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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Clinical Spotlight:

Trials of the Century: Clinical Trials Unit Seeks "Game-Changing" Results

When Associate Professor of Ophthalmology Gustavo De Moraes, MD, MPH, joined the Columbia faculty in February 2014, he was given a critical mission: develop a world-class, robust Clinical Trials Unit (CTU) within the Department of Ophthalmology.

At that time, Department investigators were independently participating in three or four clinical trials. Four years later, that number has grown exponentially, with Department faculty serving as principal investigators or co-investigators for 25 trials, all managed under the auspices of the CTU, for which Dr. De Moraes serves as Medical Director.

Gustavo De Moraes, MD, MPH

In 2017, Dr. De Moraes was joined by a co-director, Lisa Hark, PhD, RD, Professor of Ophthalmic Sciences, who previously directed Wills Eye Hospital's Department of Research and Glaucoma Research. As director of the CTU at Columbia, Dr. Hark oversees budgets and documentation and works closely with the unit's 12 full-time clinical research coordinators who manage participant recruitment, trial enrollment and all study procedures. Dr. De Moraes assists lead investigators with aspects of study design, such as defining endpoints, monitoring safety and outcomes, and HIPAA requirements. As a member of Columbia's Institutional Review Board (IRB), he also provides guidance on IRB compliance. Both directors work closely with CUIMC's central Clinical Trials Office (CTO).

"When a company calls a particular physician to ask if he or she wants to serve as principal investigator for a new trial, there are many steps that must be completed before the trial can begin, such as legal review, regulatory review, budgeting, and IRB compliance," Dr. Hark says. "Investigators no longer have to do that on their own; it's now a centrally coordinated process managed by our Clinical Trials Unit and the CUIMC CTO. With a more efficient research unit, new trials have become more financially feasible, and our trial portfolio has grown rapidly."

The trials now underway in the Department focus on developing novel drugs, innovative devices and techniques, and new diagnostic tools. They range from smaller Phase I and Phase II trials assessing safety and tolerability, to large Phase III trials aimed at determining the efficacy of a drug, device, or technique. Some are sponsored by the National Institutes of Health (NIH), while others are industry-sponsored. But they all have one thing in common: they are game-changers.

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INSIDE

From Yellow Snail Shells to Genetic Eye Disease: Ophthalmic Genetics Pioneer Joins Jonas Children's Vision Care

In the mid-1940s, a little girl, her twin brother and her cousin spent happy summers playing on the balcony of their home in northern Germany. In the nearby bushes, they had discovered colonies of land snails with beautifully colored shells. Fascinated, they collected dozens of the snails and made a habitat for them on the balcony, feeding them religiously, hoping they would breed, and trying to figure out why some had darker ringed shells while others sported colorful yellow shells.

The little girl would grow up to be Irene Maumenee, MD, and those snails would set her on a 70-year journey of genetic discovery during which she became one of the world's leading experts in genetic eye diseases, universally regarded as the founder of genetics as an ophthalmic subspecialty. In October 2017, Dr. Maumenee brought her expertise to Columbia Ophthalmology as Professor of Ophthalmic Sciences and Director of Ophthalmic Genetics for the newly established Jonas Children's Vision Care (JCVC), an integrated set of programs aimed at fighting pediatric blindness.

Irene Maumenee, MD

The founding director of the Johns Hopkins Center for Hereditary Eye Diseases at the Wilmer Eye Institute, an international referral program that since the early 1980s has evaluated, diagnosed, and treated more than 30,000 patients with rare eye diseases, Dr. Maumenee spent the past decade as director of ocular genetics at the University of Illinois College of Medicine at Chicago. She says that the decision to leave Chicago was difficult, but that Columbia's institutional commitment to genetics was too great an opportunity to pass up.

"My goal is to develop a clinical eye genetics service, to bring the technology that is being developed in genetics fully into clinical care," she says. "With Columbia's focus on precision ophthalmology as well as resources like the Institute for Genomic Medicine, we have a unique opportunity to make a real difference in understanding and treating genetic blinding diseases. Many of these diseases remain undiagnosed or improperly identified, since even the

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View from the Chair

Dear Friends,

When I first became Chair of the Department of Ophthalmology, one of my top priorities was to establish a robust infrastructure that would set Columbia apart as a world leader for clinical trials in ophthalmology. Six years later, our Clinical Trials Unit (CTU) is flourishing, with 25 major trials now underway and more on the horizon. In this issue of *Viewpoint*, we spotlight the success of the CTU, led by Gustavo De Moraes, MD, MPH, and Lisa Hark, PhD, RD, along with highlights of four of the important trials that the unit has helped to move forward.

One of those trials is led by Konstantin Petrukhin, PhD, who in more than a decade on the Columbia faculty has made great strides in developing genetically targeted therapies for Stargardt disease and wet and dry age-related macular degeneration. Most recently, Dr. Petrukhin has directed his prodigious research expertise toward glaucoma research. Our faculty profile in this issue tells the story of Dr. Petrukhin's remarkable career.

For years, scientists have pursued the goal of "regenerative medicine"—creating living, functional tissues to repair or replace function lost to age or disease. In ophthalmology as in many other medical specialties, success in these endeavors has been elusive, but at Columbia, we believe that is about to change. We have launched a novel collaboration involving gene therapy, gene surgery, and biomedical engineering that is now moving toward a clinical trial of regenerative medicine for several forms of macular degeneration. In these pages, you'll learn more about the innovative work of the investigators preparing to launch this trial, which could only be undertaken at an institution like Columbia.

Our unique resources and expertise in genetic ophthalmology have also enabled Columbia to recruit the clinician-scientist universally recognized as the founder of this sub-specialty: Irene Maumenee, MD. Honored in 2017 as the American Academy of Ophthalmology laureate, Dr. Maumenee has merged clinical genetics with laboratory investigations to establish translational genetic studies in ophthalmology. It is a great honor to have Dr. Maumenee on our faculty.

Over the past several months, two major conferences have helped to further establish Columbia as an international leader in defining the future for ophthalmology practice and research. In December, we hosted the second annual Precision Ophthalmology symposium, which focused on childhood blindness. In April, we sponsored a first-of-its-kind conference on artificial intelligence and tele-ophthalmology, which attracted more than 200 in-person and virtual attendees from around the world.

I'm also pleased to report that the new location of the Robert Burch Family Eye Center at the Lighthouse Guild International on West 64th Street has proven popular with families in the area, offering convenient access to comprehensive general and pediatric ophthalmology services in a neighborhood that was previously underserved.

Each time I write the letter that introduces a new edition of the *Viewpoint*, I am reminded anew of the extraordinary contributions of our faculty and staff to our shared goal of preventing blindness and restoring sight, not only for our own patients but for millions around the world. We could not do any of this without your continued support, and we are humbled and grateful for your commitment to our work.

Sincerely,

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

Ophthalmic Genetics Pioneer Joins Jonas Children's Vision Care

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best labs can only identify the genetic causes of about 75% of them. That gap has to be filled."

The Birth of a Geneticist

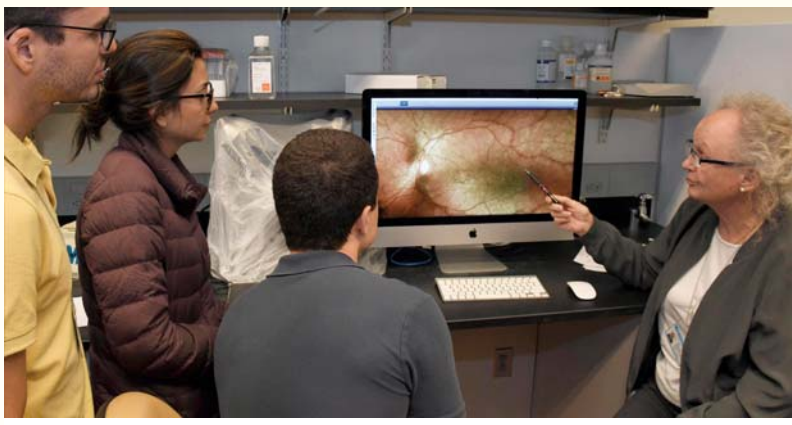
Dr. Maumenee would not learn until much later the Darwinian explanation for the brightly colored snail shells (those that lived under yellow-leaved plants and bushes were more likely to have yellow shells, and had a survival advantage over the darker-shelled snails that birds preferred to prey on). But she still traces her passion for genetics back to those days exploring the bushes near her home, and jokes that her outrage when her mother finally threw away the snail colony "made me go into genetics out of spite!"

Her complementary interest in ophthalmology would come later, after Dr. Maumenee received her medical degree at Germany's Göttingen Medical School and moved to Switzerland to pursue postgraduate research at the University of Geneva. In many remote mountain regions of Switzerland, families have tended to intermarry, producing a higher than usual rate of rare genetic diseases, including eye disease. "These geographically isolated areas have high rates of inbreeding, and every valley has its own blinding diseases," she says. Working with Professor Adolphe Franceschetti, who launched the University of Geneva's medical genetics program, Dr. Maumenee began accumulating a bounty of data on genetic blindness—and found her life's work.

Her trove of data was such a rich resource that Newton E. Morton, PhD, a population geneticist and pioneer of genetic epidemiology, invited her to analyze it in his population genetics Laboratory at the University of Hawaii in Honolulu. While there in 1968, Dr. Maumenee learned of a tiny atoll in the Western Pacific called Pingelap, part of Micronesia, which would later be described by neurologist and author Oliver Sachs, MD, in his book *The Island of the Colorblind*.

About 3,000 people lived on Pingelap at the time, and of those, about one in twenty suffered from total colorblindness (achromatopsia), along with reduced visual acuity and extreme sensitivity to light. Although she spent just a year in Hawaii, her work with the Pingelapese Islanders continued for decades and ultimately led to her group's groundbreaking identification of the first known gene for achromatopsia, CNGB3, in work published in *Nature Genetics* in 2000. To date, Dr. Maumenee has been involved with the identification of at least a dozen genes involved in eye disease, with several other candidates in the pipeline.

After her year in Hawaii, Dr. Maumenee pursued a postdoctoral fellowship at Johns Hopkins, under the mentorship of Victor McKusick, MD, founder of the Division of Medical Genetics and considered the father of medical genetics. "I decided to extend my stay for another year after my fellowship, and that somehow turned into 40 years," she says. While in Switzerland, she had primarily focused on genetic diseases of the eye; at Hopkins, she also developed an interest in systemic genetic diseases with ocular manifestations.



Irene Maumenee, MD

One of those systemic diseases is Marfan Syndrome, a potentially fatal connective tissue disorder with ocular manifestations that include dislocated lenses, spontaneous retinal detachments, and pre-senile cataracts. Dr. Maumenee plans to establish a Marfan clinic at Columbia.

Another project she has brought to Columbia is her ongoing work on achromatopsia. Fifty years after she

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Clinical Spotlight:

Second Precision Ophthalmology Symposium Targets Childhood Blindness

"Fighting Childhood Blindness: From Bench to Bedside" was the theme of Columbia's second annual Precision Ophthalmology symposium, which drew a capacity crowd of nearly 200 to the Vivian and Seymour Milstein Family Heart Center on December 8, 2017. The symposium featured sessions on genetics and gene editing in ophthalmic disease, emerging concepts and questions in pediatric ophthalmology, retinoblastoma and pediatric tumors, and retinopathy of prematurity and angiogenesis.

"We took the same multi-disciplinary approach that distinguished the inaugural Precision Ophthalmology symposium, combining speakers who discussed important basic scientific research that impacts pediatric eye care with clinical speakers," says Steven Brooks, MD, Anne S. Cohen Professor of Ophthalmology and Director of the Pediatric Ophthalmology Division, who chaired the meeting. "Our symposium is unusual in that rather than breaking apart the basic science and the clinical presentations, we mix them up. This structure emphasizes the translational aspect of what we do and the collaboration between those working in the lab to create new discoveries and the clinical faculty who are taking care of children. That in itself was a highlight, along with a stellar panel of speakers from within Columbia as well as outside guests."

Above, L. to R.: Leslie Jones, Danielle Trief, MD, MSc, Leejee Suh, MD, Janet Sparrow, PhD, Steven Kane, MD, PhD, Lauren Yeager, MD, Bryan Winn, MD, with Steven Brooks, MD at the podium

Left: Martin Friedlander, MD, PhD

Below: L. to R.: Irene Maumenee, MD and Steven Brooks, MD

Below, Left: Stephen Tsang, MD, PhD

Above: Donald Jonas with Columbia faculty

Left, L. to R.: Xin Zhang, PhD, Stephen Tsang, MD, PhD, Rando Allikmets, PhD, Andrei Tkatchenko, MD, PhD

The conference also honored Donald and Barbara Jonas, whose philanthropy helped to create Columbia's new Jonas Children's Vision Care program. Mr. and Mrs. Jonas were recognized with a brief video, and Mr. Jonas spoke with a small group of attendees during a break in the sessions.

Planning is already underway for the third Precision Ophthalmology Symposium, which will take place in December 2018.

Ophthalmic genetics pioneer Irene Maumenee, MD, who was recently named Professor of Ophthalmic Sciences and Director of Ophthalmic Genetics for Jonas Children's Vision Care (JCVC) (see page 1), presented the inaugural Jonas Lecture, on the role of genetic testing in pediatric ophthalmology.

Martin Friedlander, MD, PhD, Professor of Molecular Medicine at the Scripps Institute, delivered the A. Gerard DeVoe, MD Lecture, focused on neurovascular disease in the eye, with the provocative title, "Do We Really Want to Bash Blood Vessels with Anti-Angiogenics?"

"Dr. Friedlander is doing novel, futuristic work in how to approach many disorders, including retinopathy of prematurity, that involve abnormal growth of blood vessels in the eye," says Dr. Brooks. "What we currently do clinically often involves simply injecting Avastin or another drug that non-selectively blocks blood vessel growth. Dr. Friedlander compared that to using a big hammer, with an obvious lack of precision. He is developing a research program involving cell-based therapies, looking for solutions that are more directed at the underlying pathology of these retinopathies."

Dr. Friedlander's basic science focus was complemented by other outside speakers who addressed more clinical topics, including Leslie Jones, Director of the School for Music at the Lighthouse Guild, who discussed music for the child with low vision; David Abramson, MD, Chief of the Ophthalmic Oncology Service at Memorial Sloan-Kettering Cancer Center, who provided an update on current therapies in retinoblastoma; and Gil Binenbaum, MD, MSCE, Associate Professor of Ophthalmology at the Children's Hospital of Philadelphia, who discussed recent findings from the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Studies, a large multicenter study involving thousands of infants.

Visionaries & Luminaries

Columbia Hosts First Tele-Ophthalmology and AI Conference

A capacity crowd attended Columbia's first tele-ophthalmology and artificial intelligence (AI) conference, held on April 6 at Philanthropy New York, near Times Square. In addition to the on-site audience, live online interactive streaming allowed individuals from across the United States and around the world to participate in the meeting, which was the first of its kind and sold out for in-person participation a month in advance.

"While other conferences have focused on telehealth and AI, this was the first conference dedicated specifically to ophthalmology," says conference co-chair Lama Al-Aswad, MD, MPH, Associate Professor of Ophthalmology. "This rapidly emerging field will revolutionize how eye care will be delivered in the future, and we at Columbia wanted to create a forum to exchange knowledge, help recognize unmet needs, and guide the direction of future research. Ophthalmology has always been a cottage industry with small practices and few big institutions. Tele-ophthalmology and AI are now poised to transform the field into large interconnected national and international systems."

In addition to leaders from the Department of Ophthalmology, the conference featured key opinion leaders from other national and international institutions and industry, such as IBM, Google, Aravind, Orbis, and AI clinical decision support company Visulytix, as well as NGOs such as Helen Keller International and Orbis International.

Four keynote presentations anchored the program. Michael Chiang, MD, Knowles Professor of Ophthalmology & Medical Informatics and Clinical Epidemiology at Oregon Health & Science University (OHSU), discussed his research into telemedicine for the diagnosis of retinopathy of prematurity and other ophthalmic diseases. Kim Ramasamy, MBBS, DO, Professor of Ophthalmology at Aravind Eye Hospital and Postgraduate Institute of Ophthalmology in Madurai, Tamil Nadu, described the Indian experience with international tele-ophthalmology and population health. Retina specialist and AI pioneer Michael Abramoff, MD, the Robert C. Watzke, MD Professor in Retina Research at the University of Iowa, where he is also a Professor of Ophthalmology

Top: Michael Chiang, MD
Above: Group discussion
Left: Lama Al-Aswad, MD, MPH, launching the conference

Trials of the Century: Clinical Trials Unit Seeks "Game-Changing" Results

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"We're not interested in 'me too' studies," says Dr. De Moraes. "If a trial is testing another drug that everyone else is testing, that's not for us. We want to focus on what's novel and relevant. Just as the new motto of the medical center says: we don't practice medicine, we change the way it's practiced. That's our mission."

Learn more about four of the exciting trials that are now underway or soon to be initiated with the help of the CTU:

From HPV to Ocular Melanoma

Approximately 2,500 people are diagnosed with ocular melanoma (also known as uveal melanoma) in the United States every year. Because most of these melanomas are difficult to detect, they often are not diagnosed and treated until they have begun to produce symptoms, and larger tumors have a high risk of metastasis which currently is incurable. The only treatments now available for intraocular melanoma include vision-damaging radiation, laser, or complete removal of the affected eye. These radical therapies do cure the disease locally, but if the cancer has metastasized before local treatment, they do not improve survival.

"There hasn't been a new treatment for primary uveal melanoma for more than 70 years," says Brian Marr, MD, Professor of Ophthalmology and Director of the Ophthalmic Oncology Service at the Harkness Eye Institute, who is now leading an innovative trial that could potentially revolutionize not only the treatment of this hard-to-treat cancer, but many other cancers as well. It is based on the vaccine that prevents human papillomavirus (HPV) and, as a result, thousands of cases of cervical cancer.

The Phase Ib/II trial is testing a first-of-its-kind drug known as light-activated Au-011, which consists of non-infectious, virus-like particles bound to a photodynamic, light-activated dye. These viral nanoparticle conjugates (VNCs) are the brainchild of John Schiller, PhD, Deputy Chief of the National Cancer Institute's Laboratory of Cellular Oncology, who led the initial development and characterization of the HPV vaccines that ultimately became the commercial vaccines Cervarix and Gardasil.

"In his research, Dr. Schiller discovered that the HPV virus attaches to humans by finding spots where the skin has been abraded and the basement membrane, the thin membrane that separates the epithelium from the underlying tissue, is showing," explains Dr. Marr. "These viruses have evolved over millions of years to be very good at 'sticking' to that basement membrane, and cancer cells express that same bonding mechanism on their surfaces."

To create Au-011, the portion of the HPV vaccine that binds to the basement membrane and the cancer cells was combined with small molecules that are activated by infrared light. The conjugate of viral nanoparticles and light-activated molecules is injected directly into the eye, where it attaches to the cancer cells. A laser is then used to activate the molecules, which selectively destroy the membranes of the cancer cells and kill them without damaging the retina.

Six sites are enrolling patients in the trial nationwide, with Dr. Marr serving as the lead investigator for the entire trial. The initial safety portion of the study, which took place before Dr. Marr joined the Columbia faculty, involved six patients and found the treatment to be safe and well tolerated. The trial is currently in a dose-escalation phase to determine the maximum tolerated dose of the drug; Columbia has enrolled three patients in this phase of the trial so far.

"For this phase, our goal is to recruit a total of 23 patients nationwide by midyear," Dr. Marr says. "If it is effective, this would be the first drug to not only treat the cancer, but possibly preserve the patients' vision as well. Our study could be a proof of concept for this drug in other ophthalmic cancers, such as metastatic disease in the eye and retinoblastoma, and it may have applications beyond the eye as well. We have many treatments with complex cellular on and off switches, while this approach is simple: the molecules stick to something on the cancer and blow it up. But it's so simple that it just might work."

Hope for Stargardt Disease

There are no approved treatments to cure or even slow the progression of Stargardt disease, the most common inherited form of juvenile macular degeneration. People with Stargardt typically begin to experience significant vision loss when they are children or

and Visual Sciences, Electrical and Computer Engineering, and Biomedical Engineering, spoke on "What Is AI?" And Malvina Eydelman, MD, Director of the FDA's Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices (DONED), addressed regulatory and government issues surrounding tele-ophthalmology and AI.

In addition, Dr. Al-Aswad presented on the Columbia tele-ophthalmology experience in blindness prevention and population health. Representatives from industry, including officials from Google, IBM Watson, Visulytix and IDx-Dr, discussed the use of AI in diabetic retinopathy detection and glaucoma.

Above: Another group session
Left: Malvina Eydelman, MD
Below: Louis Pizzarello, MD

Sessions and panel discussions focused on general tele-ophthalmology (including tele-retina and tele-glaucoma), telemedicine and population health, existing and disruptive technologies for tele-ophthalmology, artificial intelligence in ophthalmology, and information technology security and the role of government. Attendees—both in person and online—were given extensive opportunity to ask questions after the panelists finished their presentations.

Participants gave the conference high marks, calling it "a superb day of learning" and "a triumph." "I don't think I have ever attended a meeting so packed with fresh ideas and remarkable talent," commented one attendee.

Dr. Al-Aswad believes that the potential for telehealth and AI applications to advance ophthalmology is virtually limitless. "AI can help us interpret and manage the data coming to us in ever-larger volumes," she says. "For example, every seven seconds, a person with diabetes loses his or her sight to diabetic retinopathy (DR). To address this problem, we need to screen large numbers of people with diabetes, which requires significant manpower. Using AI, we could potentially train a system to identify images as normal or abnormal and determine whether the person needs further assessment or not, easing the burden of screening on clinicians."

Telehealth applications could also be used to monitor conditions such as DR, macular degeneration, and glaucoma. "Patients with glaucoma typically need to see their ophthalmologist every three to six months, depending on the stability of their condition," she says. "But these individual screening visits provide limited information, because ocular pressure varies throughout the day." A home pressure checking device could transmit multiple readings, wirelessly or via smartphone, to the ophthalmologist's office, giving a more accurate picture of the patient's condition.

Dr. Al-Aswad praises the efforts of the program committee and Columbia staff in developing a successful conference and predicts that, like Columbia's popular Precision Ophthalmology symposium, it will become an annual event. "There is so much that can be done in these fields to improve the diagnosis and treatment of eye disease and help prevent blindness," she says. "This conference is all about moving the technology forward." ■

teenagers. Almost all will become legally blind during their adult lives, with a loss of central vision that makes it impossible to perform common, everyday tasks such as reading, writing, driving, or recognizing faces.

But a Phase IIb trial now underway at Columbia, led by Stephen Tsang, MD, PhD, Laszlo T. Bito Associate Professor of Ophthalmology and Associate Professor of Pathology & Cell Biology, holds the promise of changing that bleak picture.

Several years ago, Ilyas Washington, PhD, Assistant Professor of Ophthalmology, identified the damaging role that vitamin A plays in Stargardt disease. Because of a defect on a single gene, the retinas of people with the disease are unable to properly recycle vitamin A. As a result, vitamin A forms toxic polymers (called vitamin A dimers or bisretinoids), leading to the death of retinal pigment epithelium and photoreceptors in the retina.

The Phase II trial is testing ALK-001, a new once-daily oral drug designed to slow the formation of these toxic vitamin A byproducts. Originally invented and developed in Dr. Washington's lab and now licensed to Alkeus Pharmaceuticals, ALK-001 is a chemically modified form of vitamin A, in which three of the vitamin's hydrogen atoms have been replaced by three deuterium atoms. Deuterium is a naturally occurring non-radioactive isotope of hydrogen. ALK-001 replaces the body's vitamin A and works just like it, but produces up to five times fewer toxic byproducts.

A leader in Stargardt research and patient care, Columbia has enrolled more than 10 of the 50 participants in the nationwide multi-center trial. The primary outcome measure at this stage is long-term safety and tolerability, but researchers also hope to measure effects on disease progression, such as changes in the size of the lesions, best corrected visual acuity, and a variety of other advanced ocular assessments.

"To date, the study drug has shown that it is safe and could replace the majority of vitamin A in patients," says clinical trial coordinator and research associate Christine Xu.

Due to the masked design of this study, no preliminary efficacy results have been reported; however, the study sponsor has received financial support from both the Food and Drug Administration and the National Eye Institute, and has decided to expand recruitment to additional Phase II studies. "This is promising, considering the number of patients with Stargardt and the absence of treatment options," Ms. Xu says. 'These patients have been progressively losing their vision for many years, and this trial represents an exciting opportunity to potentially stop their vision loss in its tracks. Previously, there hasn't been much that they could do other than avoid vitamin A. This study gives them hope that there may be a meaningful treatment."

From 500 to 1

In fact, there may be two. A trial of another potential treatment for Stargardt disease, as well as dry age-related macular degeneration (AMD) is set to begin at Columbia later this year. With the support of an ongoing Blueprint for Neurotherapeutics grant from the National Institutes of Health, Associate Professor of Ophthalmic Sciences Konstantin Petrukhin, PhD, has taken a pool of more than 500 small-molecule drug candidates, across five novel structural classes, and narrowed it down to a single most promising drug candidate. Later this year, Dr. Petrukhin will launch the first clinical trial to test the safety and efficacy of the final candidate.

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Carol Mason, PhD, Elected to National Academy of Sciences

The Department of Ophthalmology congratulates Carol Mason, PhD, on her election to the National Academy of Sciences (NAS), one of the most prestigious learned societies in the United States.

Dr. Mason, a Professor in the Departments of Pathology & Cell Biology, Neuroscience, and Ophthalmology and a principal investigator at Columbia's Zuckerman Institute, studies the brain circuitry of the visual system, focusing on how neurons in the developing brain extend axons from the eye to destinations deep in the brain. Her research has helped to reveal the processes that guide the growth and trajectory of the visual system's neurons, opening up the possibility of repairing damage to the visual system caused by injury or disease.

Carol Mason, PhD

"We are proud of the contributions Dr. Mason's research has made to ophthalmology and vision research," says George A. (Jack) Cioffi, MD, Jean and Richard Deems Professor, Edward S. Harkness Professor, and Chairman of the Department of Ophthalmology. "She is an intellectual powerhouse, a scholar, a fantastic mentor, a leader, a superb scientist, and a fine person—a class act in every respect."

Dr. Mason is one of the 84 new members and 21 foreign associates elected this year in recognition of their distinguished and continuing achievements in original research. She is one of 21 current faculty members of the Columbia University Vagelos College of Physicians and Surgeons who are elected members of the NAS.

Brian Marr, MD

Research Spotlight:

Konstantin Petrukhin, PhD: Genetic Discoveries

It all started with a chemistry set.

As a child in Siberia in the former Soviet Union, Konstantin Petrukhin, PhD, was intrigued by rocks and minerals. He thought perhaps he might like to be a geologist. But when he was 11 or 12, his parents gave him a chemistry set, a gift that steered Dr. Petrukhin down the scientific path that ultimately led him to Columbia, where he is now Associate Professor of Ophthalmology and a noted researcher into promising treatments for age-related macular degeneration (AMD) and Stargardt disease.

"My interest in chemistry led me to join a group of kids who studied at the local university after school, called the Scientific Society for Schoolchildren," recalls Dr. Petrukhin."It was focused on practical chemistry, experiments and lab work, and I enjoyed it very much."

When he entered college in the early 1980s, the structure of the Soviet educational system meant that Dr. Petrukhin had to decide, even before enrolling, which scientific field to pursue. Would it be chemistry, his original passion, or biology, a field abuzz with excitement over the recent advances in DNA cloning and sequencing techniques? He initially chose biology, but subspecialization allowed him to combine his two interests. He completed his studies at Moscow State University—"the Harvard of the Soviet Union," he says—with a major in bioorganic chemistry, and in 1987, he received his doctorate from the Shemyakin Institute of Bioorganic Chemistry.

Dr. Petrukhin's graduate research focused on cloning genes involved in encoding sodium potassium ATPase, the molecule that is the major transporter of ions across the cell membrane. Sodium potassium ATPase maintains the intracellular salt concentration that is critical for sustaining life. At a meeting in Denmark in the late 1980s, Dr. Petrukhin met the father of the field, Isidore Edelman, MD, then the Chairman of the Department of Biochemistry and Molecular Biophysics at Columbia. Dr. Edelman's research had led to significant advances in our understanding of sodium potassium ATPase.

Dr. Edelman and Dr. Petrukhin stayed in touch, and when the chaos that ultimately led to the dissolution of the Soviet Union in 1991 made it difficult for him to continue pursuing his research in his home country, Dr. Petrukhin wrote to his friend and mentor. "He suggested that I move to New York, and found me a position in the laboratory of Conrad Gilliam, PhD, who was then Professor of Psychiatry and Genetics & Development," Dr. Petrukhin says.

Konstantin Petrukhin, PhD

The timing was fortuitous—in 1991, Dr. Edelman became the founding co-director of Columbia's new Human Genome Program, which would ultimately become the Human Genome Center. "It was a very exciting time, at the beginning of the Human Genome Project, as we were doing genetic mapping of human chromosomes," recalls Dr. Petrukhin.

While working in Dr. Gilliam's lab, Dr. Petrukhin successfully cloned the gene for Wilson disease, an inherited disorder in which copper builds up in the body, particularly in the liver, brain, and eyes. That research introduced him to the genetics of ophthalmology, and in 1996, he decided to follow the field to Merck, where he established a genetic drug development program in macular degeneration and discovered two more genes associated with the disease.

"I spent ten years at Merck, but I always missed the spirit of academic work and the freedom of inquiry and self-reliance I had found in my years at Columbia," Dr. Petrukhin says. In 2006, he accepted an offer from Stanley Chang, MD, the former Edward S. Harkness Professor and Chairman of the Department of Ophthalmology (today the K.K. Tse and Ku Teh Ying Professor of Ophthalmology) to rejoin the Columbia faculty.

Dr. Petrukhin is now preparing to launch a clinical trial of an investigational new drug, known as an RBP4 agonist, for the treatment of dry age-related macular degeneration (AMD) and Stargardt disease (see page 4). With support from the Foundation Fighting Blindness, he is already pursuing a second generation of RBP4 agonist drugs, more specifically focused on Stargardt disease. Another grant from the NIH supports the adaptation of these treatments for patients with dry AMD who may have other age-related, complicating comorbidities such as amyloidosis.

A new grant from the Glaucoma Foundation, awarded in February 2017, has also allowed Dr. Petrukhin to enter the field of glaucoma research. While most forms of glaucoma are well treated with existing drugs that lower intraocular pressure, exfoliation glaucoma (XFG), which accounts for about 25% of all cases, is not. "This form of glaucoma is caused by accumulation of exfoliation deposits in the eye, which clog the pathway for fluid outflow inducing pressure buildup," he explains. A gene called LOXL1 has been found to predispose people to XFG, and Dr. Petrukhin hopes to develop a screen for small molecules that can modulate the product of this gene.

"Thanks to the Precision Ophthalmology initiative and the long tradition of glaucoma research in this department, we have access to the tissue samples that we need to assess drug candidates," Dr. Petrukhin says. "This is the next frontier of glaucoma research."

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"We plan to submit our Investigational New Drug (IND) package to the Food and Drug Administration by the middle of 2018," says Dr. Petrukhin. "We should be able to begin the Phase I trial soon after that."

In dry AMD, as with Stargardt, vision damage is caused by the buildup of lipofuscins in the eye's retinal pigment epithelium (RPE). It is normal for lipofuscins to accumulate with age, but people with macular degenerative diseases may have much more significant buildup of these waste byproducts. Dr. Petrukhin's drug, known only as BPN-14967, is a retinol-binding protein 4 (RBP4) agonist, and decreases the accumulation of lipofuscins by lowering levels of RBP4.

BPN-14967 will first be tested in a single-ascending dose trial, in an oral form, given to healthy volunteers to assess its safety and pharmacokinetics. Even in that phase of the trial, Dr. Petrukhin and his colleagues will be able to analyze the drug's efficacy using a serum biomarker, since RBP4 levels are easily measured in the blood. "Without this biomarker, we would have to wait for the results of Phase II trials," he says. "But in this case, a simple blood test will inform us right away whether the drug is working in humans as it did in animal models during our preclinical trials."

The biotechnology company Lin Bioscience has already licensed BPN-14967. If the Phase Ia trial in healthy volunteers is successful, Lin will then launch a Phase Ib trial using multiple ascending doses in elderly patients with dry AMD. "Although this is one of several target areas for dry AMD that many scientists are working on, we hope that our drug will be the first available treatment for dry AMD patients," Dr. Petrukhin says. (For more about Dr. Petrukhin and his work, see story above.)

Gut Instincts for Thyroid Eye Disease

Graves' disease is a fairly common autoimmune condition in which antibodies attack the thyroid gland and send it into overdrive, producing symptoms such as weight loss, a racing heart rate, anxiety and other symptoms. About half of all people with hyperthyroidism—women more frequently than men—develop thyroid eye disease (TED) when the same antibodies attack certain cells in the orbital tissues called the orbital fibroblasts.

"These cells have similar receptors to those found in the thyroid gland, so the autoimmune response in this disease often attacks both of these sites," explains Bryan Winn, MD, Associate Professor of Ophthalmology and Division Director of Oculoplastic and Orbital Surgery. "The resulting inflammation produces swelling of eyelids and orbital tissues, increases the amount of fat behind the eye, and causes the muscles that move the eye to enlarge and stiffen."

People with TED frequently experience symptoms such as bulging eyes, double vision, pain in and behind the eyes, and dry eye syndrome. In a small but significant number of people—about 5%—the disease becomes severe, leading to ulcers on the cornea that can interfere with vision, or more rarely, compression of the optic nerve can cause blindness.

Treatments for TED are relatively limited. "We can offer steroids to decrease some of the inflammation, but they are not particularly effective and may not change the natural course of the disease," Dr. Winn explains. "We are also experimenting with newer biologic agents, but the results of studies are mixed as to their effectiveness."

Columbia Plans Trial of Personalized Regenerative Medicine to Treat Macular Degeneration

Investigators in the Department of Ophthalmology are laying the groundwork for the launch of a first-of-its-kind clinical trial combining stem cell therapy, genome surgery and biomedical engineering to treat several forms of macular degeneration.

"We have submitted an orphan drug designation application to the Food and Drug Administration (FDA), and once that is approved, we will be starting a pilot trial," says vitreoretinal surgeon Tarun Sharma, MD, Associate Research Scientist in the Department of Ophthalmology. Negotiations with the FDA are likely to take at least another year.

The trial is expected to involve 12 patients: three with dry age-related macular degeneration (AMD), three with wet age-related macular degeneration (AMD), and three with Best disease, also known as juvenile vitelliform macular degeneration. The clinical presentation for the fourth group of patients has yet to be determined.

The macula is a tiny spot in the center of the retina containing the photoreceptor cells responsible for perceiving fine visual detail and color, and the retinal pigment epithelium (RPE), which nourishes and protects these fragile, light-sensitive cells by disposing of waste and damaged cells and modulating immune factors. The precise pathology underlying the various types of macular degeneration varies. In all forms of the disease, however, an inflammatory process—sometimes genetically triggered, sometimes the result of age and/or exposure to environmental toxins like sun and tobacco smoke—damages the RPE and causes waste deposits to accumulate under the retina between the RPE layer and the supporting Bruch's membrane.

"The RPE is like a mother to the photoreceptor cells above," explains Tongalp Tezel, MD, Chang Family Professor of Ophthalmology and Director of the Retina Division. "Without the RPE's protection, damage to these cells ultimately leads to deterioration of the central vision."

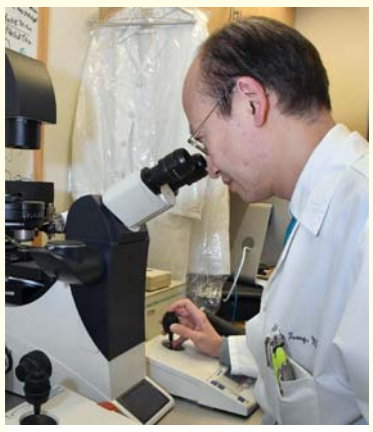
Stephen Tsang, MD, PhD, the Laszlo T. Bito Associate Professor of Ophthalmology, Associate Professor of Pathology & Cell Biology, and a member of the Columbia Stem Cell Initiative, is a pioneer in ophthalmic CRISPR-Cas9 genome surgery. Building on the platform developed by Professor of Ophthalmology Peter Gouras, MD, Columbia is ideally positioned to pioneer autologous stem cell transplantation for eye disease. "Many other world-class institutions can do the individual steps involved in this process, but Columbia is one of the few that has everything in place for all of them, including a long history with stem cell engineering as well as our Clinical Trials Unit (CTU)," Dr. Tsang says.

The Columbia Stem Cell Initiative's approach to macular degeneration involves three key steps. First, a sample of the patient's stem cells is taken from the skin underneath the arm—where sun exposure has not done cellular damage—and genetically engineered to develop into the specific retinal cells required. "We are also exploring other technologies for the development of new RPE cells," Dr. Tezel says.

Next, using genetic scissors called CRISPR-Cas9, investigators will "repair" the abnormal sequence and create healthy cells, free from DNA defects. The engineered cells can then be re-implanted in the patient. Finally, using a proprietary milieu for placement of the new cells developed by Dr. Tezel, the new cells are then re-implanted in the patient.

The proper matrix to support the transplanted cells is critical. "These RPE cells have a property called epithelial-mesenchymal transition, which means that they can transform into scar-forming cells," Dr. Tezel says. "It's very important to keep these cells differentiated both to support retinal function and to prevent the formation of scars. The signals that tell these cells to either stay differentiated or turn into mesenchymal, scar-forming cells come from the matrix they rest on."

Tongalp Tezel, MD



Stephen Tsang, MD, PhD

Other investigators have tried a number of artificial and natural scaffolds to support transplanted RPE cells, without success. Dr. Tezel has worked with Columbia's acclaimed bioengineering program to develop a supporting layer that mimics the retinal anatomy, using Bruch's membrane from human donors. This thin network of connective tissues is the natural substrate for photoreceptor cells, and offers the best environment to support their differentiated function. After the cells are nested in the substrate, they are then placed on a biogel also designed at Columbia, which serves to repair any cracks and defects in the patient's native Bruch's membrane.

Tarun Sharma, MD

"If you put a graft on a cracked Bruch's membrane, it has no chance to survive," says Dr. Tezel, who got the inspiration for the reparative biogel while in the dentist's chair. "We worked with bioengineers for 18 months to formulate this completely inert gel from natural substances. Just like a dental gel, it fills in the gaps and cracks in the membrane and polymerizes within a minute or two, without harming the retina."

The entire supporting structure ensures vertical stability for the grafted cells. "We have noticed that if these transplanted cells are on a substrate that lacks a certain degree of rigidity, they begin to contract in a process called pigment epithelial detachment," Dr. Tezel explains. "They essentially rip the matrix and form a dome-shaped elevation. Our process ensures vertical stabilization and repair of the Bruch's membrane, using a matrix on which the new RPE cells can survive."

The trial will also require new surgical tools and techniques, which will be developed by Dr. Tezel, Dr. Sharma and Stanley Chang, MD, the K.K. Tse and Ku Teh Ying Professor of Ophthalmology and the former Edward S. Harkness Professor and Chairman of the Department of Ophthalmology. "We are not just taking cell suspensions and injecting them beneath the retina," says Dr. Tezel. "This surgery will be very complicated, and questions remain about how best to cut the retina and how to make the smallest possible incision in order to minimize surgical complications."

The New York Stem Cell Foundation (NYSCF) has provided extensive support for the project, which is one of the most comprehensive ever undertaken in the field, Dr. Tezel says. "It requires tissue engineering, stem cell and gene editing technology, and the development of new surgical techniques. Columbia is one of the only places in the world where such an initiative could take place."

With a new $100,00 grant from Columbia's Irving Institute for Research, Dr. Winn is now leading a clinical trial exploring a different pathway that may offer new treatment options for thyroid eye disease: the bacteria that live in our digestive systems, also known as the gut microbiota.

"Our bodies contain more genes belonging to the gut microbiome—the genetic sequences of these microbiota—than belonging to our own genome," says Dr. Winn. "In recent years, imbalances in the gut microbiome have been implicated in a number of diseases, particularly inflammatory and autoimmune conditions."

Dr. Winn's trial aims to determine if there is a relationship between thyroid eye disease and alterations in the microbiome. He will enroll a total of 60 subjects: 15 participants who have Graves' disease without eye involvement; 15 participants with Graves' disease and TED; and 30 normal controls. A number of participants have been recruited for the trial so far, and active recruitment continues.

"We hypothesize that normal participants will have a different microbiome in the gut, the oral cavity, and the area around the eye than those who have thyroid eye disease. We hope to be able to understand which bacteria are either over- or under-represented in disease as compared to a normal state," Dr. Winn says. "That understanding will allow us to start thinking about microbiome-based therapies, such as targeted pre- and probiotics or even microbiome transplantation. This pilot trial is the first step towards establishing a gut-orbit connection to help explain this perplexing autoimmune disease." ■

CTU Clinical Research Coordinators

Jennifer Alcantara-Castillo
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Sophie Park
Vipul Patel
Maribel Rodriguez
Christine Xu
Christine Zemsky

Burch Center's New Location Welcomed by West Side Families

Patients are delighted with the convenience and easy access to services provided by the new location of the Robert Burch Family Eye Center at 250 W. 64th Street, within the offices of the Lighthouse Guild International. "Many of my patients have been happily surprised to find out that there is now a facility right in their neighborhood that they can easily walk to," says Royce Chen, MD, the Helen and Martin Kimmel Assistant Professor of Ophthalmology, who specializes in surgical and medical management of vitreoretinal disease and uveitis. "It's a very efficient space, well laid out, and people seem very pleased with it."

Assistant Professor of Ophthalmology Danielle Trief, MD, MSc, agrees. "My patients love the new location, and many who live on the West Side have specifically requested to have their appointments there."

The new third-floor space features eight exam rooms—a significant increase from the five rooms available in the Center's previous location at 15 W. 65th Street—along with a state-of-the-art diagnostic and imaging suite. "It combines the intimate, easy to navigate feel of a private office with all of the technology and services of the larger, busier sites such as the medical center," says glaucoma expert Dana Blumberg, MD, MPH, Assistant Professor of Ophthalmology.

The Center, which previously served primarily a pediatric population, is now a full-service family eye center providing comprehensive retinal, corneal, glaucoma and oculoplastic care. "Other than surgeries that can be performed only in the OR, we offer nearly the same set of services that are available on the main Columbia campus," says retinal specialist Jason Horowitz, MD, Assistant Professor of Ophthalmology.

Other clinicians providing services at the Center include Steven Brooks, MD, Anne S. Cohen Professor of Ophthalmology and Director, Pediatric Ophthalmology Division; ophthalmic plastic surgery specialist Lora Glass, MD, Assistant Professor of Ophthalmology; and primary care optometrist Yocheved Kresch, OD, Instructor in Optometric Sciences.

"The new facility is centrally located in an area of the city with dynamic residential growth, with a multitude of schools and young families," says Dr. Brooks. "We are well positioned to serves the primary and specialty eye care needs in this area, as well as being convenient to the West Side Highway for patients traveling in from New Jersey."

The center was made possible by the generosity of Robert L. Burch III, who credits Stanley Chang, MD, the K.K. Tse and Ku Ying Professor of Ophthalmology and the former Edward S. Harkness Professor and Chairman of the Department of Ophthalmology, with preserving his remaining vision from macular degeneration. "I wanted to do anything I could to make sure that as many New Yorkers as possible had access to the same superb eye care that I have enjoyed," he said in 2014 at the opening of the center's original location. ■

Ophthalmic Genetics Pioneer

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first began working with the Pingelapese people, and nearly two decades after she identified the CNGB3 gene, a clinical trial for achromatopsia gene therapy using an adeno-associated vector is about to launch under the auspices of the Department's Clinical Trials Unit (see page 1). "We have just gotten approval to begin the trial, and are now reviewing patient records to identify candidates for participation," she says. "When something you begin to work on so early in your career comes to fruition at last, it's very exciting. It's a testament to what ophthalmic genetics can accomplish for other eye diseases as well."

Dr. Maumenee envisions building a center at Columbia focused on people with rare diseases—both ophthalmic diseases and systemic diseases that may have ocular findings. "Retinal or corneal diseases may point to a systemic diagnosis, and an eye exam often will help with the diagnosis of a systemic disease that you have not been able to identify," she says. "After more than half a century of having been exposed to these rare diseases, I have seen many things that others have not."

In 2017, Dr. Maumenee was named the American Academy of Ophthalmology laureate, only the second woman in the Academy's history to receive this honor. She has also published more than 300 journal articles.

Outside the lab, Dr. Maumenee calls herself a "happy gardener." She's still looking for an apartment in New York, and will keep the farm outside Baltimore she has owned for more than 40 years. "We are trying to create a family-run farm, with everything from goats to bees to organic gardening. I go back every weekend," she says. But New York is growing on her. "I had no idea I would enjoy it so much! I love running around the city. I'm excited to enjoy the opera and the symphony and the museums. I think New York is just wonderful!" ■

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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