."

COMBINING LOSARTAN WITH CORTICOSTEROID

Today, conventional treatment of corneal injuries involves topical corticosteroids. Corticosteroids may have a slight effect on scarring but do not completely reverse it, says Dr. Wilson. And long-term use of corticosteroids is not without risk. Scarring that is reversed during short-term use may return when use is stopped.

However, according to the Wilson team's study in *Translational Vision Science & Technology*, a combination of losartan and corticosteroid may be the most effective treatment for any infections, burns or other corneal scarring conditions with high levels of inflammation.[4]

The team is taking a closer look at that thanks to a new three-year Department of Defense grant beginning in late 2022. They also will study the effect of topical losartan in different corneal injury models, in preexisting injuries, in different treatment regimens and when combined with neovascularization-reducing drugs.

"Topical losartan likely can prevent or reverse scarring anywhere in the anterior segment of the eye, anywhere there are myofibroblasts, which cause the most severe, persistent types of scarring," says Dr. Wilson. "That would include conjunctival fibrosis from etiologies like trachoma or scarring of conjunctival blebs after glaucoma surgery. If myofibroblasts are the cause of the scarring and the topical drug can reach the site of scarring, losartan is likely to be effective." ■

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‘SECOND GENERATION’ BRILLOUIN MICROSCOPY MAY BETTER IDENTIFY PATIENTS FOR REFRACTIVE SURGERY, CORNEAL CROSS-LINKING

LASIK CAUSES TWICE AS MUCH CORNEAL WEAKENING AS SMILE OR PRK, SHOWS STUDY

With the prevalence of myopia significantly increasing and the prevalence of keratoconus much higher than previously believed, the need for direct, focal corneal biomechanical data in vivo is greater than ever. These data would contribute to more accurate laser vision correction surgeries and corneal cross-linking treatments for progressive keratoconus, as well as improve the laser vision correction screening process and early keratoconus detection. It also could allow surgeons to individualize corneal cross-linking treatment and more quickly pinpoint patients who are at risk of ectatic corneal disease.

Unfortunately, the devices currently available for analyzing corneal alterations have limited efficacy, “partly because it has been challenging to measure biomechanics in the living human eye,” says J. Bradley Randleman, MD, a cornea and refractive surgery specialist at Cleveland Clinic Cole Eye Institute.

As part of a National Institutes of Health (NIH) grant, Dr. Randleman’s research team developed a motion-tracking Brillouin microscope for in vivo corneal biomechanics mapping.

“Previous iterations of the Brillouin imaging device have been around,” he says. “The device has performed well in the lab, but it was not very accurate with in vivo measurements. We’ve made some significant upgrades, essentially creating a ‘second generation’ Brillouin microscopy device.”

One of the populations Dr. Randleman’s ongoing prospective study is evaluating is postoperative refractive surgery patients.

“We have anticipated that we weaken the cornea with any refractive procedure, but how much is unclear,” he says. “And is there a difference in how much we’re weakening the cornea based on procedure?”

Dr. Randleman presented the initial results of the NIH-funded study at the 2022 American Academy of Ophthalmology annual meeting. Publication of results is pending.

J. Bradley Randleman, MD

MOTION-TRACKING BRILLOUIN MICROSCOPY IS EFFECTIVE AND SENSITIVE

The upgraded Brillouin microscope performed well in the study.

“The most important takeaway is that this device is extremely sensitive to changes after laser vision correction, which is the first time this has been shown,” says Dr. Randleman.

Using motion-tracking Brillouin imaging before laser vision correction and three months after, the study results showed no differences in group demographics or in preoperative Brillouin shift values between the groups.

However, the results showed meaningful differences in postoperative biomechanical change:

- LASIK, SMILE and PRK all weakened the cornea.
- LASIK caused the most weakening, twice as much as SMILE and PRK.
- SMILE and PRK caused similar weakening.

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"IF WE HAVE DIRECT BIOMECHANICAL INFORMATION, WE'LL SCREEN A LOT MORE PEOPLE IN THAN WE DO NOW, AND WE'LL HELP PROTECT PEOPLE WHO AREN'T GOOD SURGERY CANDIDATES." **– J. BRADLEY RANDLEMAN, MD**

Dr. Randleman believed that SMILE would be midway between LASIK and PRK in terms of biomechanical change, so he was surprised that SMILE and PRK have similar impacts.

"This is a very small study thus far, but if this turns out to be true over larger populations, it could allow patients to shift to SMILE instead of PRK for many of our cases," he says.

OTHER POTENTIAL OUTCOMES OF BRILLOUIN ANALYSIS

Dr. Randleman hopes to be able to eventually identify two groups of patients with keratoconus: those who are about to experience vision loss and those who are more susceptible to developing postoperative corneal ectasia.

"We want to identify the people who need corneal cross-linking as early as possible, but we also want to avoid operating on people who are not optimal candidates for refractive surgery," he says.

The primary reason for rejecting patients for laser vision correction is concern about their corneal strength. Because laser vision correction is elective, most surgeons are conservative in their screening, potentially rejecting candidates who actually may tolerate surgery well.

"If we have direct biomechanical information, we'll screen a lot more people in than we do now, and we'll help protect people who aren't good surgery candidates," says Dr. Randleman.

NEXT STEPS

Ultimately, Dr. Randleman hopes to be able to tailor treatment to an individual's preoperative biomechanical state to improve both safety and efficacy.

"We're still many steps away from that, but this study is the first step in looking at what the procedures do in similar patient populations," he says. "This is an ongoing project, so we're also going to be looking directly at patients who are having cross-linking to see how much that impacts their cornea. Our goal is to expand that scope." ■

CHOROIDAL NEVUS OR MELANOMA?
MACHINE LEARNING-BASED MODEL MAY HELP IMPROVE DIAGNOSIS

MODEL DISTINGUISHES BETWEEN CONDITIONS WITH 86% ACCURACY

Arun D. Singh, MD

A novel machine learning-based model may help improve the diagnosis of choroidal melanoma, an aggressive ocular malignancy. A study recently published in *Ocular Oncology and Pathology* confirmed that the model can distinguish between a benign choroidal nevus and melanoma of the eye with a high 86% accuracy.[1]

"This model has a direct implication on reducing the number of suspected cases of small choroidal melanoma and reducing overtreatment," says study co-author Arun D. Singh, MD, Director of Ophthalmic Oncology at Cleveland Clinic Cole Eye Institute.

DIAGNOSTIC UNCERTAINTY COMPLICATES MANAGEMENT

Dr. Singh explains that diagnostic uncertainty complicates the management of patients with suspected small choroidal melanoma. Distinguishing between a choroidal nevus and melanoma is difficult, especially when the lesion is small. This is because conventional imaging technologies, such as optical coherence tomography (OCT) and ultrasound, are not discriminative enough for small lesions, while biopsies of eye tissues carry significant risks.

"Choroidal nevi are very common, and choroidal melanoma is very rare," says Dr. Singh. "But we know that some nevi will transform into melanoma. Also, some melanomas will arise de novo in the eye and will look like the nevus initially, but they're actually evolving melanomas (Figure). So, when we look at something small, it's hard for us to know if it's a nevus that's been there for a long time and we need to do nothing about it, or if it's melanoma that's evolving and we need to do something about it."

Small choroidal melanoma is typically diagnosed based on an eye exam and clinical features.

"About 50% of cases of melanoma of the eye will metastasize over 15 years," says Dr. Singh.

BUILDING A PREDICTIVE DIAGNOSTIC MODEL

The recent study aimed to develop and validate a machine learning model for diagnosing small choroidal melanoma. Data used to develop the model were collected from 123 patients diagnosed with a small choroidal melanocytic tumor based on Collaborative Ocular Melanoma Study criteria. Sixty-one patients with melanoma had documented growth or pathologic confirmation; 62 patients with stable choroidal nevi served as negative controls. The model was validated using an external validation data set that included 240 patients with small choroidal melanocytic tumors. The study's primary outcome was the model's probability of predicting small choroidal melanoma.

Dr. Singh explains that his team used machine learning to integrate important features of small choroidal melanoma into a predictive algorithm.

"We looked at many parameters that are traditionally known to be significant for these tumors, such as the size, location, orange pigmentation, presence of drusen and height," he says. "When you put the features into this model, you're able to figure out mathematically the chance that a certain tumor is melanoma."

The model's predictive capability, validated on the external data set, was 0.861. This means that the model can distinguish between a choroidal nevus and melanoma with a very high discrimination accuracy of 86%.

Figure. A 33-year-old man was initially diagnosed with a choroidal nevus of the left eye and observed for three years. During this time, the lesion doubled in size, leading to a referral to the Cole Eye Institute. At presentation, the patient had no symptoms and had visual acuity of 20/20. Fundus examination of the left eye revealed a small choroidal melanocytic tumor (4.5 mm x 3 mm in basal dimension) with minimal elevation of about 1 mm. A presumptive clinical diagnosis of small choroidal melanoma was made, and he was treated with episcleral brachytherapy. He has remained free from local recurrence and metastasis for the past 10 years.

"The performance of this model is better than any other prediction tool available," he says.

An additional advantage is that the model relies on data obtained from noninvasive diagnostic testing, such as exams typically performed in an ophthalmology office.

PREVENTING OVERTREATMENT

The predictive model is already being implemented and used successfully in research studies at Cleveland Clinic.

In a recent retrospective review of approximately 150 cases of suspected small choroidal melanoma, Dr. Singh's team found that approximately 25% of cases potentially had been overtreated. This is because, at the time of evaluation, the patients erred on the side of caution and opted for treatment even though their diagnosis could not be confirmed.

Dr. Singh is optimistic that the new model's high discriminative ability will prevent the overtreatment of patients in the future.

"That is the whole idea," he says. "When the diagnosis is more certain, then the overtreatment component will go down."

In conclusion, he emphasizes that novel diagnostic techniques should continue to incorporate newer statistical methods, such as those employed in machine learning, because of their more accurate predictive ability. ■

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UNLOCKING THE POTENTIAL OF OCT: FROM IMAGING TO BIOMARKER DISCOVERY

INNOVATIVE WORK EARNS ASRS AND MACULA SOCIETY AWARDS FOR JUSTIS P. EHLERS, MD

The emergence and evolution of optical coherence tomography (OCT) have occurred alongside the medical career of vitreoretinal surgeon Justis P. Ehlers, MD — and in some cases, because of it.

As Director of the Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research at Cleveland Clinic Cole Eye Institute, Dr. Ehlers has helped reveal the unique phenotyping capabilities of OCT. That has triggered the development of multiple analytic platforms that can provide novel insights into disease features and differential therapeutic responses.

Dr. Ehlers' work in OCT and imaging biomarkers during his 12-year career has produced nearly 200 peer-reviewed publications and a collection of patents and awards. In 2022, he won the Young Investigator Award from both the American Society of Retina Specialists (ASRS) and the Macula Society.

"My team is exploring how to use traditional imaging and advanced technology, like artificial intelligence, to better understand retinal disease, characterize imaging phenotypes and predict treatment response," says Dr. Ehlers. "Our goal is precision medicine, where we tailor treatment for an individual based on an enhanced profile of their disease that we can identify through imaging."

"BIOMARKERS AND PRECISION MEDICINE ARE A KEY PART OF HOW THE ONCOLOGY FIELD DETERMINES OPTIMAL TREATMENT, AND WE HOPE TO ONE DAY DO THE SAME IN OPHTHALMOLOGY." – JUSTIS P. EHLERS, MD

A LOOK BACK: PIONEERING MICROSCOPE-INTEGRATED OCT

The first generation of OCT, time-domain OCT, which uses a moving reference mirror to slowly capture axial scans, began appearing in ophthalmology clinics in the 1990s. Far from the workhorse OCT is today, early OCT was used to evaluate only select eye conditions, such as vitreoretinal interface disorders. Spectral-domain OCT (SD-OCT), which provides faster scanning speed and higher axial resolution, became more prominent in the 2000s, when Dr. Ehlers was a resident at Wills Eye Hospital. It provided a whole new level of visualization, allowing ophthalmologists to see detailed retinal anatomy down to a micron level and in large volumetric data sets.

During his retina fellowship at Duke Eye Center from 2008 to 2010, Dr. Ehlers realized opportunities for innovation in imaging, such as with handheld SD-OCT.

"At that time, most eye clinics didn't have a conventional SD-OCT system, much less a handheld device," he says. "But one of my mentors at Duke [Cynthia A. Toth, MD] was transforming the field through innovation in OCT devices, initially developing a handheld system that enabled surgical imaging. As a result, during surgical procedures, we were visualizing the impact of surgical maneuvers on underlying tissues with newfound detail."

OCT was becoming the backbone of decision-making in the clinic, so it was a natural step to use it in the OR, he adds. But while handheld SD-OCT was a huge leap forward, getting the images that a surgeon needed wasn't so simple. Using the device required a learning curve, not to mention pausing the surgical procedure.

"To advance the technology, Dr. Toth began developing a microscope-integrated OCT system that would provide OCT imaging in line with the optics of the surgical microscope, offering real-time visualization of tissue manipulation," says Dr. Ehlers. "As a fellow, I was incredibly fortunate to be part of the very first imaging that her lab conducted, using model eyes. We were one of only a few places in the world doing it at the time."

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Justis P. Ehle, M
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A STEP FORWARD: LAUNCHING THE FIELD'S LARGEST PROSPECTIVE STUDY

In 2010, when Dr. Ehlers joined the Cole Eye Institute, he carried the flame passed to him from Dr. Toth. The institute had not yet begun using intraoperative OCT. However, Cole Eye Institute surgeon Peter K. Kaiser, MD, was a leader in using SD-OCT to diagnose and manage vitreoretinal diseases. Vitreoretinal surgeon Sunil K. Srivastava, MD, who joined Cleveland Clinic at the same time as Dr. Ehlers, also had a background in intraoperative OCT through his connection with the Duke team. The combination of these forces sparked the Cole Eye Institute's intraoperative OCT research program, now with more than 3,000 enrolled patients.

Among the team's efforts was the landmark DISCOVER study, the largest prospective microscope-integrated intraoperative OCT study to date. At three years, more than 800 patients had been enrolled. Successful imaging was obtained in 98% of cases, and the imaging findings had direct impact on surgical decision-making in over 40% of anterior segment cases and nearly 30% of posterior segment cases.[1]

"The study demonstrated that intraoperative OCT was not only possible but useful in a significant portion of cases," says Dr. Ehlers. "For example, in some cases when surgeons thought there were more membranes to peel, OCT revealed that the clinical objective had been met and the procedures could be concluded without additional manipulation."

A NEW ERA IN OCT: BIOMARKER DISCOVERY

As the team learned more about using OCT during surgery, they realized an insufficiency in the software used to analyze the images.

"In the clinic, we look at things that change over days, weeks or years," says Dr. Ehlers. "In the OR, we look at things that change immediately. The same software tools used in the clinic wouldn't be effective for use in the OR. In addition, intraoperative OCT was identifying subtle, previously unrecognized tissue alterations, such as an expansion of the distance between the ellipsoid zone and retinal pigment epithelium [RPE]."

In response, the team started to develop new image analysis platforms to:

- Study the change in specific retinal features as a result of surgical manipulations, specifically the relationship between the outer retina and RPE
- Analyze macular holes — not just measuring width, but creating volumetric segmentation platforms to better understand how change in shape during surgery may predict how quickly a hole closes following surgery
- Enable volumetric measurement of therapeutic delivery, such as subretinal injections

In a surprising twist, the software developed for intraoperative OCT turned out to be transformational for understanding clinical retinal diseases and the dynamics of therapeutic response. For example, rather than detect the mere presence of fluid in the eye of a patient with diabetic macular edema, the software could measure the volume of fluid across the macula and use those measurements to determine the cadence of recovery following a certain treatment. Ophthalmologists potentially could make treatment decisions based on fluid-distribution patterns, cadence of fluid response or high-resolution assessment of exudative volatility.

Revelations like that prompted a new era in the Ehlers team's research: biomarker discovery.

"We've pushed our software to start assessing different features of dry macular degeneration, wet macular degeneration and diabetic eye disease," says Dr. Ehlers. "Our current research is focused on this technology pipeline and creating an opportunity for new clinical endpoints and personalized care. It's an exciting area due to its potential to impact an incredibly large number of patients by helping us better understand their disease."

In 2021 alone, the team presented more than 40 abstracts at national and international ophthalmology meetings and published more than 20 peer-reviewed articles, including these notable findings:

- Retinal fluid index volatility may help determine ideal intervals of anti-VEGF injections in diabetic macular edema.[2]
- OCT biomarkers, such as fluid features, are associated with intraocular cytokine expression and linked to treatment response in patients with diabetic macular edema.[3]
- Quantitative measures of ellipsoid zone integrity and subretinal hyperreflective material volume are associated with visual acuity during anti-VEGF treatment for neovascular age-related macular degeneration (nAMD).[4]
- Radiomics-based features of specific retinal/pathologic compartments are linked to treatment durability and interval tolerance in macular edema secondary to retinal vascular disease.[5]

EYE ON THE FUTURE: PERSONALIZED RETINAL MEDICINE

Next for Dr. Ehlers is the design and execution of a randomized clinical trial to validate the role of intraoperative OCT in patient care and to further explore opportunities provided by newer technologies, such as 3D visualization systems and new software platforms.

As for biomarker discovery, the work is just beginning — particularly with emerging therapeutics.

"For many of the diseases we manage on a day-to-day basis, investigational treatments are showing great promise," says Dr. Ehlers. "There is a huge population of patients that can benefit from knowing if they are more or less likely to respond to these new drugs based on features we can assess on imaging."

For example, Dr. Ehlers' team has demonstrated the potential for quantifiable outer retinal integrity and ellipsoid zone integrity to be important therapeutic markers and endpoints in the investigational treatment of dry macular degeneration. They also could be prognostic features for disease progression[6] and treatment response.[7]

"These imaging biomarkers could be invaluable in determining which patients should be enrolled in a trial, identifying which patients might benefit from a specific treatment and providing more in-depth patient education," he says. "Today, biomarkers and precision medicine are a key part of how the oncology field determines optimal treatment, and we hope to one day do the same in ophthalmology. Thanks to advances in technology, we believe that personalized retinal disease management is on the horizon." ■

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CASE STUDY: WHEN OCULAR MIGRAINE SYMPTOMS INDICATE IMPENDING STROKE

SUBTLE BUT IMPORTANT DISTINCTIONS FOR OPHTHALMOLOGISTS

Nicole Bajic, MD

A 65-year-old woman presented at Cleveland Clinic Cole Eye Institute with symptoms of ocular migraine. She reported a pixelated area in the visual field of her left eye. The phenomenon was transitory, but was increasing in frequency, lasting from seconds to minutes. Most recently, she had experienced a total loss of vision in her left eye, lasting for approximately 30 minutes.

Patients with ocular migraine have described the visual aura in various ways, including "seeing sparkles," shimmering and "like a kaleidoscope." Some patients report having blind spots. Symptoms typically last less than an hour. Sometimes the visual aura can be followed by a headache. Patients may have a history of migraine.

"Ocular migraine symptoms, such as scintillating scotoma, are usually bilateral," says ophthalmologist Nicole Bajic, MD, of the Cole Eye Institute. "Even if patients initially report symptoms in only one eye, upon further investigation they often will identify symptoms in the second eye. That didn't happen with the patient in this case, however. She had checked each eye and insisted that her symptoms were unilateral."

IMPORTANCE OF A DILATED FUNDUS EXAM

A dilated fundus exam often can reveal ischemia, which sometimes causes symptoms similar to an ocular migraine. Ocular migraine is a diagnosis of exclusion after an unremarkable exam.

"If there's an ischemic issue, on a dilation exam you'll often see spots of blood in the midperiphery of the retina," says Dr. Bajic. "There also may be other signs of insufficient blood flow to the eye, such as neovascularization in the anterior segment."

While the patient in this case had no remarkable findings on fundus exam, the unilateral symptoms and temporary loss of vision caused Dr. Bajic to suspect a vascular diagnosis rather than ocular migraine.

"My suspicion was based totally on the symptoms she had described to me," says Dr. Bajic. "The patient was preparing for a trip out of town, but I urged her to go to the ED right away and then placed orders for blood tests, a CT/CTA and a possible echocardiogram."

AMAUROSIS FUGAX DUE TO CAROTID STENOSIS

In the emergency department, the patient had a CT/CTA scan of the head and neck that revealed severe atherosclerosis of the carotid arteries — 85% blockage on the left side and 45% blockage on the right. Vascular surgeon Javier Alvarez-Tostado, MD, of Cleveland Clinic's Heart, Vascular & Thoracic Institute diagnosed the patient with symptomatic carotid stenosis and left amaurosis fugax (temporary vision loss) due to restricted blood flow to the retina. The patient was admitted to the hospital and scheduled for a carotid endarterectomy.

Amaurosis fugax may or may not be due to a vascular condition. In this case, stenosis of the left carotid artery had caused transient ischemia of the central retinal artery, a branch of the carotid.

"Some plaque or a blood clot can block circulation to the retina, causing loss of vision," says Dr. Alvarez-Tostado. "It can be transitory, as in this case, or it can cause complete occlusion and damage to the retina."

Narrowing of the carotid artery likely had been progressing throughout the patient's life, he says. While visual complaints are not common in vascular stenosis, amaurosis fugax has been known to be a classic symptom of occlusive carotid disease.

Ophthalmologist **Nicole Bajic, MD,** examines a patient one month after endarterectomy. An 85% blockage in the patient's left carotid artery had caused visual aura originally thought to be ocular migraine.

"Losing vision for 30 minutes is much longer than we typically see in amaurosis fugax due to underlying carotid disease, which is typically seconds to minutes of vision loss," says Dr. Bajic. "This patient's symptom duration actually was more typical of an ocular migraine. However, the increasing frequency and severity of symptoms only in the left eye are what prompted me to send her to the ED. The total blackout of vision in the most recent episode was the most concerning."

ENDARTERECTOMY REDUCES RISK OF STROKE AND RETINAL DAMAGE

Within days of diagnosis, Dr. Alvarez-Tostado performed the endarterectomy. An incision in the neck exposed the carotid artery. After clamping the artery above and below the occlusion, he removed the plaque and repaired the artery with a patch.

One month later, at her follow-up visit with Dr. Alvarez-Tostado, the patient reported no further episodes of amaurosis. She was symptom-free, and ultrasound showed that her left carotid artery was patent. At her follow-up visit with Dr. Bajic, the patient had no damage to the retina.

"This patient's condition was severe and symptomatic," says Dr. Alvarez-Tostado. "Carotid blockage that is symptomatic increases risk for a major stroke. In this case involving ocular symptoms, the patient was also at risk for retinal damage."

Typically, patients with symptomatic blockage are referred for vascular surgery, as are asymptomatic patients with a blockage of 80% or greater.

EYE EXAMS CAN DETECT LIFE-THREATENING CONDITIONS

This case illustrates the value of eye exams in detecting life-threatening health conditions.

"It's important to conduct a dilation exam when patients have suspected ocular migraine, to help rule out ischemic causes for the symptoms," says Dr. Bajic. "While in this case the results of that exam didn't indicate ischemia, I was not convinced. Worsening severity and frequency of symptoms leading to a total blackout of vision is not normal and should prompt further workup or evaluation."

Indications that visual symptoms may be due to ischemia rather than ocular migraine include:

- Unilateral presentation
- Total loss of vision, even if transitory

"This was an unusual presentation," says Dr. Bajic. "The patient's exam findings did not support severe arterial stenosis, but listening to the patient and considering the overall clinical picture helped us provide the correct care and ensure a favorable outcome." ■

AMBLYOPIA: EYE MOVEMENT RECORDINGS ENHANCE UNDERSTANDING OF VISUAL DEFICITS

PATIENTS FREQUENTLY HAVE PROBLEMS WITH DEPTH PERCEPTION AND INTEROCULAR SUPPRESSION

Fatema Ghasia, MD

Once thought to be a monocular vision condition, amblyopia is increasingly recognized as a binocular disorder that can impact overall vision function. Additionally, patients with amblyopia can have instability of gaze (fixation instability) due to altered fixation eye movements (FEMs) and nystagmus.

Because patient response to amblyopia treatment can vary widely, researchers at Cleveland Clinic Cole Eye Institute analyzed how FEM abnormalities in amblyopia affect binocular visual functions, such as interocular suppression and stereopsis.

"We know that patients with amblyopia have problems with depth perception, but now we also recognize that they frequently experience interocular suppression, which may contribute to the visual acuity deficit of the amblyopic eye," says Fatema Ghasia, MD, a pediatric ophthalmologist at the Cole Eye Institute.

RECORDING FIXATION EYE MOVEMENTS

"There is a spectrum of visual function abnormalities in amblyopia, yet visual functions are not affected to the same extent in each patient. We wanted to evaluate eye movements to see if there's a pattern of visual function deficit observed in patients with amblyopia," says Dr. Ghasia, who presented the study at the Association for Research in Vision and Ophthalmology (ARVO) 2022 meeting.

Most of the study's participants — 34 with amblyopia and seven without — were children. Their eye movements were recorded with infrared video-oculography while viewing with their amblyopic eye, their fellow eye and both eyes.

Researchers analyzed participants' eye movement traces and categorized amblyopic patients into two groups: those with nystagmus and those without. They further evaluated the eye movement traces to see if participants with nystagmus had fusion maldevelopment nystagmus (FMN), a signature eye movement abnormality that suggests amblyopia will develop in early life, perhaps during infancy.

"Sometimes you can see FMN clinically, but there are plenty of times you need high-resolution eye recordings to pick up subtle nystagmus that may not be obvious," explains Dr. Ghasia.

MEASURING INTEROCULAR SUPPRESSION AND STEREOACUITY

Interocular suppression measurement was the primary element of the experiment. Rather than employing the tests used for clinical measurements, researchers used a psychophysical paradigm involving a 3D LCD monitor and polarized glasses. This allowed them to present a different stimulus to each eye to see how the brain perceived it.

"We presented noise dots to the fellow eye and signal dots to the amblyopic eye, and patients were asked to indicate the direction in which the signal dots were moving," says Dr. Ghasia. "If they could perceive what they were seeing with their amblyopic eye, they would be able to accurately identify the direction of the dots."

In addition, the team used the Titmus fly test to measure participants' stereoacuity. They found that patients with FMN who received traditional amblyopia treatment could potentially improve their ability to read an eye chart yet still have poor depth perception. Patients who did not have FMN had stereopsis abnormalities that correlated with their visual acuity abnormalities.

A BETTER UNDERSTANDING OF TREATMENT RESPONSE AND PROGNOSIS

Researchers found that patients with nystagmus and those with FMN were more likely to have abnormal binocular visual functions.

"We learned that studying eye movement recordings in addition to looking at the clinical type of amblyopia helps us better understand the pattern of visual function deficits," says Dr. Ghasia. "It also may give us a better idea of a patient's prognosis."

Regarding FMN, Dr. Ghasia says the tendency is to consider treatment successful when the patient's vision is 20/20. However, patients who have abnormalities in depth perception or those who are actively suppressing the input from one eye still will have issues with vision quality. Their everyday visual motor tasks can be affected.

"Now that we have identified these patterns, we may need to reconsider our endpoint for improvement in visual acuity of the amblyopic eye," says Dr. Ghasia. "We may need to consider other aspects of vision, like contrast sensitivity, suppression and stereopsis."

FUTURE DIRECTIONS

As eye tracking apps become more widespread, Dr. Ghasia and her team are investigating one app's utility compared with standard eye trackers. Their hope is that eye tracking will be able to bridge the gap for younger children who are unable to reliably explain what they see.

"Eye movement recordings can play a role because you can have a toddler sit and watch a cartoon character while you capture their eye movements and see if they have an unstable fixation," says Dr. Ghasia.

This would give pediatricians a better sense of when and when not to refer kids to an ophthalmologist. It also could help guide ophthalmologists on when to start treatment.

"The sooner you detect and treat amblyopia, the better the long-term outcomes," Dr. Ghasia concludes. ■

RESTORING THE RETINA: HOW TO REGENERATE PHOTORECEPTORS IN INHERITED RETINAL DYSTROPHY

NOTCH PATHWAY INHIBITION PRESERVES RETINAL NEURONS AND PROMOTES REGROWTH IN ZEBRAFISH

Brian Perkins, PhD

Unlike humans and other mammals, zebrafish have the ability to activate stem cells to regenerate retinal neurons killed by high-intensity light damage or injury. After being blasted with light, lost or damaged photoreceptors in zebrafish regrow. So, why doesn't the same thing happen when zebrafish photoreceptors degenerate due to disease?

A team led by ophthalmic researcher Brian Perkins, PhD, of Cleveland Clinic Cole Eye Institute has discovered that it can. Their findings were published recently in the *Journal of Neuroscience.*[1]

"Ours is one of the first studies that uses a disease model of progressive retinal dystrophy to understand retinal regeneration," says Dr. Perkins. "Physicians typically aren't seeing patients who forgot to wear sunglasses and stared at the sun for 20 minutes. They're treating patients with retinitis pigmentosa; macular degeneration; and slow, progressive inflammatory responses and diseases."

FINDINGS SHINE A LIGHT ON SLOW DISEASE MODELS

In a zebrafish model of inherited retinal dystrophy, Dr. Perkins' team used single-cell RNA sequencing to dissociate cells in the retina and sequence genes that were turning on in individual cells.

"We found that in the Müller glia — which can act as endogenous stem cells in the retina — the expression of one particular gene called *notch3* was enhanced," Dr. Perkins explains. "Previous research had shown that following light damage, expression of *notch3* was decreased."

Those contrasting findings suggested that inhibiting the Notch pathway would send the regeneration process into overdrive. Dr. Perkins' research team proved it by using a *notch3*-inhibiting drug to trigger regeneration, leading to a complete preservation of photoreceptors (Figure).

"In these disease models, it was the enhancement of Notch signaling that was preventing zebrafish from regenerating photoreceptors," Dr. Perkins says.

UNLIKE HUMANS AND OTHER MAMMALS, **ZEBRAFISH** HAVE THE ABILITY TO ACTIVATE STEM CELLS TO REGENERATE RETINAL NEURONS KILLED BY HIGH-INTENSITY LIGHT DAMAGE OR INJURY.

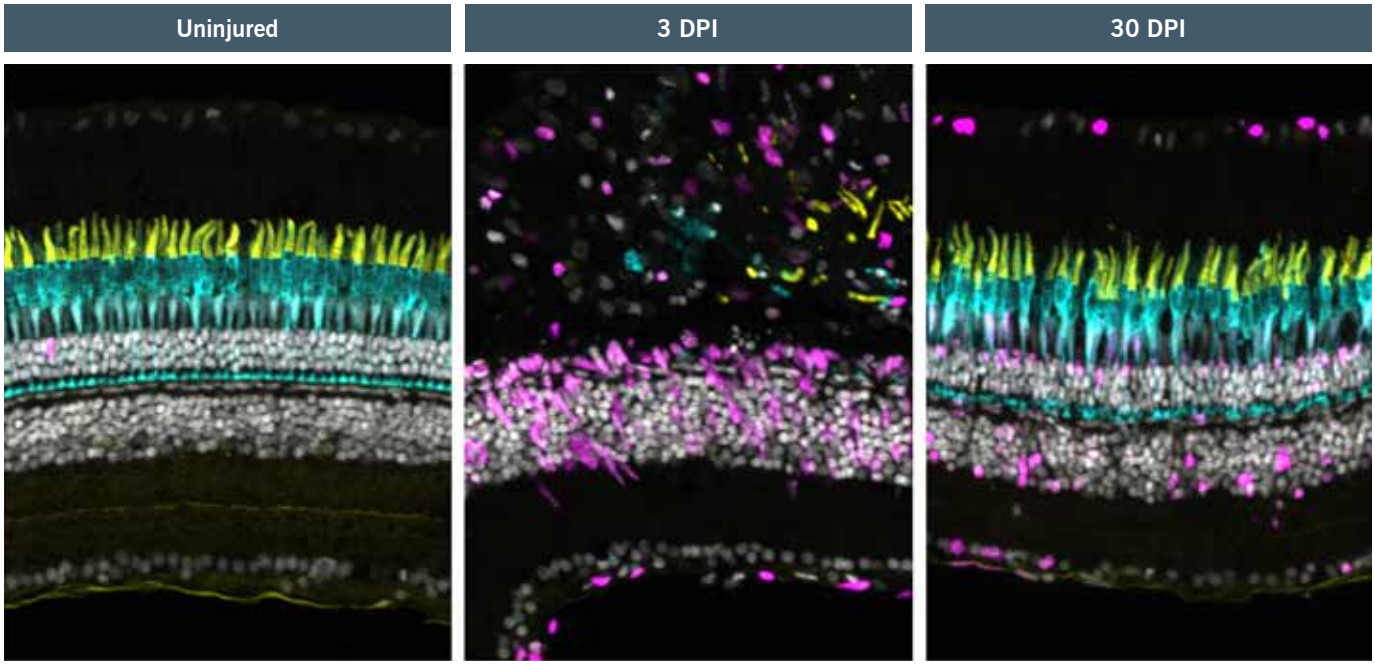

Figure. The retina in zebrafish regenerates following light damage. Cone photoreceptors are shown in yellow/cyan. Active stem cells are in magenta. At three days post injury (3 dpi), the photoreceptors have been completely destroyed. At 30 days post injury (30 dpi), they have been completely regenerated.

MITIGATING INFLAMMATION SLOWS RETINAL DEGENERATION

The team also reported that immunosuppression mitigated the effects of retinal degeneration.

By breeding the zebrafish model of inherited retinal dystrophy with a second zebrafish mutant that lacked immune cells in the eye, the team developed fish that carried a mutation for retinal degeneration but no inflammation. In those fish, the photoreceptors did not degenerate despite having the mutation.

While there's still debate about the utility of immunosuppressants in people with inherited retinal dystrophy, Dr. Perkins says his findings support the idea that reducing inflammation slows degeneration of photoreceptors.

NEXT STEPS: GENERALIZING THE FINDINGS TO OTHER GENETIC MODELS

Dr. Perkins plans to continue researching the link between inflammation and Notch signaling. He and his team hope to show similar findings in other disease models.

"There's a lot left to explore," he says. "We looked at one particular genetic model. We fully expect this to be generalized, but we need to confirm it."

The team also intends to look more closely at single-cell RNA sequencing and uncover other gene expression changes that are occurring.

"We plan to further study how other pathways are responding differently in disease models compared to injury models," says Dr. Perkins. "There's a solid and deep foundation for what happens following light damage or acute injury, but that's not necessarily transferable to a slow disease state." ■

Reference

1. Fogerty J, Song P, Boyd P, et al. Notch inhibition promotes regeneration and immunosuppression supports cone survival in a zebrafish model of inherited retinal dystrophy. *J Neurosci.* 2022;42(26):5144-5158.

CLINICAL TRIALS

LISTED BELOW IS A SAMPLE OF STUDIES CURRENTLY ENROLLING NEW PATIENTS.

Retinal Diseases

› ALEXION: A Phase 2, Double-Masked, Placebo-Controlled, Dose-Range-Finding Study of Danicopan (ALXN2040) in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

Contacts: Sumit Sharma, MD (216.445.4904)
Teresa Randle (216.444.3735)

› DEXTENZA: Intracanalicular Dexamethasone Insert for Management of Postoperative Pain and Inflammation in Patients Undergoing Vitreoretinal Surgery

Contacts: Katherine Talcott, MD (440.988.4040)
Thais Conti (216.445.3840)

› DRCR Protocol AF: A Randomized Clinical Trial Evaluating Fenofibrate for Prevention of Diabetic Retinopathy Worsening

Contacts: Aleksandra Rachitskaya, MD (216.445.9519)
Thais Conti (216.445.3840)

› HONU: A Multicenter, Prospective, Observational Study of the Progression of Intermediate Age-Related Macular Degeneration (GE43220)

Contacts: Sumit Sharma, MD (216.445.4904)
Angela Meador (216.445.7176)

› HORNBILL: A Study to Test Different Doses of BI 764524 in Patients Who Have Had Laser Treatment for a Type of Diabetic Eye Disease Called Diabetic Retinopathy with Diabetic Macular Ischemia

Contacts: Katherine Talcott, MD (440.988.4040)
Angela Meador (216.445.7176)

› IONIS: 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

Contacts: Sumit Sharma, MD (216.445.4904)
Theresa Kovacs (216.445.3762)

Uveitis

› DOVETAIL: A Multicenter, 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 or Uveitic Macular Edema

Contacts: Sumit Sharma, MD (216.445.4904)
Danielle Burton (216.444.1765)

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

Contacts: Sunil Srivastava, MD (216.636.2286)
Danielle Burton (216.444.1765)

Gene Therapy

› ATMOSPHERE: A Randomized, Partially Masked, Controlled, Phase 2b/3 Study to Evaluate the Efficacy and Safety of RGX-314 Gene Therapy in Participants with nAMD

Contacts: Alex Yuan, MD, PhD (216.444.0079)
Theresa Kovacs (216.445.3762)

› VISTA: A Phase 2/3, Randomized, Controlled, Masked, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Two Doses of AGTC-501, a Recombinant Adeno-Associated Virus Vector Expressing RPGR (rAAV2tYF-GRK1-RPGR) Compared to an Untreated Control Group in Male Subjects with X-Linked Retinitis Pigmentosa Confirmed by a Pathogenic Variant in the *RPGR* Gene

Contacts: Aleksandra Rachitskaya, MD (216.445.9519)
Angela Meador (216.445.7176)

Glaucoma

› COAST: Clarifying the Optimal Application of SLT Therapy

Contacts: Ang Li, MD (216.445.0346)
Theresa Kovacs (216.445.3762)

› PILOCARPINE: In-Office Pilocarpine Challenge as Predictor of Goniotomy Outcome — Pilot Project

Contacts: Ang Li, MD (216.445.0346)
Thais Conti (216.445.3840)

Cornea and Refractive Surgery

› ZEDS: A Multicenter, Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Suppressive Valacyclovir for One Year in Immunocompetent Study Participants with an Episode of Dendriform Epithelial Keratitis, Stromal Keratitis, Endothelial Keratitis and/or Iritis Due to Herpes Zoster Ophthalmicus in the Year Prior to Enrollment

Contacts: Craig See, MD (216.444.5898)
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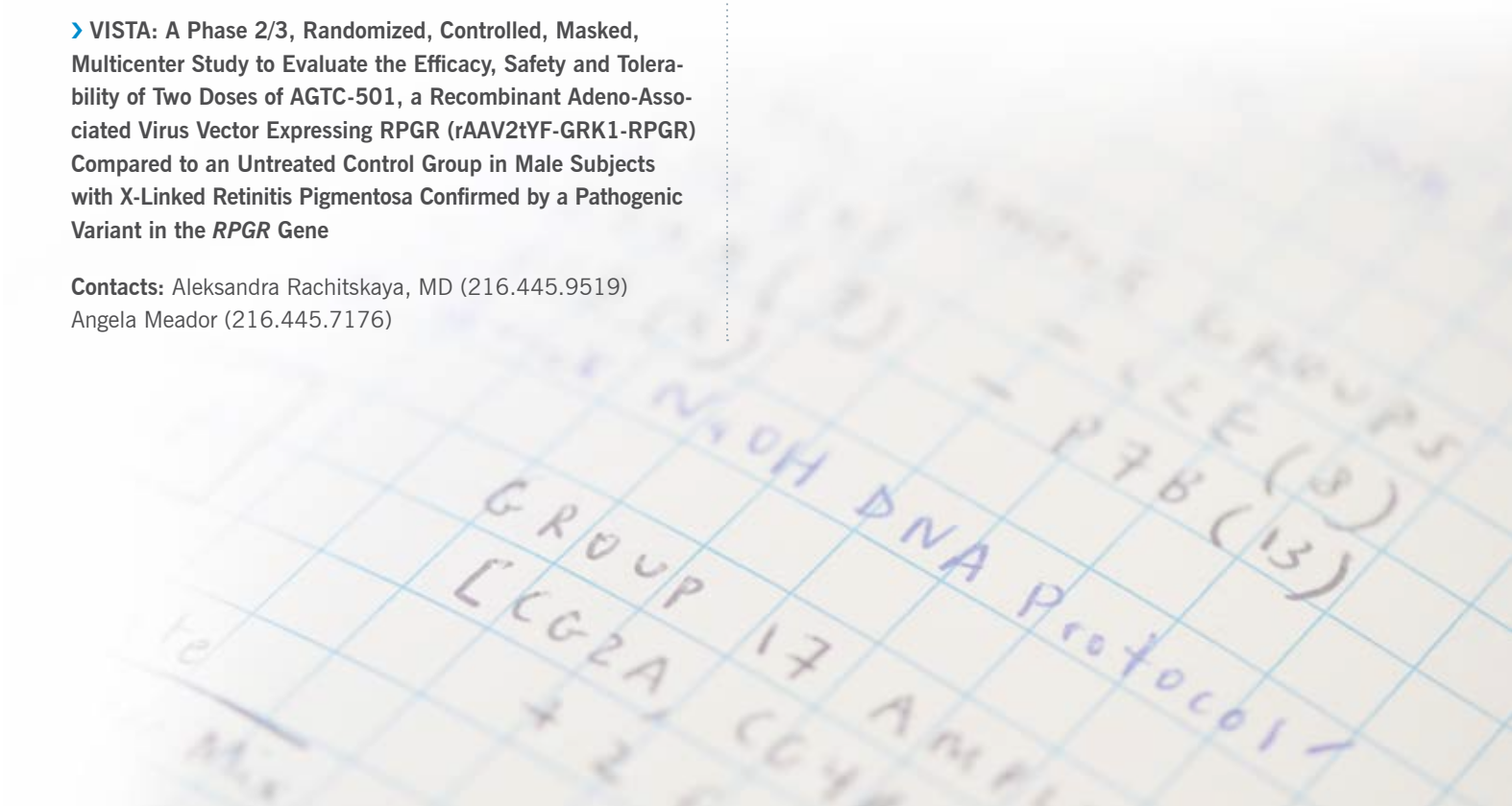

NEW STAFF

THE COLE EYE INSTITUTE WELCOMED THESE NEW STAFF MEMBERS IN 2021 AND 2022.

Kristen Borriello, OD, joined Cleveland Clinic in 2022 after graduating from The Ohio State University College of Optometry. Dr. Borriello has completed numerous internships, including in pediatric optometry, contact lenses, vision therapy and advanced ocular disease. Her specialty interests include contact lenses, diabetic eye examinations and pediatric optometry.

Cassandra Brooks, MD, is a cornea specialist with clinical expertise in laser vision correction; corneal transplantation; advanced medical, surgical and laser treatment of corneal pathology; and cataract surgery. She completed a cornea, external disease and refractive surgery fellowship at the Cole Eye Institute in 2022. Previously, she completed an ophthalmology residency at the Duke University Eye Center, where she earned the K. Alexander Dastgheib Surgical Excellence Award for distinction in surgical skills and judgment. Dr. Brooks has written numerous peer-reviewed articles as well as book chapters about corneal disease and ophthalmic surgery.

Lindsay Clark, OD, specializes in contact lenses and ocular disease. She graduated from University of Missouri–St. Louis College of Optometry and subsequently completed a residency in ocular disease at Louis Stokes Cleveland VA Medical Center.

Devon Cohen, MD, is a neuro-ophthalmologist with specialty interests in idiopathic intracranial hypertension, vascular optic neuropathies, multiple sclerosis, myasthenia gravis and other autoimmune neuro-ophthalmic conditions. After graduating from the University of Miami Miller School of Medicine, Dr. Cohen completed her neurology residency at Mayo Clinic, followed by a neuro-ophthalmology fellowship at Massachusetts Eye and Ear. Her current research focuses include idiopathic intracranial hypertension and anterior ischemic optic neuropathies.

James Hackley, OD, joined the Cole Eye Institute after seven years in private practice and was previously with the Department of Ophthalmology at MetroHealth in Cleveland. Dr. Hackley graduated from The Ohio State University College of Optometry. His specialty interests include contact lenses and dry eye management. He has volunteered for the OneSight Vision Van and the Special Olympics Lions Clubs International Opening Eyes program.

Megan Holmes, OD, MA, specializes in adult and pediatric optometry, diabetic eye examinations, contact lenses and eyeglasses. A fellow of the American Academy of Optometry, she graduated from The Ohio State University College of Optometry and completed a residency in ocular disease at Louis Stokes Cleveland VA Medical Center. Before joining Cleveland Clinic, Dr. Holmes was a staff optometrist at MetroHealth in Cleveland. She spent many years there as Chief Preceptor of the optometry externship program with the Ohio State College of Optometry.

Erica Keller, OD, specializes in primary care, ocular disease and specialty contact lenses. She graduated from The Ohio State University College of Optometry in 2016 and completed a residency in primary care and ocular disease at VA medical centers in Columbus and Chillicothe, Ohio. Erica achieved her Fellowship in the American Academy of Optometry in 2020. She is active in the Ohio Optometric Association, serving as a Zone Governor in 2021 and 2022 and currently as Membership Committee Chair.

Alexander Lamorgese, OD, specializes in adult optometry, eyeglasses and contact lenses with an interest in fitting contact lenses for patients with irregular corneas. He graduated from The Ohio State University College of Optometry in 2021.

Phoebe Lin, MD, PhD, is a vitreoretinal surgeon and uveitis specialist at the Cole Eye Institute as well as a researcher at Cleveland Clinic's Lerner Research Institute. Previously, she was an associate professor at Oregon Health & Science University's Casey Eye Institute. Dr. Lin earned her medical degree at University of Illinois, where she also earned a PhD in pharmacology. She then completed an ophthalmology residency at University of California, San Francisco; a fellowship in vitreoretinal surgery at Duke University; and a fellowship in uveitis at Oregon Health & Science University. Her research is focused on the role of intestinal microbiota in altering systemic immunity toward the development of ocular inflammation.

Danny A. Mammo, MD, is a retina and uveitis specialist who completed a fellowship in vitreoretinal surgery and uveitis at the Cole Eye Institute in 2022. Previously, he completed a residency in ophthalmology at University of Minnesota after earning his medical degree from Oakland University William Beaumont School of Medicine. Among his numerous honors, Dr. Mammo was a 2021 Heed Fellow and the Cole Eye Fellow Teacher of the Year in 2022.

Daniel Petkovsek, MD, is a glaucoma specialist who returned to the Cole Eye Institute in 2021 after completing a fellowship in glaucoma at Wills Eye Hospital. Earlier, he completed a residency in ophthalmology at Cleveland Clinic following his graduation from Case Western Reserve University School of Medicine. Dr. Petkovsek's research interests include applications of intraoperative imaging technology to glaucoma surgery.

Michael Quist, MD, specializes in the medical and surgical treatment of glaucoma and cataracts. He earned his medical degree from the Duke University School of Medicine and completed his ophthalmology residency and glaucoma fellowship at the Duke Eye Center. Among other awards, Dr. Quist received the Heed Fellowship Award and Duke Ocular Innovation Award, and was named a Copeland fellow for his devotion to patient advocacy.

Kevin Wang, MD, is a comprehensive ophthalmologist with clinical interests in cataracts and comprehensive eye care. He completed a residency at the Cole Eye Institute after earning his medical degree from Case Western Reserve University School of Medicine and a graduate degree in cell biology from the University of Toronto.

LOUISE TIMKEN INITIATIVE FOR AGE-RELATED MACULAR DEGENERATION RESEARCH

RECRUITING RESEARCHERS, DISCOVERING BIOMARKERS, DEVELOPING THE MOST INNOVATIVE AMD CARE

Cleveland Clinic's new initiative in AMD research is named in honor of Louise Timken. The first woman to pilot her own private jet, Louise kept flying into her 80s, until AMD grounded her.

One in four people over the age of 70 will develop age-related macular degeneration (AMD) that will threaten their central vision. AMD is the leading cause of permanent blindness worldwide.

At Cleveland Clinic, the new Louise Timken Initiative for Age-Related Macular Degeneration Research will set out to change that. It has been established with a $10 million gift from the Timken Foundation, of Canton, Ohio.

The initiative promises to build on the Cole Eye Institute's existing strengths and recruit the brightest AMD researchers in the field. A key focus will be discovering biomarkers that will lead to significant changes in treatment for patients. In addition to aligning its efforts with the Lerner Research Institute and the new Cleveland Innovation District, the initiative plans to leverage Cleveland Clinic's global health system to offer the most innovative AMD care in the world.

"Our goal is twofold," says Daniel F. Martin, MD, Chair of the Cole Eye Institute. "First, we aim to identify new therapeutic targets and to develop drugs for those targets in an effort to improve outcomes in those who develop AMD. Second, we hope to significantly advance our understanding of the mechanisms that cause the disease so that we might prevent it altogether. We are deeply grateful to the Timken Foundation for providing a catalyst for new research that we are confident will lead to important progress in the fight against this disease."

The new initiative is named in honor of Louise Timken (1910-1998), a high-flying pioneer who served in the Civil Air Patrol during World War II. She later became the first woman to pilot her own private jet. She kept flying into her 80s, until AMD grounded her. Her joy of flying was shared by her husband, the late H.H. Timken Jr., former chairman of the Timken Company.

The Timken Foundation has a track record of generous support for the Cole Eye Institute. Previous gifts provided funding for the expansion of the institute as well as for the creation of the Louise Timken Microsurgical Education Lab and the Louise Timken Ophthalmic Education Center. ■

RESOURCES FOR **PHYSICIANS**

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The Cole Eye Institute is one of the few dedicated, comprehensive eye institutes in the world. Our internationally recognized staff diagnoses and treats the entire spectrum of eye conditions, managing more than 310,000 clinical visits and performing more than 16,000 surgeries annually. The institute is part of Cleveland Clinic, a nonprofit, multispecialty academic medical center integrating outpatient and hospital care with research and education for better patient outcomes and experience. More than 4,500 staff physicians and researchers provide services through 20 patient-centered institutes. Cleveland Clinic is currently ranked as one of the nation's top hospitals by *U.S. News & World Report*.
clevelandclinic.org

OPHTHALMOLOGY UPDATE

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