Columbia University Medical Center

Viewpoint

A publication of The Edward S. Harkness Eye Institute and The Department of Ophthalmology in the College of Physicians and Surgeons

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Deciphering the Genetics of Glaucoma: The Brown Initiative

With the help of a major award from The Brown Foundation, the Department of Ophthalmology has launched an ambitious new glaucoma genetics research program. The five-year gift supports the Brown Glaucoma Genetics Initiative, a continuum of investigative and therapeutic projects focused on the discovery of novel genes and genetic treatments for glaucoma. This generous award represents the third major gift to the Department of Ophthalmology from Shirlee and Bernard Brown's foundation, including their sponsorship of the Brown Glaucoma Laboratory and the Brown Glaucoma Professorship. Mr. and Mrs. Brown have served as members of the Department's Board of Advisors for more than 15 years.

Jeffrey Liebmann, MD with Shirlee and Bernard Brown

The Brown Glaucoma Genetics Initiative has three major phases that will run concurrently.

"While several genes associated with glaucoma have been identified, they still account for fewer than 10% of all cases of the disease," explains Jeffrey Liebmann, MD, the Shirlee and Bernard Brown Professor of Ophthalmology, Glaucoma Service Director, and Vice-Chair of the Department of Ophthalmology. "The research funded by The Brown Foundation will enable us to address each subtype of glaucoma one by one with the goal of eventually identifying all the associated gene alterations. Ultimately, we hope to develop a blood test that can assess a person's risk for developing glaucoma, as well as unique treatments for each type."

Pigmentary glaucoma, the first form of the disease that the Brown Initiative will investigate, is most often diagnosed in young people in their 20s and 30s. Although relatively uncommon—it has been reported to occur in 1-2% of the population—pigmentary glaucoma is a significant cause of disability because it causes blindness early on in life. "This form of glaucoma can be very aggressive, leading to vision loss during a person's most productive years," notes Dr. Liebmann. "It is urgent that we develop a better understanding of this disease."

Pigmentary glaucoma occurs when the pigment granules that line the back of the iris shed into the aqueous humor—the clear fluid that nourishes the eye's tissues. This fluid flows out of the eye through a drainage system called the trabecular meshwork. The pigment granules damage the cells that drain the aqueous humor, causing increased fluid pressure inside the eye (intraocular pressure). This condition

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INSIDE

Research Spotlight:

Andrei Tkatchenko, MD, PhD The Genetics of Myopia

With its global prevalence expected to reach 50% by 2050, myopia has emerged as one of the leading causes of vision loss in several parts of the world. The excessive eye growth that produces nearsightedness also leads to serious vision-threatening complications such as retinal tears and detachment, myopic macular degeneration, and glaucoma (see feature, page 3).

Andrei V. Tkatchenko, MD, PhD, Associate Professor of Ophthalmic Sciences (in Ophthalmology and Pathology and Cell Biology), made international headlines in 2015 when he identified variations in the gene APLP2 as an important factor in the development of myopia in children. His latest research, published in *PLOS Biology* in October 2018, identifies two distinct molecular signaling pathways involved with the mechanisms controlling eye growth and optical development. Understanding these pathways is an essential step toward developing candidate drugs to effectively treat myopia.

"While there are some optics-based treatments and drugs that can

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L. to R.: Andrei V. Tkatchenko, MD, PhD, Tatiana Tkatchenko, MD, and Sergey Yaklichkin, PhD

View from the Chair

Dear Friends,

For many people, the idea of myopia (nearsightedness) does not cause concern about long-term risk to a person's sight. A child has trouble seeing the blackboard, is diagnosed with myopia, and is prescribed glasses. Perhaps at an older age he or she will get contact lenses or undergo corrective laser surgery. These things may be seen as an inconvenience and an expense, but nothing worse than that.

As you will read in this issue of *Viewpoint*, however, the increasing prevalence of myopia, both in the United States and around the world, does indeed pose a serious risk to the eyesight of hundreds of thousands of people. The elongation of the eye that causes myopia can ultimately lead to retinal detachment, glaucoma, cataracts, and other vision-threatening conditions.

Columbia's Department of Ophthalmology has taken on a leading role in combating the vision risks posed by myopia with both clinical and research initiatives. In early 2019, we will launch a new Myopia Control Clinic, one of only a handful of such programs in the nation. Led by Y. Shira Kresch, OD, MS, FAAO, Andrei V. Tkatchenko, MD, PhD, Steven Brooks, MD, and Suzanne Sherman, OD, FAAO, this clinic will offer several leading-edge interventions aimed at stemming myopia progression and preserving vision. Dr. Tkatchkenko has also recently published exciting new research on the genetic basis of myopia, identifying clearly different molecular pathways involved in the development of nearsightedness and farsightedness.

It has long been the accepted wisdom in ophthalmology that glaucoma is primarily a disorder of the peripheral vision, with damage to the central vision occurring only quite late in the disease process. Within the past several years, however, Dana Blumberg, MD, MPH, and Donald Hood, PhD, have published pivotal research demonstrating that in many people, the functional center of the retina known as the macula sustains damage much earlier in the course of glaucoma than previously thought. Now, Dr. Blumberg is launching a first-of-its-kind clinical trial to assess how patterns of macular damage affect patients' vision in glaucoma.

We are also very pleased to announce two new grants that will support important translational research projects. The first, a major new Program Project Grant from the Foundation Fighting Blindness, supports a multi-faceted, four-investigator effort, led by Rando Allikmets, PhD, to identify targeted therapies for specific subtypes of Stargardt disease. The second is a significant award from The Brown Foundation to launch a new initiative focused on the genetics of glaucoma, with the aim of developing treatments for specific subtypes of the disease. Jeffrey Liebmann, MD, will direct the Brown Glaucoma Genetics Initiative.

Our Precision Ophthalmology program, as well as other promising new advances in ophthalmology, were also discussed at two recent events: the biannual Abraham Spector Prize Lecture, and Vision: 20/20, the 11th installment of DocTalks, a series of specialized clinical panels hosted by Columbia Dean Lee Goldman, MD.

The Department of Ophthalmology's commitment to our patients doesn't stop at the walls of the medical center. If you were at this year's Velocity Ride Against Cancer, Columbia's creative new kind of fundraising bike race, you might have seen ocular oncologist Brian Marr, MD, riding alongside one of his patients as part of the "Eyes Against Cancer" team that raised over $10,000 for cancer research.

None of these efforts would be possible without your continued support for our shared mission. As always, I am deeply grateful to each of you, and I look forward to having even more good news about our work to share with you in the coming year.

Sincerely,

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

Research Spotlight: Andrei Tkatchenko, MD, PhD, The Genetics of Myopia *continued from page 1*

be used now to slow progression of myopia, their effectiveness is limited," Dr. Tkatchenko says. "The main obstacle that prevents us from developing more effective therapies is our incomplete knowledge of the molecular mechanisms that control visually guided eye growth and development. We hope that our research will help to overcome that obstacle."

What Causes Myopia?

The majority of babies are born hyperopic, or farsighted, which means that a typical newborn can see a teddy bear located on the other side of the room much better than if it's near her face.

"In infants, the anterior segment of the eye—the region that includes the cornea, anterior chamber and crystalline lens—is almost fully developed, but the posterior segment is very small in most cases," explains Dr. Tkatchenko. "As a result, images are focused behind the retina, which leads to farsightedness. During the first years of life, eyes gradually develop focus through a process known as emmetropization, as the length of the eye increases until the focal point coincides with the retina. When images are focused precisely on the retina, an individual has perfect vision and can see well both near and at a distance." But in an increasing number of children, the length of the eye continues to grow beyond that point of perfect vision, causing myopia.

Scientists have long believed that myopia is caused by an interacting combination of environmental and genetic factors, but until recently, hard proof of this theory was lacking. Then, in research published in *PLOS Genetics* in 2015, Dr. Tkatchenko and colleagues showed that children with a specific variation of APLP2 have an increased susceptibility to myopia—but only if they spend large amounts of time per day reading or doing other close work. "We found that children with this variation were five times more likely to develop myopia if they also spent at least an hour a day reading," he says. The study was the first known evidence of gene-environment interaction in myopia.

Two Different Pathways

Dr. Tkatchenko's latest research builds on those findings and challenges a commonly held assumption about myopia and hyperopia: that these two ocular conditions are caused by opposing changes in the same genes and

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Clinical Spotlight:

New Myopia Management Clinic Takes Aim at Major Cause of Eye Disease

If you use glasses or contact lenses, or had LASIK or other corrective surgery for myopia (nearsightedness), you are far from alone. Almost half the U.S. population is now estimated to be myopic, a figure that has almost doubled over the past four decades. Myopia is also on the rise worldwide: in many East and South Asian countries, myopia rates have reached 80% to 90%.

Why are myopia rates increasing so dramatically? Genetic factors play a major role in the development of myopia. Children are more likely to be nearsighted if one or both parents also have the condition, and a large number of myopia-related genes have been identified. But environmental factors such as close-up work, reading or working on a computer play a very important role in the development of myopia. For example, research published in the 1990s found that teenage boys in Israel who attended yeshivas where they spent long days studying religious texts had significantly higher rates of myopia than students who did not attend such schools.

"Over the past four decades, the level of near work has significantly increased in most of the world, because of computers, mobile devices and smartphones," says Andrei V. Tkatchenko, MD, PhD, Associate Professor of Ophthalmic Sciences (in Ophthalmology and Pathology and Cell Biology). "Myopia rates have increased as a result."

While glasses, contact lenses and surgery can correct the effects of myopia and allow clear distance vision, they treat the symptoms of the condition, not the cause. The underlying defect in myopia is an excessively elongated eyeball, which means that the lens focuses light in *front* of the retina, rather than directly on it. And this abnormality is more than just an inconvenience: it poses long-term hazards to a person's vision.

"When the eye becomes longer, the tissue of the retina and the structures supporting the optic nerve in the back of the eye stretch and become thinner," says Y. Shira Kresch, OD, MS, FAAO, Instructor in Optometric Science. "This elongation increases the risk of eye diseases that can cause visual impairment or even blindness, including cataracts, myopic maculopathy, retinal detachment and glaucoma. Earlier onset of myopia is linked with faster and more significant progression, which greatly increases the risk of these myopia-associated diseases. In fact, myopia is one of the five ocular conditions identified as an immediate priority by the World Health Organization's Global Health Initiative for the Elimination of Preventable Blindness. What was once considered as a mostly benign condition is becoming a serious concern."

Putting the Brakes on Myopia Progression

In spite of the high rate of myopia, there may be a window of time in children and young adults when proper intervention can substantially slow its progression. "There is a clearly defined treatable period between ages eight and 25 during which there is the greatest progression of myopia," says Dr. Tkatchenko. "Myopia control is most effective during those years."

The Department of Ophthalmology will be taking a leading role in tackling this major threat to ocular health by launching one of the first myopia control clinics in the greater New York City area. The clinic will officially open in early 2019, under the directorship of Dr. Kresch.

"Any child or young adult with myopia, especially if accompanied with signs of progression, should be considered for referral to our clinic," Dr. Kresch says. "We can now predict with a fair amount of accuracy which individuals are most likely to progress and recommend specific interventions that may slow down the progression rate. By slowing the rate at which myopia advances, we hope to prevent more serious complications later on. As an academic medical center we maintain a critical approach to carefully evaluating the scientific evidence underlying any treatment we recommend, and we will also be involved in the investigation of new treatment strategies."

After a comprehensive baseline eye examination with one of the Department's pediatric optometrists or ophthalmologists, children and their parents will meet with the clinic's faculty to discuss whether or not the child is eligible for myopia control and, if so, which available treatment option is best.

There are three main modalities that show evidence of slowing the progression of myopia, although none have yet received approval from the Food and Drug Administration (FDA). These include ophthalmic atropine eye drops, soft multifocal contact lenses with a center distance design, and orthokeratology (gas-permeable contact lenses that temporarily reshape the cornea). Adjunctive treatments include progressive or bifocal spectacles. Recommendation for a specific treatment plan will be determined on an individual basis with the agreement of the child, parents and treating physician. Orthokeratology will not be offered at this time due its slightly increased risk of infection compared to the other options. There may be opportunities in the near future for enrollment in myopia-related studies. Although these modalities seem promising, there is still no guarantee about the effectiveness of myopia control.

The Great Outdoors

Parents, teachers, and other caregivers can also help slow down the progression of a child's myopia with one simple prescription that has no detrimental side effects and many other health benefits: spending time outside.

"A number of studies over the last several years have shown that outside activities suppress the development of myopia," says Dr. Tkatchenko. For example, an Australian study called ROAM (Role of Outdoor Activity in Myopia) followed 101 children aged 10-15. The children wore wristwatch light sensors to record their light exposure and physical activity. The children who habitually spent less than 60 minutes a day outdoors had significantly faster eye growth compared with those who spent more time outside. And it appears to be time spent outside, not exercise, that protects against myopia. This and other studies found no relationship between physical activity level and myopia progression. "Go outside and play," says Dr. Tkatchenko. "That's the best thing parents can tell their children to help prevent myopia."

"The emerging research, both clinical and scientific, gives us optimism that halting the progression of myopia may now be within reach," says Steven Brooks, MD, the Anne S. Cohen Professor of Pediatric Ophthalmology and Chief of Pediatric Ophthalmology at the Harkness Eye Institute. "We are excited to offer patients the latest treatment options, and to continue exploring new and better ways to deal with this worldwide problem affecting vision." More information about scheduling an appointment with the Myopia Management Clinic will be available after it opens in early 2019. ■

Visionaries & Luminaries

Spector Lecture Features David Sabatini, MD, PhD, Discoverer of Cell Growth Regulator mTOR

Above: David Sabatini, MD, PhD
Top: Dr. Sabatini and
G. A. (Jack) Cioffi, MD

David Sabatini, MD, PhD, a member of the Whitehead Institute for Biomedical Research and Professor of Biology at the Massachusetts Institute of Technology, presented the 7th Abraham Spector Prize Lecture on Thursday, October 4.

The lecture concluded a full afternoon of presentations and discussions commemorating the life and work of Abraham Spector, PhD, whose nearly 50-year career at Columbia included eight years as Research Director of the Department of Ophthalmology, from 1996 until his retirement in 2004. Dr. Spector's laboratory was internationally recognized for its work on the lens of the eye, including research on lens proteins, aging, transparency, and the mechanisms of cataract formation. Dr. Spector passed away in April 2016.

As a young MD-PhD student at Johns Hopkins University in the early 1990s, Dr. Sabatini identified a novel protein kinase known as mTOR (mechanistic target of rapamycin), which ultimately proved to be a critical regulator of cellular growth. In his Spector Lecture, Dr. Sabatini discussed the role of mTOR and lysosomes in growth control and disease. "Because the mTOR pathway is dysregulated in aging and in diseases such as cancer, epilepsy and diabetes, his research has attracted wide interest," noted Janet Sparrow, PhD, Anthony Donn Professor of Ophthalmic Sciences and Professor of Pathology and Cell Biology, who introduced Dr. Sabatini.

Additional guest speakers included Lois Smith, MD, PhD, Professor of Ophthalmology at Harvard Medical School, who spoke on regulation of retinal angiogenesis by lipid and glucose metabolism; James Hurley, PhD, Professor of Biochemistry at the University of Washington, who discussed the retina as a metabolic ecosystem; and Douglas Wallace, PhD, Professor of Pathology and Laboratory Medicine at the University of Pennsylvania Perelman School of Medicine and Michael and Charles Barnett Endowed Chair in Pediatric Mitochondrial Medicine and Metabolic Disease at Children's Hospital of Philadelphia, who presented on mitochondria dysfunction in neuro-ophthalmological disease.

"The Spector Lecture serves as an important venue for us to advance the shared interests and research goals of scientists at Columbia and other institutions," Dr. Sparrow said. "It was an enlightening and thought-provoking event for an audience that spanned the Columbia scientific community."

Deciphering the Genetics of Glaucoma: The Brown Initiative *continued from page 1*

occurs more commonly in nearsighted people. Even though it is known to be hereditary, there has been very little genetic research on pigmentary glaucoma.

In Phase 1 of the research sponsored by the Brown Initiative, at least 200 people with pigmentary glaucoma will be recruited for genetic analysis. "If they have affected family members, we will ask them to come in as well," Dr. Liebmann says. "We hope to identify the relevant gene involved with the disease and derive a treatment aimed at disease-causing defects in that gene—possibly gene therapy or another novel treatment." If successful, the pigmentary glaucoma project will be used as a model for other gene-identification studies in glaucoma. Working with the entire research division, as well as Dr. Rando Allikmets, the Brown initiative hopes to unravel the genetic underpinnings of this unique form of glaucoma.

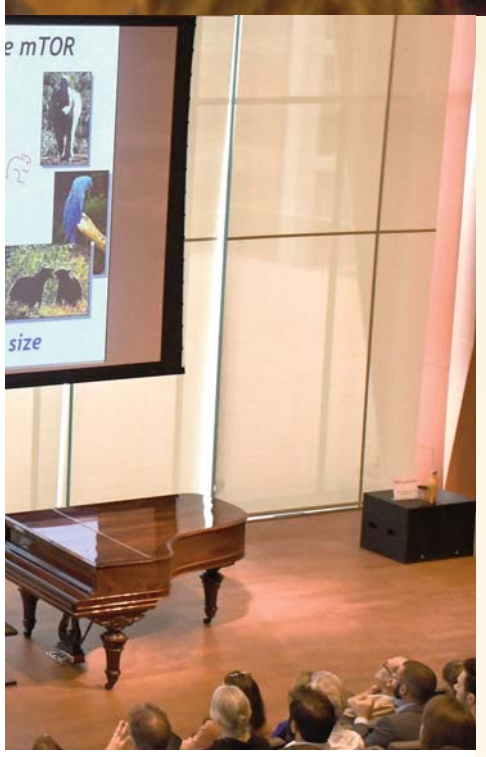
Phase 2 of the Brown Initiative will focus on a form of glaucoma that already has a promising genetic target: exfoliation syndrome. In about 5-10% of

Jeffrey Liebmann, MD and his research team, from L. to R.: Ioannis Michalopoulos, Elizabeth Stidham, and Lam Lu

people over age 50, a whitish material that looks like tiny flakes of dandruff is rubbed off the lens by movement of the iris and clogs the trabecular meshwork. People with exfoliation syndrome are six times more likely to develop glaucoma than those without the syndrome.

Associate Professor of Ophthalmology Konstantin Petrukhin, PhD, has been developing a screening process for small molecules that can modulate one of the genes associated with exfoliation syndrome, LOXL1. Building on Dr. Petrukhin's work, the Brown Initiative will support harvesting discarded cells from glaucoma surgery to generate exfoliation material in the laboratory. These specimens will be used to assess disease response to novel targeted treatments.

Phase 3 of the Initiative is a clinical trial of vitamin B3 as a treatment for primary open-angle glaucoma. In a study published in the journal *Science* in 2017, researchers from the Jackson Laboratory in Maine demonstrated that nicotinamide, a form of vitamin B3, halted the development of glaucoma in mice. Nicotinamide supplements were able to prevent glaucoma in 70% of mice predisposed to the disease. Adding gene therapy to nicotinamide treatment conferred even more protection. Dr. Liebmann and G. A. (Jack) Cioffi, MD, Jean and Richard Deems Professor, Edward S. Harkness Professor, and Chairman of the Department of Ophthalmology, co-authored a commentary which was published in *New England*



Journal of Medicine, calling for clinical trials to test the concept in humans.

The pilot vitamin B3 study will recruit approximately 60 patients with primary open-angle glaucoma, half of whom will receive vitamin B3 and half of whom will receive a placebo. Over the course of the trial, participants will undergo multiple visual field tests to assess the effectiveness of the treatment. If successful, it would be the first proven vitamin therapy for glaucoma. "It's hard to find seed money for innovative projects," says Dr. Liebmann. "This generous gift is a demonstration of Shirlee and Bernard Brown's ongoing commitment to cutting-edge glaucoma research."

For more information on the Initiative and how to participate in the trial, contact: Ms. Elizabeth Stidham, study coordinator, at 646-457-0940.

Strong Growth for Jonas Children's Vision Care

Pediatric patient visits to the Department of Ophthalmology have increased significantly since the opening of Jonas Children's Vision Care at Columbia in January 2017, reports Administrative Director Lisa Hark, PhD, RD, Professor of Ophthalmic Sciences. In 2015-2016, a total of 3,802 children with vision issues were seen in the Department; by 2017-2018, that number had increased to 4,710. "We now have a strong network of about 50 physicians in the area who are regularly referring patients to Jonas Children's Vision Care," says Dr. Hark.

A first-of-its-kind, multidisciplinary program, Jonas Children's Vision Care combines the efforts of leading pediatric ophthalmologists, scientists, educators, and genetics experts to create a world-class center for pediatric eye care in a compassionate, family-centered environment. In addition to comprehensive medical and surgical pediatric eye care, Jonas Children's Vision Care offers subspecialty services in retinopathy of prematurity, pediatric cornea, pediatric glaucoma and pediatric retina, along with ocular oncology, neuro-ophthalmology, and oculoplastics. Children are evaluated and treated at all Columbia Ophthalmology practice sites.

Vision specialists outside of Columbia University Irving Medical Center can also refer their patients to Jonas Children's Vision Care for advanced diagnostic testing services using state-of-the-art ophthalmic imaging and other technology, such as optical coherence tomography, retinal photography, portable electroretinography, and advanced corneal topographic analysis. Many of the tests are specifically adapted for children.

A Top-Notch Clinical Team

These coordinated diagnostic, clinical and surgical services for infants, children, and adolescents are provided by an outstanding core team assembled by Steven Brooks, MD, Anne S. Cohen Professor of Pediatric Ophthalmology and Medical Director of Jonas Children's Vision Care. The faculty includes:

General pediatric ophthalmology
Dr. Steven Brooks and Lauren Yeager, MD, Assistant Professor of Ophthalmology

Pediatric retina
Stephen Tsang, MD, PhD, Laszlo T. Bito Associate Professor of Ophthalmology and Associate Professor of Pathology and Cell Biology; Jason Horowitz, MD, Assistant Professor of Ophthalmology; and Robert Lopez, MD, Clinical Professor of Ophthalmology

Pediatric ocular oncology
Brian Marr, MD, John Wilson Espy, MD Professor of Ophthalmology and Director of the Ophthalmic Oncology Service

Pediatric ophthalmic genetics
Irene Maumenee, MD, Professor of Ophthalmology and Director of Ophthalmic Genetics

Pediatric oculoplastic surgery
Lora Glass, MD, Assistant Professor of Ophthalmology

Pediatric corneal disease
Danielle Trief, MD, Assistant Professor of Ophthalmology

Pediatric glaucoma and cataract
Dr. Brooks and Steven Kane, MD, PhD, Associate Clinical Professor of Ophthalmology

Pediatric contact lenses and optometry
Y. Shira Kresch, OD, MS, FAAO, Instructor in Ophthalmic Science
Suzanne Sherman, OD, FAAO, Instructor in Ophthalmic Science

Pediatric low vision services
The Lighthouse Guild

Advisory Board Established

John Jonas, the son of philanthropists Donald and the late Barbara Jonas, whose generosity helped to create Jonas Children's Vision Care, recently joined the program's Advisory Board. In addition to Mr. Jonas, Dr. Hark, Dr. Brooks, and Dr. Tsang, the Board's membership also includes:

G. A. (Jack) Cioffi, MD, Jean and Richard Deems Professor, Edward S. Harkness Professor, and Chairman, Department of Ophthalmology
Jeff Todd, Executive Vice President, Prevent Blindness
Alan Morse, PhD, JD, President and Chief Executive Officer, The Lighthouse Guild
Craig Albanese, MD, Senior Vice President/Chief Operating Officer, NewYork-Presbyterian Hospital-Morgan Stanley Children's Hospital of New York

Advancing Pediatric Vision Research

Jonas Children's Vision Care also provides seed funding to promote groundbreaking research in pediatric ophthalmology. "We intend to focus our support on pilot projects from young investigators and new research directions for more established researchers," Dr. Hark explains.

So far, the program has awarded three $40,000, one-year grants. Dr. Trief received funding for research on corneal neovascularization, a condition in which blood vessels grow in the normally clear, translucent cornea. Janet Sparrow, PhD, Anthony Donn Professor of Ophthalmic Sciences and Professor of Pathology and Cell Biology, is studying the use of near-infrared imaging for retinal disorders in children. And post-doctoral research fellow Chenqi Tao, PhD, under the mentorship of Xin Zhang, PhD, Associate Professor of Ophthalmic Sciences, is investigating novel approaches to preventing retinopathy of prematurity, the leading cause of blindness in premature infants. Dr. Tao has also been named the 2018 Jonas Children's Vision Care Research Scholar.

"We are very proud of the progress that Jonas Children's Vision Care has made in a very short time toward our goals of fighting childhood blindness and improving access to pediatric eye care," says Dr. Hark. "The commitment of the Jonas family has enabled us to create a truly world-class center for pediatric eye care in a friendly and compassionate environment."

To make an appointment with Jonas Children's Vision Care, please call **212-305-9535**

Faculty Spotlight:

Unraveling the Macular Mystery in Glaucoma

Traditionally, ophthalmologists who treat glaucoma have not paid a significant amount of attention to the macula, the tiny portion of the retina responsible for focusing central vision in the eye. It has long been accepted that glaucoma is a disorder of the peripheral vision and that damage to the central visual field only takes place late in the disease process.

Despite this, Assistant Professor of Ophthalmology Dana Blumberg, MD, MPH, frequently hears her glaucoma patients report difficulty with low contrast, glare from bright lights, and difficulty adjusting to the dark. These tasks are all related to central visual function, which presumably should not be impacted until late in the disease course. "These findings are hard to explain using the traditional model of glaucoma damage," Dr. Blumberg says.

Several years ago, she reached out to Donald Hood, PhD, James F. Bender Professor of Psychology and Professor of Ophthalmic Science (in Ophthalmology), whose work has been pivotal in recognizing that the macula is impaired much earlier on in glaucoma progression than was previously thought. In collaboration with Dr. Hood, she hypothesized that damage to the macula helped explain many of the visual complaints of glaucoma patients that could not be otherwise explained.

"The 24-2 visual field test that has classically been used in diagnosing glaucoma is not sensitive for detecting changes in the macula," explains Dr. Blumberg. "Traditional visual field testing has also correlated poorly with patients' self-reported visual function and ability to perform activities of daily living."

Visual field testing of the macula, on the other hand, strongly correlates with patients' self-reported visual function, as Dr. Blumberg and her colleagues have recently demonstrated in several published articles. "We also found that patients who report disproportionate levels of difficulty with daily visual function compared to the findings from their standard glaucoma visual field testing almost always have macular damage that previously went undetected," she says. "In other words, if your day-to-day vision is much worse than your 24-2 visual field test results might suggest, the odds are very good that you also have macular damage."

Certain specific visual complaints, in particular, point to macular damage. "For example, complaints related to luminance—difficulty adapting to changes in light level, like going into a dark movie theater or experiencing glare on a sunny day at the beach—are commonly reported by glaucoma patients who also have damage to the macula," Dr. Blumberg says.

Dr. Blumberg and her colleagues will be testing these hypotheses in an innovative prospective study that will explore whether glaucoma patients with macular damage have diminished contrast sensitivity, impaired vision with glare testing, and difficulty with adaptation to the dark. These associations have never been explored before.

"If we can better understand how patterns of macular damage affect patients' vision, ophthalmologists could start looking for these patterns earlier in the disease course and could target treatment toward the macula if it proves to be involved," she says. "If we could align early changes in the macula with these specific visual dysfunctions, we may have the missing piece in terms of understanding glaucomatous functional visual loss. Not every patient with glaucoma experiences damage in the macula, but those who do seem to experience more visual disability."

The encouraging results of the pilot studies speak to Dr. Blumberg's skills as both a clinician and a scientist. She explains that the foundation for this research came from carefully listening to each patient and studying their examination findings. "I am grateful to several patients who were able to articulate their visual difficulties. Were it not for these patients, the idea for this study may not have happened."

Dana Blumberg, MD, MPH and patient

Research Spotlight: Andrei Tkatchenko, MD, PhD
The Genetics of Myopia

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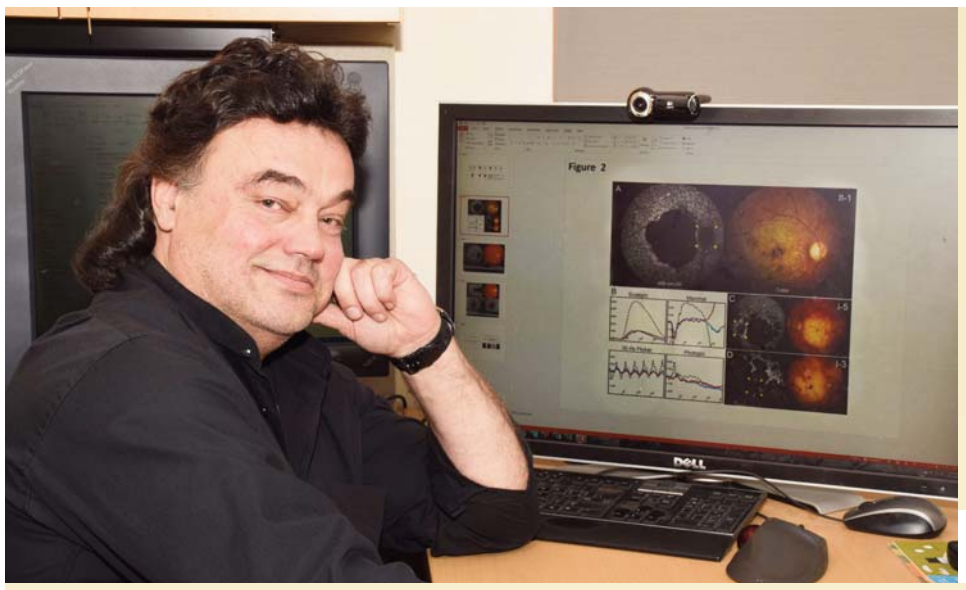
pathways. Instead, Dr. Tkatchenko's group found that distinctly different molecular pathways are activated in myopia and hyperopia.

In a primate model, Dr. Tkatchenko and colleagues used specially designed contact lenses to induce the development of either myopia or hyperopia. They observed that the animals' eyes were stimulated to either increase or decrease their axial length (the distance between the front and back of the eye) in response to the artificially created defocus. Next, they conducted a whole-genome gene expression analysis on each of the retinas that had been treated with optical defocus. They identified large-scale changes in gene expression controlling metabolism and cell signaling in the retina—but those changes involved almost completely different sets of genes and signaling pathways for hyperopia and myopia.

"Our findings show that the retina can distinguish between myopic and hyperopic defocus," Dr. Tkatchenko says. "Now that we have identified the pathways underlying the eye's response to optical defocus, we have a better understanding of the mechanisms that control refractive eye development. Our next step will be to identify druggable targets within these pathways, and candidate drugs that can modulate those targets and counteract the development of myopia."

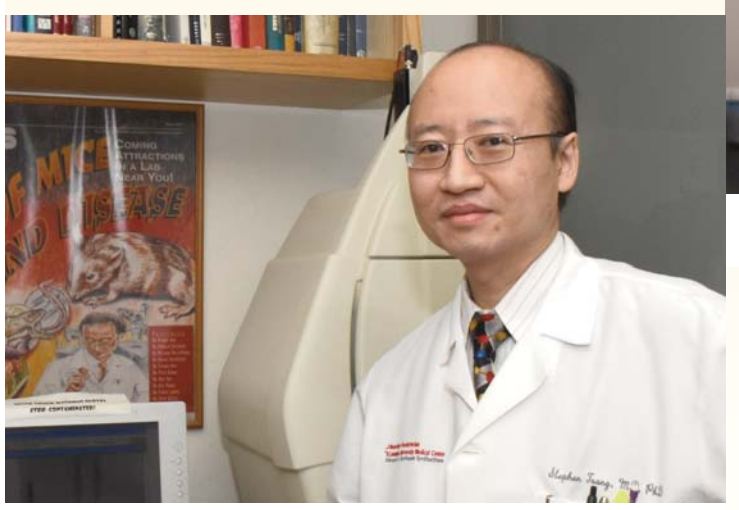


Rando Allikmets, PhD

Major FFB Grant Will Help Develop Targeted Stargardt Disease Trials

A new five-year, $2.5 million Program Project Grant from the Foundation Fighting Blindness (FFB) will support a Columbia initiative to identify specific subgroups of patients with Stargardt disease for clinical trials of novel targeted therapies.

Autosomal recessive Stargardt disease is caused by mutations in the *ABCA4* gene, first identified by Rando Allikmets, PhD, William and Donna Acquavella Professor of Ophthalmic Sciences (in Ophthalmology and Pathology and Cell Biology) and Research Director of the Edward S. Harkness Eye Institute. There are more than 1,000 known such mutations, and depending on their combination, the disease can also manifest as other vision disorders such as cone-rod dystrophy, occult maculopathy, and retinitis pigmentosa-like retinal dystrophy. At least 5% of the general population carries a disease-related variation in ABCA4. Together, all forms of ABCA4 disease represent the most prevalent inherited cause of retinal/macular disease and vision loss in both children and adults.



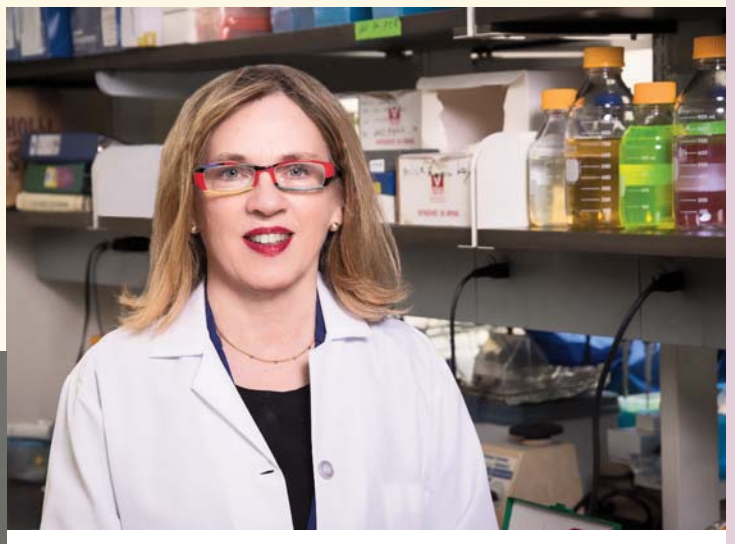
Stephen Tsang, MD, PhD

While there are currently no approved treatments for ABCA4 disease, several promising therapeutic options are in, or close to, clinical trials. The new Program Project uses combinations of genetic and clinical information to categorize patients with the disease into precise subgroups for these trials. "We will systematically integrate data from a number of innovative, cutting-edge clinical and genetic methods to create a unique prediction matrix for ABCA4 disease," says Dr. Allikmets, who will lead the overall Program Project.

The Program Project includes four complementary components:

• Project 1, led by Stephen Tsang, MD, PhD, Laszlo T. Bito Associate Professor of Ophthalmology and Associate Professor of Pathology and Cell Biology, will recruit and evaluate patients and family members with ABCA4 disease. The researchers will document each participant's disease characteristics and progression rates.

• Project 2, led by Janet Sparrow, PhD, Anthony Donn Professor of Ophthalmic Sciences and Professor of Pathology and Cell Biology, will use advanced imaging studies (including near-infrared autofluorescence, quantitative fundus autofluorescence, and spectral domain optical coherence tomography) to develop key biomarkers.



Janet Sparrow, PhD

• Project 3, led by Dr. Allikmets, will analyze how variations in the ABCA4 gene interact with other potentially modifying genes to identify specific subcategories of disease, such as slow and fast progressors.

• Project 4, led by Andrei V. Tkatchenko, MD, PhD, Associate Professor of Ophthalmic Sciences (in Ophthalmology and Pathology and Cell Biology), will use a mouse mapping strategy to identify new genes that modify ABCA4 disease, in order to guide the human genetic studies and create new models for testing treatments.

"We are very grateful to the FFB for this major grant, which recognizes and rewards the Department's Precision Ophthalmology approach to science," says Dr. Allikmets. "We have spent decades building a successful integrated program in which our expertise and efforts are combined. A grant like this ties everything together, and we believe it will substantially improve outcomes for patients in clinical trials." ■

DocTalks Presents "Vision 20/20"

Leading experts from the Department of Ophthalmology answered questions about Precision Ophthalmology and recent advances in vision care at "Vision 20/20," the 11th installment of DocTalks, on October 24. This lecture and discussion series provides Columbia's friends and benefactors with an opportunity to learn from our world-class faculty about the latest in healthcare and medical research.

The evening was hosted by Lee Goldman, MD, Harold and Margaret Hatch Professor, Dean of the Faculties of Health Sciences and Medicine, and Chief Executive of Columbia University Irving Medical Center, and moderated by G.A. (Jack) Cioffi, MD, Jean and Richard Deems Professor of Ophthalmology, Edward S. Harkness Professor of Ophthalmology, and Chairman of the Department of Ophthalmology.

Panelists included Stanley Chang, MD, K.K. Tse and Ku Teh Ying Professor of Ophthalmology and Chairman Emeritus of the Department of Ophthalmology; Jeffrey Liebmann, MD, the Shirlee and Bernard Brown Professor of Ophthalmology, Glaucoma Service Director, and Vice-Chair of the Department of Ophthalmology; Brian Marr, MD, John Wilson Espy, MD Professor of Ophthalmology and Director of the Ophthalmic Oncology Service; Irene Maumenee, MD, Professor of Ophthalmic Sciences and Director of Ophthalmic Genetics; and Leejee Suh, MD, Miranda Wong Tang Associate Professor of Ophthalmology and Director of the Refractive Surgery Service and Cornea Service.

The group discussed a wide range of topics under the unifying theme of Precision Ophthalmology, including advances in diagnostic and imaging techniques, the genetic basis of diseases such as glaucoma and keratoconus, and the prospects for gene therapy to treat blinding conditions. Dr. Chang spoke about some of the most important recent genetic advances in retinal disease, while Dr. Maumenee and Dr. Suh addressed the relationship between genetic approaches to rare disorders, such as keratoconus, and more common conditions, such as dry eye. All members of the panel shared their visions for how their fields will change over the next five years, and how the Precision Ophthalmology program will transform the way they practice.

About 80 people attended the event, including members of the Department's Board of Advisors as well as friends and donors from the larger Columbia community. ■

Ophthalmology Cycling Team Achieves High "Velocity"

Eyes Against Cancer Team

A team of cyclists representing the Department of Ophthalmology raised $10,600 for cancer research and treatment in Columbia's second annual Velocity ride to end cancer, held on October 7. Calling themselves Eyes Against Cancer, the ophthalmology riders were led by Brian Marr, MD, John Wilson Espy, MD Professor of Ophthalmology and Director of the Ophthalmic Oncology Service, and Susan Tarbous, a patient whom Dr. Marr successfully treated for uveal melanoma.

Velocity allows cyclists to join the ride at any of several points along the course: those at the Silver starting point ride the full 62.5 miles, while Yellow riders join in with 45 miles to go, Green riders at 25 miles, and Blue riders at 10 miles. As the ride's mission statement explains, this course design "symbolizes the idea that when we come together, we gain momentum. And that momentum makes big things happen, even the end of cancer."

The Eyes Against Cancer team also included G. A. (Jack) Cioffi, MD, Jean and Richard Deems Professor, Edward S. Harkness Professor, and Chairman of the Department of Ophthalmology; Lisa Park, MD, Associate Professor of Ophthalmology; Maria Luz Amaro-Quireza, OD, Instructor in Optometric Science; physician assistant, Dmitry Bogomolny; postdoctoral fellow Rahul Kapoor, PhD; and Lucy, Mia and Noreen McCarthy, all family members of Ms. Tarbous. Together with over 1,000 other Velocity riders, they helped to raise more than $1.1 million for Columbia's cancer programs.

Ms. Tarbous was diagnosed with uveal melanoma, one of the most common types of ocular cancer, in February 2018. Dr. Marr treated her with plaque brachytherapy, in which a gold or steel bowl containing small radioactive "seeds" is attached to the wall of the eye, covering the base of the tumor. "This potentially deadly malignancy can rob patients of their vision, but she had a very good outcome and is quite motivated to raise awareness about this disease," he says.

Dr. Marr confesses that he didn't do much training for the ride. "I was dreading the 25-mile distance, but it was such a great time that I probably could have done the full distance," he says. "It was wonderful having our whole team go over the George Washington Bridge. I love that Velocity brought together so many people with the motivation and heart to do something like this. And I can't wait for next year!"

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**

Viewpoint

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