COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

Viewpoint

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and The Department of Ophthalmology in the
Vagelos College of Physicians and Surgeons

2020

Reaching People Where They Live: Columbia Launches Novel Eye Care Study in NYC Affordable Housing Buildings

Thousands of individuals who live in New York City's public housing developments will receive free vision screenings, eye glasses, and essential follow-up eye care, all within their own apartment complex, as part of a new community-based initiative headed by Columbia Department of Ophthalmology researchers and funded by the Centers for Disease Control and Prevention (CDC). The Manhattan Vision Screening and Follow-Up Study in Vulnerable Populations is a five-year, randomized controlled trial, open to any New York City resident over 40 years of age living independently in one of ten adult and senior housing buildings owned by the New York City Housing Authority (NYCHA), one of Columbia's partners for the study.

Lisa Hark, PhD, RD with resident

"The four leading causes of blindness in the United States are diabetic retinopathy, glaucoma, age-related macular degeneration (AMD), and cataracts," says lead investigator Lisa Hark, PhD, RD, Professor of Ophthalmic Sciences (in Ophthalmology), who directs the Department of Ophthalmology's Clinical Trials Unit. Without effective interventions, vision impairment and blindness caused by these four conditions are expected to increase 150% by 2050. "These eye conditions disproportionately affect low-income and vulnerable populations, and can often be treated effectively if diagnosed early, preventing blindness. But the biggest barrier is follow-up eye care. Fewer than 40% of people follow up and get effective ocular treatment after an abnormal vision screening."

That low follow-up rate is not because these individuals don't want to take care of their vision. "People in underserved communities face child care burdens, insurance limitations, transportation challenges, and employment issues. It's hard to get to an eye doctor's appointment if your boss tells you you'll be fired for taking two hours off," says James Auran, MD, Professor of Ophthalmology, who served as Chief of Ophthalmology at Harlem Hospital. "And people may not

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INSIDE

Minimally Invasive Glaucoma Surgery Expert Joins Faculty

Noga Harizman, MD, a leading expert in minimally invasive techniques for the treatment of glaucoma, has joined the Department as Associate Professor of Ophthalmology. Dr. Harizman, who also specializes in the management of corneal ulcers, endophthalmitis, and endothelial keratoplasty, previously served as the Director of Glaucoma Services at the New York Eye and Ear Infirmary of Mount Sinai, where she helped to create the glaucoma curriculum and ran a citywide comprehensive glaucoma surgical course for residents.

Born in the United States to Israeli parents, Dr. Harizman moved to Israel as a child, where she received her medical education and completed her residency at Tel Aviv University Medical School. She returned to the United States in 2004 and completed sequential fellowships in glaucoma and cornea at the New York Eye and Ear Infirmary before joining its full-time faculty in 2008. There, she worked with Jeffrey Liebmann, MD, now the Shirlee and Bernard Brown Professor of Ophthalmology, Glaucoma Service Director, and Vice-Chair of the Department of Ophthalmology at Columbia, who recently recruited her to join the Columbia faculty.

"I love the challenge of the anterior segment surgeries, and when it became time to choose a career path, I couldn't decide between glaucoma and cornea," Dr. Harizman says of her dual subspecialties. Although there are a handful of other ophthalmologists specializing in both areas, she is the only one in New York. "Glaucoma and corneal disorders are often seen in concert, so I have the training to address both issues in the same patient."

Noga Harizman, MD

Dr. Harizman is developing a rotation in complex glaucoma and cornea cases at Harlem Hospital for residents and fellows. "Columbia has had a mission of serving Harlem Hospital for many years now, and I would like to strengthen that mission," she says. "My plan is to practice at Harlem two days a week. I will review complex cases with residents and fellows on the clinical day, and then we can perform all the surgical procedures in-house on the surgical day. We will be able to provide

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VIEW FROM THE CHAIR

Dear Friends,

Given the extraordinary pressures on all of us over the last several months, it may have slipped your notice that you did not receive the expected Fall 2019-Winter 2020 edition of the *Viewpoint*, originally set to be distributed in early March. The COVID-19 pandemic required us to set aside all but our most essential work in patient care, research and teaching in order to focus on getting our patients, staff and community safely through the pandemic's worst impact on the city.

From mid-March through mid-May, the Department was closed to all but urgent cases, with our volume greatly diminished. Beginning in the middle of May we started seeing our regular patients again, with thorough safety protocols that include repeated sanitizing of all spaces throughout the day, extensive use of personal protective equipment (PPE), and new screening personnel. These were significant and unanticipated costs to our practice, but essential in order to keep our commitment to the safety of our patients and staff.

By the end of July, we had reached approximately 90% of our regular case load, and we are now catching up on postponements and delays, using extended hours to fit in all patients with sufficient social distancing.

Over the past year, we have been successful in recruiting new faculty, and our research has continued with critical laboratory experiments—as you will read in this delayed, but still very relevant, issue of the *Viewpoint*.

The Nobel Prize-winning biochemist Arthur Kornberg, MD, who discovered the chemical catalyst responsible for the synthesis of DNA, once remarked, "No matter how counter-intuitive it may seem, basic research has proven over and over to be the lifeline of practical advances in medicine." Here at Columbia Ophthalmology, where we now have one of the largest basic science programs in ophthalmology in the country, we see the truth of Dr. Kornberg's statement every day. In the pages that follow, you will learn how our growing cadre of discovery scientists, some of the top experts in their field, use their basic science investigations to inform the work of their clinical colleagues—and how those clinicians, in turn, inspire basic science researchers to ask new fundamental questions.

This kind of robust interplay between basic and clinical science was evident at the fourth Precision Ophthalmology Symposium, held in December 2019. Focusing on applied genetics, the symposium provided a rich series of lectures and practical case studies demonstrating how we are taking genetic discoveries from the laboratory and moving them rapidly into clinical practice.

Columbia is now undertaking one of the largest and most comprehensive research initiatives on ocular disease in underserved populations, under the leadership of Lisa Hark, PhD, RD. Dr. Hark has accomplished the Herculean task of uniting multiple city agencies, including the New York City Housing Authority (NYCHA), to bring a novel screening and follow-up program directly to people in need, in city-run apartment buildings.

As our faculty continues to grow, I'm pleased to announce that Noga Harizman, MD, an expert in minimally invasive approaches to glaucoma surgery, has joined Columbia Ophthalmology. Formerly the Director of Glaucoma Services at the New York Eye and Ear Infirmary of Mount Sinai, where she helped to create the glaucoma surgical curriculum, Dr. Harizman will practice both at Columbia and at Harlem Hospital.

The spotlight is on ocular oncology in our "Making History at Harkness" series. This program has a rich history dating back to the 1930s, when it was founded by Algernon Reese, MD, widely considered to be the father of the subspecialty. Today, it is once again vigorous and growing under the leadership of Brian Marr, MD.

Finally, I would like to congratulate Irene Maumenee, MD, who was presented with the 2020 Jules Francois Golden Medal by the International Council of Ophthalmology (ICO) at their virtual meeting in June. It is no exaggeration to say that the field of ophthalmic genetics would not be where it is today without Dr. Maumenee's extraordinary contributions.

I would like to close by sharing my heartfelt wishes that all of you in our network of patients and friends are safe, healthy and well, and that you have been able to find strength and support in your own beloved communities during this extraordinarily difficult time. We are committed to continuing to serve you no matter the obstacles, and we are grateful for your ongoing support.

Sincerely,

G.A. (Jack) Cioffi, MD
Jean and Richard Deems Professor
Edward S. Harkness Professor
Chairman, Department of Ophthalmology

Faculty Promotions

Srilaxmi Bearelly, MD, MHS, to Associate Professor of Ophthalmology at CUMC, effective October 1, 2020

Xin Zhang, PhD, to Professor of Ophthlamic Sciences (in Ophthalmology and Pathology and Cell Biology) at Columbia University with tenure, effective January 1, 2021

Minimally Invasive Glaucoma Surgery Expert Joins Faculty

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care for an underserved population while giving residents and fellows exposure to these cases."

She also aims to expand Columbia's existing research programs in glaucoma and cornea, including studies that will evaluate the relationship between glaucoma and corneal disease. "I'm interested in assessing how corneal endothelial cells—the cells that maintain the cornea's healthy state—are lost as a result of different glaucoma procedures, as well as other relationships between the two disease states," she says.

When she is not mentoring residents and fellows, treating patients or conducting research, Dr. Harizman can be found enthusiastically taking in all New York City has to offer, something she hopes to resume doing as soon as pandemic restrictions allow. "I used to go to see a lot of shows, both Broadway and off-Broadway, as well as concerts and dance performances. I trained as a dancer when I was a child, particularly modern dance, and I would come to the city sometimes to pursue summer courses," she says. "It's so nice to live here now, and I look forward to being able to enjoy the city fully again soon!"

Many of her weekends are taken up by track and field meets, as her two younger children, sons in middle school and high school, are distance runners. She also has a daughter who graduated from LaGuardia High School and is now attending Wesleyan University.

"I'm very excited to be at Columbia working with these amazing professionals," Dr. Harizman says. "The atmosphere is so positive and everyone is so supportive of each other. My colleagues appear to be very happy to come to their workplace, and I think that says a lot about the way the department is run. This level of warmth is unusual and I really appreciate it."

Far More than Just the Basics: Columbia's Discovery Science Program

Basic ophthalmic science has long been a top priority of G. A. (Jack) Cioffi, MD, Jean and Richard Deems Professor, Edward S. Harkness Professor, and Chairman of the Department of Ophthalmology, and his predecessor, Stanley Chang, MD, K.K. Tse and Ku Teh Ying Professor of Ophthalmology and Chairman Emeritus of the Department of Ophthalmology. Over the past decade, they have strategically assembled a cadre of some of the best scientists in the field.

Between 2010 and 2020, the number of faculty members doing research in the department has nearly doubled, with a total of 19 investigators whose areas of focus encompass genetics, proteomics and metabolomics; drug discovery and development; imaging development, application and interpretation; biomarker identification and development; neuroscience and neurodegeneration; tissue and organ growth and development; the application of basic science to the development of clinical trials; and biostatistics and population health.

The latest faculty members to join the Department are two highly accomplished basic scientists: Simon John, PhD, Robert Burch Professor of Ophthalmic Sciences (in Ophthalmology), and Tingting Yang, PhD, Assistant Professor of Ophthalmic Sciences (in Ophthalmology). Total direct and indirect funding for basic science research in ophthalmology at Columbia from the NIH (National Institutes of Health) has reached more than $10 million this year, and total annual research funding is approximately $15 million.

"I believe that the interaction between clinicians and bench scientists is critical," says Dr. Cioffi. "Discovery science is the only way that we can ask and answer the most fundamental questions that will form the underpinnings of the therapeutic and diagnostic developments of tomorrow."

"My primary goal, since becoming the Research Director of the Harkness Eye Institute more than 16 years ago, has been to foster collaboration between basic science and clinical research," says Rando Allikmets, PhD, William and Donna Acquavella Professor of Ophthalmic Sciences (in Ophthalmology and Pathology and Cell Biology).

From Basic Science to Clinical Experience and Back Again

For more than two years, Janet Sparrow, PhD, Anthony Donn Professor of Ophthalmic Sciences (in Ophthalmology) and Professor of Pathology and Cell Biology, has been developing and studying knockout mouse models of cellular retinaldehyde-binding protein (CRALBP), which plays an important role in the visual cycle.

The visual cycle begins in the retina, when two different types of photoreceptor cells—rod photoreceptors and cone photoreceptors—detect light. The highly sensitive rods mediate vision in dim light, while cones function in bright light and also control acuity and color vision. Both of these photoreceptor cells rely on 11-cis-retinal, a photosensitive form of vitamin A, to do their work. Each time 11-cis-retinal absorbs a photon of light, it undergoes a change in shape, and must then be regenerated back into its original shape in order to absorb yet more light. CRALBP is essential to this perpetual shape-renewing process.

To understand how CRALBP deficiencies produce vision loss, Dr. Sparrow utilizes multiple forms of imaging in the mouse model, including quantitative fundus autofluorescence (qAF), an imaging technique for assessing retinal health that she and other Columbia scientists developed in collaboration with François Delori, PhD, a Professor of Ophthalmology at Harvard.

Basic Science Team

When parents came to the clinic at Columbia with their two adolescent daughters, both of whom had problems with night vision, Dr. Sparrow had the opportunity to use those mouse models as a guide to study CRALBP deficiencies in an entire family with different genetic variations.

Genetic analysis conducted by Stephen Tsang, MD, PhD, Laszlo T. Bito Professor of Ophthalmology and Professor of Pathology and Cell Biology, showed that both girls were compound heterozygous for mutations in the RLBP1 gene that encodes the CRALB protein. In other words, they each had two *different* mutations at this genetic locus, one on each chromosome. The combined effect of these mutations meant that they couldn't generate 11-cis-retinal fast enough for their eyes to adapt to dimming light. This type of early-onset night blindness, associated with RLBP1 gene mutations, typically progresses to macular atrophy and blindness in adulthood.

Jose Ronaldo de Carvalho, PhD, a research fellow who worked with both Dr. Tsang and Dr. Sparrow, brought the genetic findings to Dr. Sparrow. The girls' parents were both carriers of recessive mutations on the RLBP1 gene: the mother had a deletion in the gene, while the father had a mis-sense mutation, in which a single base pair change alters the genetic code so that it produces a different amino acid. Neither parent appeared to have any visual problems.

But guided by Dr. Sparrow's mouse model, clinical and research scientists identified two previously undescribed manifestations of the genetic mutation present in the carrier parents. Although they hadn't noticed any visual symptoms yet, their RLBP mutations were having a subtle influence on their ocular health. "It was not previously known whether carrier parents with only one mutated copy of the RLBP1 gene would have any sort of clinical phenotype," Dr. Sparrow says.

Using the same techniques that they employ in mice, Dr. Sparrow and her colleagues found that the parents had subnormal findings on both aAF and another measure, near-infrared autofluorescence. Those findings suggest an early loss of the protective pigment melanin in retinal pigment epithelial (RPE) cells, which nourish the fragile nerve tissue of the retina.

"No one had carried out measurements like these in such a family before," says Dr. Sparrow. "Eventually, if we can follow seemingly asymptomatic carriers of genetic mutations such as these and do additional imaging and analysis, there

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Fourth Precision Ophthalmology Symposium Highlights Applied Genetics

Moving genetic discoveries out of the laboratory and into clinical practice was the focus of the fourth annual Precision Ophthalmology Symposium, held on December 6, 2019 at the University Club. "Applying Genetics to Eye Care Today" drew more than 200 participants from around the country for a packed full-day agenda featuring a dozen practical, real-world case presentations on genetically linked ocular conditions ranging from exfoliation syndrome and Leber congenital amaurosis to Stargardt disease and retinitis pigmentosa. Framing the case presentations were lectures on topics such as choosing a DNA test, reading a sequencing report, and the basics of genetic counseling.

G.A. (Jack) Cioffi, MD

"We are undergoing a seismic shift in the way we think about genetics in ocular disease, and disease in general," says Irene Maumenee, MD, Professor of Ophthalmology and Director of Clinical Ophthalmic Genetics, who co-chaired the symposium along with Stephen Tsang, MD, PhD, Laszlo T. Bito Professor of Ophthalmology and Professor of Pathology and Cell Biology. "A cataract isn't just a cataract, but a genetic disease, and we have to bring that understanding into the forefront of patient care. Soon we will no longer treat ophthalmic diseases as surgical or medical conditions, but as genetic disorders. The future of the management of ocular conditions depends upon the integration of genetic concepts into eye care."

The second annual Donald and Barbara Jonas Lecture was presented by Reed E. Pyeritz, MD, PhD, the William Smilow Professor of Medicine in the Division of Translational Medicine and Human Genetics at the University of Pennsylvania's Perelman School of Medicine. Dr. Pyeritz is widely regarded as the preeminent scholar and clinician specializing in Marfan Syndrome, which is frequently accompanied by ocular complications such as dislocated lenses, cataracts, retinal detachments and glaucoma. He discussed genomic testing and uncertainties about interpreting and applying the results.

Dr. Pyeritz is also one of the founders of the Marfan Foundation and has served on its advisory board since its inception. "Foundations like this one are playing a major role in moving rare disease research forward," says Dr. Maumenee. "To date, we have identified at least 7,000 genetic diseases, and there are probably more, many of them very rare. The government cannot fund the research for all of them."

Retinal gene therapy for ABCA4 Stargardt Disease was the topic of the Arthur Gerard DeVoe, MD Lecture, given by William Hauswirth, PhD, the Maida and Morris Rybaczki Eminent Scholar Chair in Ophthalmic Sciences at the University of Florida. Dr. Hauswirth is a pioneer in ocular gene therapy using viral vectors. Viruses, modified so that they cannot cause disease, are often used as carriers to deliver new genes directly into cells by "infecting" them.

Marius Ueffing, PhD, Director of the Institute for Ophthalmic Research in Tübingen, Germany, presented the John H. Dunnington, MD Memorial Fund Lecture. A renowned expert in protein biochemistry, Dr. Ueffing was a doctoral research fellow at Columbia in the late 1980s. "He has been very influential in understanding the influence of protein networks and protein complexes in ocular diseases such as age-related macular degeneration (AMD) and retinal degeneration," says Dr. Maumenee. Dr. Ueffing shared insights from the European EYE-RISK Project, a systems level analysis of the combined role of genetic and non-genetic factors for developing AMD.

"At our first Precision Ophthalmology Symposium in 2016, the focus was primarily descriptive," says Dr. Tsang, who presented a session on advances in genome surgery, including his own groundbreaking work. "The field has made so much progress in such a short time that this year's agenda was all about treatment. Many people still think of gene therapy as primarily the province of research, but we are rapidly moving forward to precision treatment in the clinic at the level of an individual DNA base pair. At Columbia, we are positioning ourselves as the first institution in the tri-state area to offer both genomic medicine and gene surgery for the eye, which will happen within the next year. By the time we are ready for the 2021 Precision Ophthalmology Symposium, the agenda will be all about how we are improving gene therapy and gene surgery."

Attendee at check-in

Below: L. to R.: Dr. Tsang, Irene Maumenee, MD, and Marius Ueffing, PhD, a guest speaker

FACULTY SPOTLIGHT

Irene Maumenee, MD, Honored with Prestigious Jules François Medal

Irene Maumenee, MD, Professor of Ophthalmology and Director of Clinical Ophthalmic Genetics, has been named as the recipient of the 2020 Jules François Golden Medal by the International Council of Ophthalmology (ICO). The François Medal is awarded every four years for "ophthalmic work of high scientific quality." Due to the ongoing COVID-19 pandemic, the award was presented online, at the "WOC2020 Virtual" meeting of the World Ophthalmology Congress in June 2020.

A Belgian ophthalmologist, Jules François, MD, directed the eye clinic at the University of Ghent, where he conducted important research on the anatomy of the ophthalmic artery as well as the central retinal artery. He devoted a large part of his career to studies of hereditary diseases of the eye. "I cannot think of a more deserving person for this honor than Irene Maumenee," said G. A. (Jack) Cioffi, MD, Jean and Richard Deems Professor, Edward S. Harkness Professor, and Chairman of the Department of Ophthalmology. "Over her career, she has defined the field of ocular genetics. Here at Columbia, she is helping us launch the next generation of clinician-scientists who will be dual-boarded in Ophthalmology and Human Genetics."

"To receive an award named after Jules François is a tremendous honor," says Dr. Maumenee. "He was one of the eminent ophthalmologists of the last century and very prominent in the development of the field of ophthalmic genetics. There are many small rural communities near Ghent, where he lived and worked, so he observed and described a number of inbred genetic eye diseases there. His name is integrally associated with the understanding of genetic eye diseases that has developed over the last century."

Dr. Maumenee became acquainted with Dr. François in the mid-1960s as a postgraduate researcher at the University of Geneva under the tutelage of Professor Adolphe Franceschetti, who launched the university's medical genetics program. "The same principle of inbreeding in geographically isolated areas of Belgium was also prevalent in remote Swiss mountain regions," she says. "Dr. François collaborated closely with Dr. Franceschetti, and he came to Geneva frequently. He was very inspiring and generous with his time and his insights, and he brought so many people in the field together. If I live up to his standards, I will be very happy."

Irene Maumenee, MD

Top: L. to R.: Peter Crowley, attendee and Stephen Tsang, MD, PhD

Above: P. Roy Vagelos, MD, Chair, Board of Advisors, VCP&S and CUIMC

Left: Attendees

Columbia Launches Novel Eye Care Study in NYC Affordable Housing Buildings

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understand why they need an eye exam if they have not yet noticed any vision changes. All this means that there are many people with undiagnosed and untreated eye conditions outside of our health care system in desperate need of vision care."

The study aims to reach people by conducting vision screenings where they live, in the community room or senior center located in the lobby of their own apartment buildings. Its protocols have been adapted for the COVID-19 pandemic, and investigators have been approved by the Institutional Review Board (IRB) to obtain consent from residents over the telephone. During this phone call, residents will also be asked about their ocular, medical, and family history, vision-related quality of life and history of falling.

Once this pre-check is completed, residents will be scheduled for a 30-minute in-person vision screening that includes a visual acuity check using the standard Snellen chart, eye pressure measurements, and retina/optic nerve photography. Prior to these visits, NYCHA residents will be required to receive a negative COVID test within five days of attending the vision screening. "We will help enrolled participants find the closest place to get tested and make an appointment, if needed," says Dr. Hark. Individuals with abnormal vision screening results will be scheduled for follow-up eye exam appointments with optometrist Y. Shira Kresch, OD, MS, FAAO, Instructor in Optometric Sciences (in Ophthalmology).

Residents in seven of the 10 buildings will be randomized to the "enhanced intervention" arm of the study. Those who are referred to an ophthalmologist will be scheduled for an eye exam at the Harkness Eye Clinic or Harlem Hospital Ophthalmology and guided through all aspects of follow-up eye care by patient navigators. Residents who need vision correction will receive free eye glasses, provided by Warby Parker. "If these individuals do not attend follow-up appointments, the navigators will reach out to help them reschedule. They will also assist with logistical and scheduling hurdles, such as transportation and making eye exam appointments," says Dr. Hark. Such navigators have proven effective in cancer care.

Residents in three of the 10 buildings will serve as the study's control arm. If they fail the screening and require an ophthalmology consultation, they will have their first appointment made for them, either at the Harkness Eye Clinic or at Harlem Hospital Ophthalmology, but they will not be given the enhanced navigator support. If they attend this appointment, and need vision correction, they will receive a prescription for eye glasses and a list of nearby optical shops. All enrolled residents in both the intervention and the control group will receive a follow-up phone call at 12 months after their vision screening to schedule an eye exam.

A pilot phase of the study was conducted in February at the Riverstone Senior Center, which is operated by the city's Department for the Aging (DFTA). (Because this phase took place prior to the pandemic, all visits were conducted in person.) During the pilot, 42 people were screened, and 33 of them—nearly 80% of participants—failed their initial vision screening and were referred to the "on-site" optometrist, Dr. Kresch, for an eye exam. Of the 33 who were referred to Dr. Kresch, 28 attended their appointments and 18 were referred to ophthalmology. "We were very pleased with how many patients attended their optometrist exam," Dr. Hark said. "Because this was a pilot phase of the study to assess our procedures, we did not have a control arm; everyone received navigator support. We provided free eyeglasses to 13 study participants."

Participants were highly satisfied with their experience. When asked how likely they would be to attend a referred appointment with an ophthalmologist, 89% said "very likely," and 88% said that they were also very likely to recommend the vision screening to family, friends, and neighbors.

Dr. Hark expects approximately 1,500 residents across 10 NYCHA buildings to participate in the vision screening during the two-year recruitment phase. All enrolled residents will then be followed prospectively for one year to evaluate the effects of the intervention on visual acuity and health-related quality of life, as well as secondary outcomes including adherence to follow-up appointments and cataract surgery, risk and rates of falls, and participants' satisfaction rates. "This study is innovative, longitudinal, and can be easily scaled up," Dr. Hark says. "It's a great way to reach vulnerable populations and get them the vision care they need

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Far More than Just the Basics: Columbia's Discovery Science Program

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could even come a day when it might be beneficial for carrier parents like these to have gene therapy."

Taking a New Look at a Gene

Developmental biologist Xin Zhang, PhD, the Jules & Doris Stein Research to Prevent Blindness Professor and an Associate Professor of Ophthalmic Science (in Ophthalmology and in Pathology and Cell Biology), says that his research into genes that cause abnormalities in the eye during embryonic development has been dramatically enhanced by regular interaction with clinicians. "We have created a mouse model of PAX6, a gene that plays a fundamental role in very early development of ocular tissue," he says. "When you knock out the function of this gene, the eye doesn't develop at all. The dogma has been that any clinical manifestations produced by mutations on this gene take place in utero, and are complete by the time the child is born."

But conversations with clinical colleagues such as Irene Maumenee, MD, Professor of Ophthalmology and Director of Clinical Ophthalmic Genetics, led Dr. Zhang and his team to study aniridia, a rare genetic disorder characterized by abnormal development of the iris and associated with PAX6 mutations. People with aniridia are born with functioning eyesight, although they may have limited visual acuity; their vision begins to deteriorate early in life and conditions such as glaucoma and cataracts are common.

"Although these patients are born with a genetic disease, there are ample opportunities to address the pathology during a person's life," says Dr. Zhang. "We had never thought about this as a research question before, because our own view about how this gene works prevented us from considering that it might play a role after embryogenesis."

Dr. Zhang is now working on the development of a mouse model to answer the question of which specific abnormalities caused by PAX6 mutations are complete after an embryo develops, and which continue to evolve. "If there are ways to modulate PAX6 levels so that we can prevent some of the later-onset disorders of vision, that will substantially improve the quality of life for people with these genetic variations."

Continuing Breakthroughs

The rich, interconnected research environment at Columbia is what drew Dr. Simon John to the program. His extensive basic science portfolio includes mouse-model research identifying the importance of age-related metabolic decline in nicotinamide adenine dinucleotide (NAD) to the progression of glaucoma. "Our clinical colleagues guided our choice of a molecule with a good safety profile to treat this decline, which is why we selected a very specific form of vitamin B3 called nicotinamide as a potential therapy," he says. "After success in the mouse model, we have completed enrollment in the first human clinical trial of this treatment."

Basic science research in the Department of Ophthalmology has led to a host of recent discoveries with profound implications for clinical care. In 2017, Dr. Rando Allikmets, who originally identified ABCA4, the gene responsible for Stargardt disease and cone-rod dystrophy, described a new class of very mild ABCA4 mutations, called hypomorphs.

"These variants were previously considered benign, because they are very frequent in the general population. It was thus assumed that they could not possibly cause disease, or Stargardt/ABCA4 disease would be much more prevalent," he says. "But we determined that under certain conditions in which both copies of the gene are mutated these hypomorphic variants are disease-causing. If one copy of the ABCA4 gene has a total loss of function, then a very mild variation on the other copy produces late-onset disease that has often been confused with age-related macular degeneration. This discovery defines more than 10% of the entire population affected by ABCA4 disease."

In collaboration with Dutch researchers, Dr. Allikmets' group has also recently identified another major source of ABCA4 disease: the intron, a segment of a DNA molecule which does not code for proteins and interspaces the coding sequence of genes. "Introns used to be neglected in the search for disease-causing mutations, but we have determined that about 10% of all ABCA4 disease is caused by deep intronic variants."

Both of these advances will significantly improve diagnosis, Dr. Allikmets says, and will help clinicians fine-tune a patient's course of treatment. "Taken together, these discoveries explain ABCA4 disease in an additional 20-25% of the population with the disease. Combining these genetic insights with advanced imaging techniques like Dr. Sparrow's allows us to predict which treatments will apply best to which patients."

Most recently, Dr. Allikmets' laboratory has made a major breakthrough in understanding the genetic roots of macular telangiectasia type 2 (MacTel), a rare disease of the retina that affects the macula and damages central vision. For the past 14 years, Dr. Allikmets has led a team of genetic researchers, supported by the Lowy Medical Research Institute (LMRI), in a quest to identify MacTel's genetic risk factors. "It's proven a very difficult disease to crack genetically," he says.

In research published in the *New England Journal of Medicine* in September 2019, he and his colleagues reported the discovery of the first two causal genes for MacTel. Known as SPTLC1 and SPTLC2, these genes are also associated with a rare childhood-onset genetic condition called Hereditary Sensory Neuropathy Type 1 (HSAN 1). "These two genes were first described as neuropathy genes, and then we discovered that there is a link between some of these cases of neuropathy and MacTel, where patients are affected with both diseases," Dr. Allikmets says.

By themselves, those two genetic variants explain less than 1% of cases of MacTel, but insights gleaned from their identification gave Dr. Allikmets a window into the underlying biological process of the disease. "It turns out that MacTel is primarily a metabolic disease, involving disturbances in the biosynthesis of serine, an amino acid that plays a fundamental role in metabolism," he says. Building on this understanding, he directed a large genome-wide association study that included contributions from both LMRI's research group, as well as Columbia's Institute of Genetic Medicine, directed by David B. Goldstein, PhD, John E. Borne Professor of Medical and Surgical Research (in Genetics and Development) in the Institute for Genomic Medicine and Neurology.

That study, soon to be published in *Nature Metabolism*, identified another gene, PHGDH, as a major factor in MacTel, with mutations in this gene responsible for approximately 4% of the disease. "The study confirmed our metabolic leads and identified PHGDH as the first significant locus for MacTel that explains the typical disease phenotype," Dr. Allikmets says. "It also provides a basis for novel treatment options, including serine supplementation. The MacTel initiative exemplifies the critical importance of synergy between basic and clinical research in ophthalmology."

Constant two-way exchange between basic and clinical scientists is vital. For a program to stay at the cutting edge, having a full complement of highly talented and committed basic researchers in regular contact with clinical scientists is a key part of that, says Dr. John. "If we are isolated from the clinical researchers, they can't become bridges and translators. We can be a filter as to the quality of the basic research that is most important, and new questions will come out of it. And because of their understanding of what is feasible, we might ask questions we never would have thought of otherwise."

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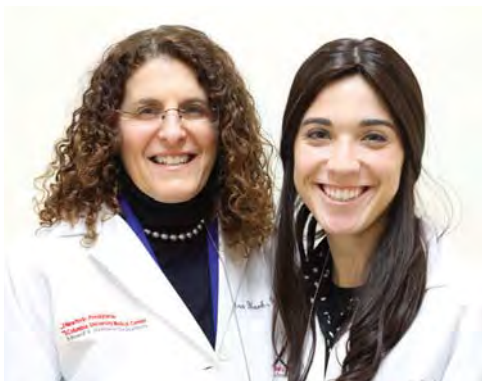

L. to R.: Lisa Hark, PhD, RD and Y. Shira Kresch, OD, MS, FAAO

by making it very easy and convenient. If we are successful at detecting new cases of eye disease and improving follow-up eye care in a cost-effective manner, the CDC would like to expand the program in New York City and replicate it in other cities."

Therefore, Dr. Hark has also partnered with Assaf Zeevi, PhD, Kravis Professor of Business at Columbia University and Laura Pizzi, PharmD, MPH, Director, Center for Health Outcomes, Policy, and Economics at Rutgers University, to conduct an economic analysis of the cost per case detected in the community for these leading causes of eye disease.

Dr. Auran predicts that the project will be very successful. "Community vision screenings, which we already conduct frequently, identify many patients with the kind of vision conditions Dr. Hark hopes to identify and treat," he says. "But many of these people are outside the system. They may not even have a working phone number. Intensive follow-up with a navigator who can shepherd people through a complex and confusing health care system, and all the personal obstacles they may face accessing

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MAKING HISTORY AT HARKNESS

This Viewpoint column will spotlight milestones in ophthalmic care that have taken place at Columbia, from the early "firsts" to the latest achievements.

Ocular Oncology Comes Full Circle

In the early part of the 20th century, retinoblastoma was considered a death sentence, with a survival rate of only about 10% under the best of circumstances. The few children who did survive this rare pediatric cancer, now understood to be most commonly caused by a randomly occurring genetic mutation in chromosome 13, almost always lost their eyes to save their lives.

Brian P. Marr, MD with patient

Today, the survival rate for retinoblastoma has approached 100%, with 90% of those surviving children retaining their vision in at least one eye. This remarkable success story has many authors, but many of the pioneering developments that helped to conquer retinoblastoma can be credited to Algernon B. Reese, MD and Robert Ellsworth, MD, who together built the ocular oncology division at Columbia between the 1930s and the 1970s. Their skill in treating ocular cancers such as retinoblastoma and ocular melanoma earned the program an international reputation, drawing patients from around the world.

Dr. Reese, who launched the program in the 1930s, is considered the father of ophthalmic oncology. His textbook, *Tumors of the Eye*, first published in 1951 with two subsequent editions, remains a seminal work in the field. "Reese was the last and the greatest of the Renaissance figures in the field he founded, because all aspects of ophthalmic oncology were his legitimate province," wrote Frederick Jacobiec, MD, a former colleague of Dr. Reese's at Columbia who chaired the Department of Ophthalmology at Harvard for nearly 15 years, after Dr. Reese's death in 1981. "Besides helping hundreds of patients with retinoblastoma and uveal melanoma, his work with orbital tumors was unparalleled."

The march toward defeat of retinoblastoma began when Dr. Reese teamed with Memorial Sloan-Kettering Cancer Center surgeon Hayes Martin, MD, to experiment with new radiation therapy approaches for the treatment of the disease. After Dr. Ellsworth joined the Columbia faculty in the early 1950s, the two clinicians developed radiation techniques that employed lower dosages, avoided vulnerable parts of the ocular anatomy such as the anterior segment, and were delivered over multiple days (an approach known as fractionation), all of which helped to increase survival rates while minimizing damage to the eye. In the 1960s, they published the Reese-Ellsworth Classification System for Intraocular Retinoblastoma, which allowed investigators to compare their results using different techniques. It became the standard worldwide staging system for decades.

The two noted ophthalmologists treated many famous individuals over the years. *The New York Times* covered Dr. Reese's treatment of Bob Hope, who had suffered an eye injury attributed to a blood clot during his annual Christmas tour in 1958. Other celebrity patients included Babe Ruth, George Gershwin, and Ernest Hemingway.

But to the parents of the children they treated, Drs. Reese and Ellsworth were something much better than eminent, world-renowned leaders in their field: they were the men who gave them hope. Dr. Reese understood the devastating financial and emotional burden that a young child's cancer diagnosis places on a family, so he purchased a townhouse near the Eye Institute where families could stay free of charge while their children received treatment. "Reese House" became a home away from home for many worried parents and their children.

And when those children were finally discharged from treatment, their parents often got a surprise from Dr. Ellsworth. "He would tell them, 'Well, I think everything's going just fine with your child,' and hand them an envelope," recalls D. Jackson Coleman, MD, Professor of Ophthalmology, a pioneer in ocular ultrasound who worked with Dr. Ellsworth on ultrasound techniques in ocular melanoma. "He'd tell them not to open the envelope until they arrived home. When they did, they would find that it contained the money they had paid for their child's treatment, with a note from Dr. Ellsworth telling them to put it in a college fund."

D. Jackson Coleman, MD

It was his way of not only easing the parents' financial burden, but also giving them hope that their child would survive to adulthood.

Dr. Reese and Dr. Ellsworth guided the careers of some of the next generation's greatest ophthalmic oncology leaders. Their trainees included the late Barrett G. Haik, MD, who built the ophthalmic oncology service at St. Jude Children's Research Hospital in Memphis and established an outreach initiative to create retinoblastoma centers of excellence throughout the developing world, and David Abramson, MD, now the chief of the ophthalmic oncology program at Memorial Sloan-Kettering Cancer Center.

After flourishing throughout the middle of the 20th century, ocular oncology at Columbia entered a fallow period in 1979, when Dr. Coleman was appointed Chairman of the Ophthalmology Department at The New York Hospital and John Milton McLean Professor of Ophthalmology at Weill Cornell Medicine. Dr. Ellsworth, Dr. Haik and Dr. Abramson joined him on the Weill Cornell faculty.

More than three decades later, the program was revitalized with the 2015 recruitment of Brian P. Marr, MD, a renowned ophthalmic oncologist from Memorial Sloan-Kettering Cancer Center and one of only a handful of experts trained in all aspects of eye cancer, to lead a new division of ocular oncology. He rejoined Dr. Coleman, who had returned to Columbia in 2012. "Everything came full circle," says Dr. Marr, the John Wilson Espy, MD, Professor of Ophthalmology. "Dr. Reese originally began his career at New York Eye and Ear Infirmary, where I did my residency. Then he worked at Memorial Sloan-Kettering before coming to Columbia, which is almost the same pathway I took."

During his nearly two decades of practice prior to joining the Columbia faculty, first at the Wills Eye Hospital in Philadelphia and then at Memorial Sloan-Kettering, Dr. Marr devised and performed thousands of surgical procedures to treat tumors of the eye, eyelid, orbit, and conjunctiva in adults, children, and infants. He is experienced in the resection of intraocular tumors, as well as laser, radiation, and chemotherapy treatments. In the five years since he joined the faculty, Dr. Marr has re-established a comprehensive ocular oncology program managing every type of cancer that affects the eye. "We are one of only a few such programs on the East Coast," he says.

The most common condition in ocular oncology is uveal melanoma—cancer of the iris, the ciliary body and choroid. Tumors in the uvea develop within the pigment cells (melanocytes) that give color to the eye. Columbia's uveal melanoma service is now one of the top ten in the country in terms of volume, Dr. Marr says, treating well over 100 cases annually.

Working closely with Richard D. Carvajal, MD, Director of Experimental Therapeutics and Director of the Melanoma Service at Columbia, Dr. Marr has also established a basic research program in uveal melanoma, in which he is piloting a project studying a novel liquid biopsy technique for the diagnosis of metastatic disease.

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Dr. Kresch, study optometrist, using a portable slit lamp in the community

Columbia Launches Novel Eye Care Study in NYC Affordable Housing Buildings

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care, will be a game-changer for this community. It's the first time I know of that anyone has undertaken an initiative of this kind to prevent blindness."

In addition to NYCHA, other partners in the study who are represented on the Advisory Board include the New York City Department for the Aging, the New York City Department of Health and Mental Hygiene, the New York Academy of Medicine, the New York City Health and Hospitals Corporation/Harlem Hospital, the New York-Presbyterian Ambulatory Care Network, City University of New York School of Medicine, the Lighthouse Guild, Live-On New York, Warby Parker, Volk Optical, Inc. and VISIONS/Services for the Blind and Visually Impaired. Dr. Hark is also contracting with Westat, Inc. to conduct the study evaluation over five years.

Dr. Hark's co-investigators at Columbia University include Dr. Auran; Dr. Kresch; Jeffrey Liebmann, MD, the Shirlee and Bernard Brown Professor of Ophthalmology, Glaucoma Service Director, and Vice-Chair of the Department of Ophthalmology; C. Gustavo De Moraes, MD, MPH, Associate Professor of Ophthalmology and Medical Director of the Clinical Trial Unit; Lisa Park, MD, Associate Professor of Ophthalmology; Jason Horowitz, MD, Associate Professor of Ophthalmology and Medical Director of the Harkness Eye Clinic; Noga Harizman, MD, Associate Professor of Ophthalmology; Prakash Gorroochurn, PhD, Associate Professor of Biostatistics at the Columbia University Mailman School of Public Health; and Olajide Williams, MD, MPH, Associate Professor of Neurology and Co-Director of the Columbia Wellness Center. Stella Stempel, MSW and Stefania Maruri are serving as study coordinators. In addition, numerous Columbia University experts are serving on the Advisory Board, including representatives from the School of Nursing, Mailman School of Public Health, Office of Government and Community Affairs, and Occupational Therapy Programs.

L. to R.: Stefania Maruri, BS, Stella Stempel, LCSW, Lisa Hark, PhD, RD, and Bianca Lambert, MD, MS

Ocular Oncology Comes Full Circle

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"A key challenge with uveal melanoma is that it may appear that the primary cancer was treated successfully with surgery or radiation, but years later, the patient can still develop metastatic disease," he says. "We have discovered that we can identify exosomes, chunks of nucleic acid that tumor cells excrete and circulate through the bloodstream. We are collecting tissue samples from patients with varying stages of melanoma as well as normal controls, to determine if the exosomes differ in these different stages of disease. Ideally, we could use them to predict a patient's disease state noninvasively, like a PSA test for prostate cancer."

Dr. Marr is working to build the retinoblastoma program back to its former stature. "There are only about 300 cases of retinoblastoma in the country, so it takes a major commitment of time, energy and resources to put a program in place for a small number of patients," he says. "We are now working to develop the kind of dedicated facilities and faculty to make a comprehensive retinoblastoma service possible."

Ultimately, he would like to expand into a larger, dedicated space that can be a comprehensive full-service destination center for ophthalmic oncology. "The tradition of this program, created by some of the greatest minds in ophthalmology, goes back almost a century," he says. "Columbia is now once again at the forefront of new innovations in the field that would make them proud."

Viewpoint

IMPORTANT PATIENT CARE INFORMATION

Specialties:
Cornea/External Ocular Disease
Glaucoma
Pediatric Ophthalmology and Strabismus
Refractive Surgery/LASIK
Vitreoretinal and Uveitis

For inquiries and appointments, please call 212.305.9535

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