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PRECISION

OPHTHALMOLOGY™

2020

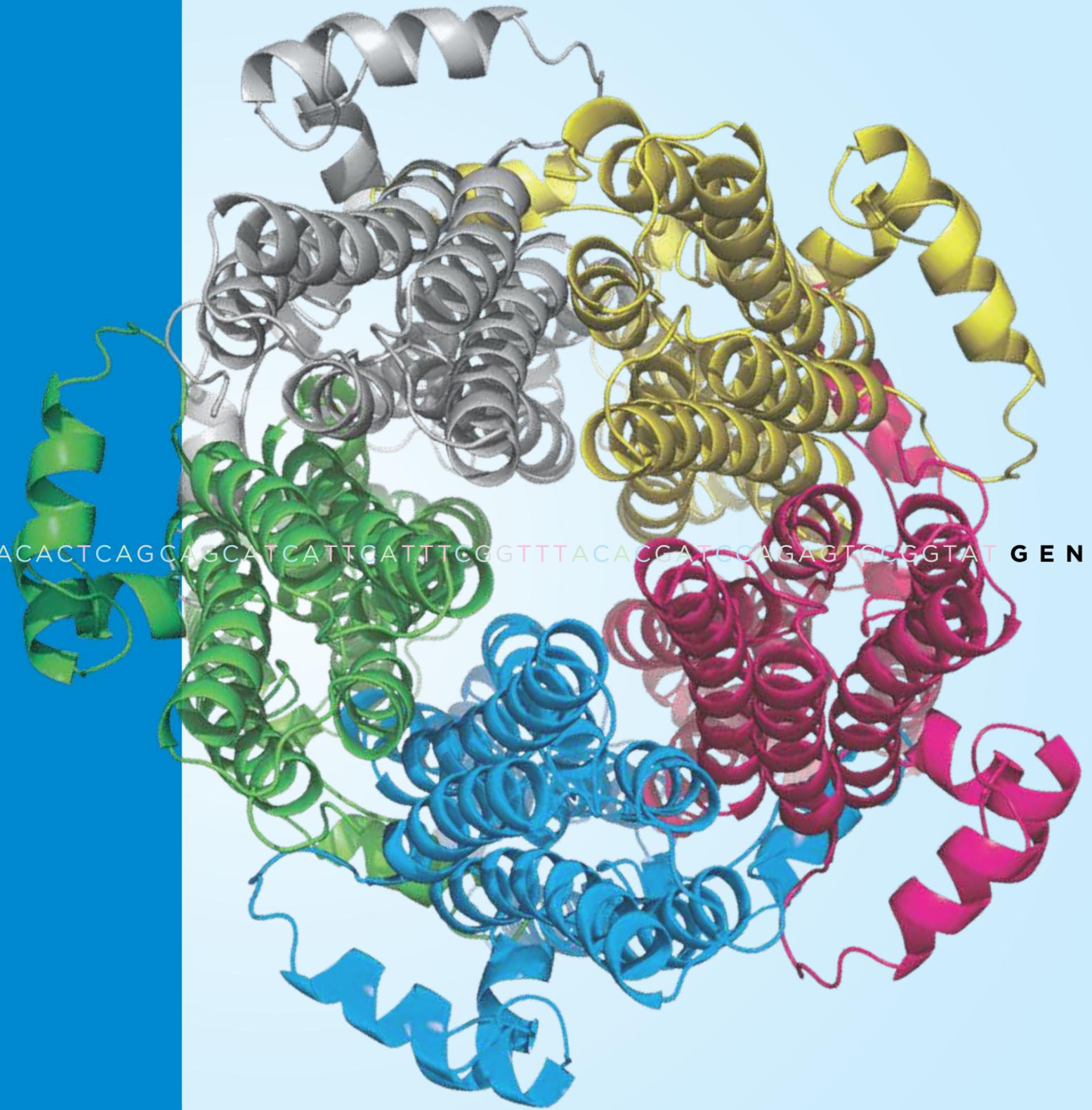
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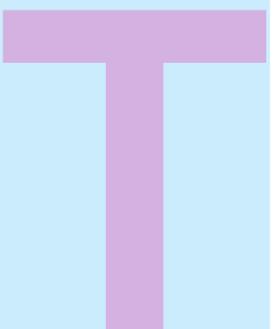
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The Department of Ophthalmology

at Columbia University Irving Medical Center is a leading international center for the management of sight-threatening disorders and scientific exploration to elucidate disease mechanisms and discover novel treatments. These aspirations are realized through seamless collaborations between our outstanding, compassionate physicians and our talented scientists.

At the same time, we train ophthalmologists and researchers to be the future leaders in the field. We have successfully developed new drugs, devices and procedures to enhance the lives of our patients and have launched the Applied Genetics Initiative at Columbia Ophthalmology. That groundbreaking tradition continues today with [Precision Ophthalmology™ 2020](#), as described in the following pages.



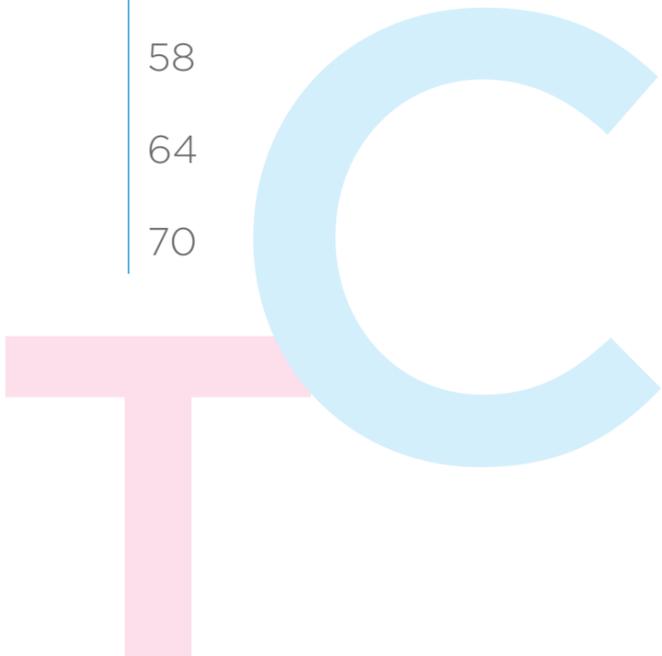
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COLUMBIA UNIVERSITY
DEPARTMENT OF OPHTHALMOLOGY

Department Milestones	06
Genetics Primer	14
Foundational Biology	16
Vision Science Today	24
The Inheritance Question	32
Genetic Testing & Therapies	38
Disease-Specific Applications	46
Gene Discovery	58
Clinical Trials	64
The Future	70

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FROM THE CHAIRMAN

Over the last two decades, our ability to interrogate the human genome has radically transformed medicine. Sequencing the genome went from a billion-dollar project that required more than ten years of exhaustive effort, to a routine task that is regularly completed overnight in our labs for a few hundred dollars.

With that achievement has come virtually limitless opportunities to take what we know about the genetics of disease and risk, and the possibility of treating faulty genes, and deliver that knowledge to patients in a way that makes a

meaningful difference in their lives. This new field of ophthalmology, and in fact all of medicine, is known as Applied Genetics. Precision Ophthalmology™ 2020 explores the promise of this growing field, and the work that is being done within the new Applied Genetics Initiative at the Columbia University Department of Ophthalmology, to make the most of those possibilities.

We do not need to wait for full-fledged gene-based “cures” for diseases to leverage our genetic knowledge in ways that can transform people’s lives. Understanding an individual’s genotype, and how that genetic code interacts with environmental factors to produce the observable traits or characteristics that we call phenotype, already yields

critical information for the diagnosis, prognosis and treatment of disease. In addition to determining if an individual is at risk for developing a certain disease, we will also be able to advise them about the risk that their children or other loved ones will develop it as well. In the related and emerging field of pharmacogenetics, we no longer have to deliver drugs by trial and error. Instead, we are increasingly able to use genetic information to predict a person’s response to available drug treatment options and select the therapy that is most likely to work for them.

There are also evolving treatments that are directed specifically at particular genetically determined diseases. Many of the most significant advances in gene therapy for the treatment of disease have occurred in ophthalmology, including the first FDA-approved gene therapy for the treatment of any disease.

So, while we can expect further great leaps forward in gene therapy and gene surgery in the very near future, we already have the ability, today, to leverage the genome for diagnosing, counseling and treating individuals with genetic eye disease. Applied Genetics informs every step of the process: determining who should be tested, how testing can be best utilized, and evaluation of the personal and family implications of being tested.

In our previous book, we introduced the concept of Precision Ophthalmology™: using each individual’s own genetic profile to tailor a course of treatment specifically designed for him or her. Columbia’s Applied Genetics Initiative in Ophthalmology is a global leader and is making Precision Ophthalmology™ a reality for our patients today. In these pages, we’ll show you how.



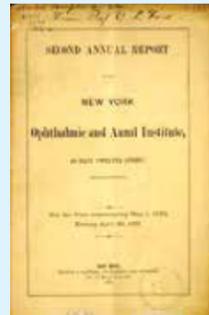
G.A. (Jack) Cioffi, MD
Edward S. Harkness Professor
Jean and Richard Deems Professor
Chair, Department of Ophthalmology

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DEPARTMENT MILESTONES



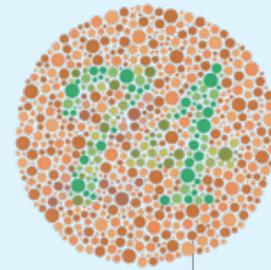
1866 Cornelius R. Agnew, MD, establishes an ophthalmology clinic at the College of Physicians and Surgeons.



1869 Herman J. Knapp, MD, establishes the New York Ophthalmic and Aural Institute, which later becomes the Herman Knapp Memorial Hospital.



1903 Arnold H. Knapp, MD, son of Herman, appointed professor of ophthalmology at P&S and becomes the third clinic director.



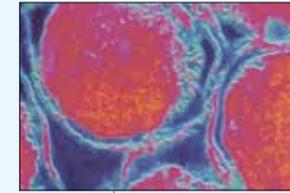
1911 Edmund B. Wilson, PhD, maps color blindness onto the X chromosome.



1933 The Department moves into the Edward S. Harkness Eye Institute on 165th Street.

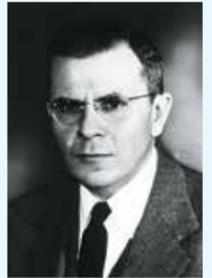


1931 Edward S. Harkness pledges money to build a separate Eye Institute at the new medical center.



1935-36 Discovery of hyaluronic acid by Dr. Karl Meyer. Phillips Thygeson, MD, OphD, describes the microbiologic transmission of trachoma.

1938 Dr. Castroviejo urges people to will their eyes to science, leading to the development of today's eye banks.

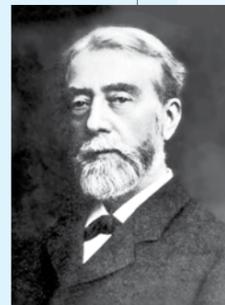


1943 Raymond L. Pfeiffer, MD, is the first to delineate the landmarks of the ocular orbit on plain x-rays.

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1867 Dr. Agnew is appointed the first professor of ophthalmology at P&S, marking the official beginning of the program.



1888 Dr. Herman Knapp is appointed professor of ophthalmology at P&S, and becomes the second clinic director.



1911 Herman Knapp Memorial Eye Hospital, founded by Arnold Knapp, opens at 10th Avenue and 57th Street, two blocks from P&S. The Eye staff at P&S hold appointments at the new hospital.



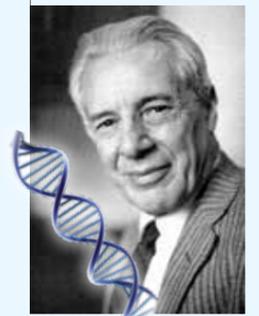
1928 Presbyterian Hospital moves to 168th Street, and the Vanderbilt Clinic—the clinical care unit of P&S, with its Ophthalmology service—moves uptown with it. John M. Wheeler, MD, DSc, becomes the first chair of the Department of Ophthalmology.



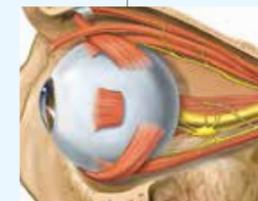
1933 Ramon Castroviejo, MD, performs the first corneal transplant on a human.



1939 Dr. Thygeson becomes the fourth clinic director, serving until 1945.



1940-41 New methods for quantitative analysis of intracellular sugars are developed by Dr. Zacharias Dische. The Knapp Hospital closes, and the Knapp Memorial Library of Physiological Optics opens.



1936 The Muscle Clinic becomes the Eye Institute's first subspecialty clinic.



1st Clinic Director
CORNELIUS R. AGNEW, MD
1867-1888



2nd Clinic Director
HERMAN J. KNAPP, MD
1888-1902



3rd Clinic Director
ARNOLD H. KNAPP, MD
1903-1928



1st Department Chair
JOHN M. WHEELER, MD, DSC
1928-1939

DEPARTMENT MILESTONES



1947 First retinoblastoma, pediatric, and adult ocular tumor clinics are established by Dr. Algernon B. Reese.



1948 Willis Knighton, MD, establishes a Glaucoma Clinic on the newly remodeled fifth floor of the Eye Institute.



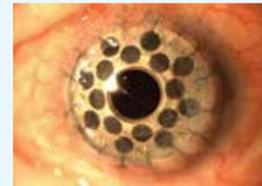
1956 George Merriam Jr., MD, with Elizabeth Focht, MD, of NYU, establishes a relationship between cataract formation and radiation. This leads to the development of standards of ocular radiation safety still in use today.



1958 World's first retina clinic is established by Charles J. Campbell, MD, PhD.



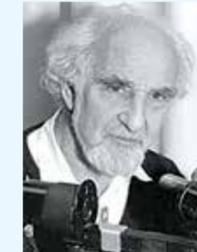
1961 Frank Carroll, MD, a leader in research on diseases of the optic nerve, establishes an Optic Nerve Clinic.



1962 First keratoprosthesis, developed by Hernando Cardona, MD, is presented to the 19th International Congress of Ophthalmology.



1966 Saiichi Mishima, MD, develops a system for preserving corneas until transplantation.



1968 David Maurice, MD, and Dr. Donn are first to use confocal microscopy to detect new structural features of the eye. American Optical Company releases its monocular indirect ophthalmoscope, developed in part by Dr. Campbell.



1969 D. Jackson Coleman, MD, develops the first commercially available hand-operated ultrasound B-scan system for ophthalmic evaluation.



1964 First basic and clinical corneal research center established by Drs. Gerard DeVoe and Anthony Donn.

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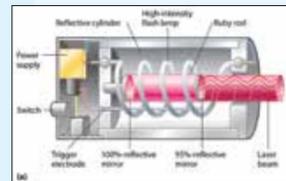
1948 The pupillography laboratory is established by Otto Lowenstein, MD, PhD, a pioneer in the quantitative measurement of pupil function.



1955 American Optical releases the AO HRR color vision test, developed by LeGrand Hardy, MD, director of the Knapp Memorial Physiological Optics Laboratories, and M. Catherine Rittler, working with Gertrude Rand, PhD, of Johns Hopkins.



1957 Irene Loewenfeld, PhD, and Dr. Lowenstein build an "electronic pupillograph" that incorporates infrared technology. It is the first device to accurately measure and analyze the diameter of the pupils.



1961 Dr. Campbell is first to use the ruby laser in humans, working with Rittler and Charles Koester, MD. Fight for Sight Children's Eye Clinic added to the Eye Institute, headed by Phillip Knapp, MD.



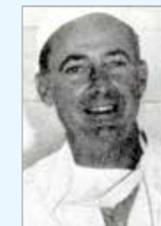
1962 John W. Espy, MD, creates the Eye Institute's Contact Lens Clinic, which he directs for 25 years.



1965 Black Medical Research Building is completed. From 1965 to 1969, the 15th floor is heavily utilized for ophthalmology laboratories.



1966 Max Forbes, MD, describes indentation gonioscopy in closed-angle glaucoma.



1969 Dr. Phillip Knapp describes a muscle transposition procedure for paralytic strabismus that becomes known as the "Knapp procedure" and remains in common use to this day.



1968 First argon laser is used to treat human disease by Francis L'Esperance Jr., MD. Harold Spalter, MD, is among the first to publish on the use of lasers for the treatment of diabetic macular edema and central serous retinopathy.



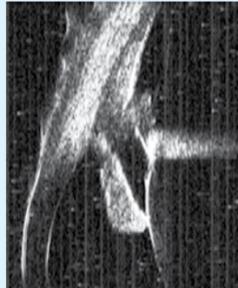
2nd Department Chair
JOHN H. DUNNINGTON, MD
1946-1959



3rd Department Chair
A. GERALD DEVOE, MD
1959-1974

DEPARTMENT MILESTONES

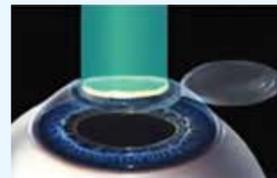
1973 Using the ultrasound he developed, Dr. Coleman demonstrates that operating at an earlier stage in ocular trauma can vastly improve the patient's prognosis for recovery.



1983 Dr. Trokel publishes a major paper introducing the idea of using the laser to reshape or sculpt the cornea. Dr. Trokel and Dr. L'Esperance (pictured) patent the excimer laser for vision correction.



1983 Endre Balasz, MD, Malcolm P. Aldrich Research Professor and Director of Research in the department, develops Healon, a hyaluronic acid polymer that transforms cataract and corneal surgery.



1987 Stephen Trokel performs the first human excimer laser surgery for vision correction.

1980 Stephen Trokel, MD, publishes findings on techniques for submillimeter resolution CT scanning of orbital diseases.



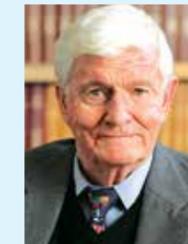
1998 R. Duff and Carol Kurland establish the Anne S. Cohen Professor of Pediatric Ophthalmology.



2000 John Flynn, MD, joins the Department as the first Anne S. Cohen Professor of Pediatric Ophthalmology.

2005 The Bernard and Shirlee Brown Glaucoma Research Laboratory opens.

1997 Latanoprost (Xalatan™) for the treatment of glaucoma, developed by Dr. Laszlo Bito, is marketed worldwide.



1994 Peter Gouras, MD, PhD, performs the first human retinal cell transplants.



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1972 Abraham Spector, PhD, publishes research on protein aggregation and cataract formation. His laboratory will become one of the world's leading cataract research laboratories.



1986 Basil V. Worgul, PhD, who directs Columbia's Eye Radiation and Environmental Research Lab, is named American director of the Ukrainian/American Chernobyl Ocular Study.



1993 Dr. Trokel describes orbital fat removal for orbital decompression.

1996 The FDA approves the use of perfluorocarbons for retinal surgery through the work of Dr. Stanley Chang.

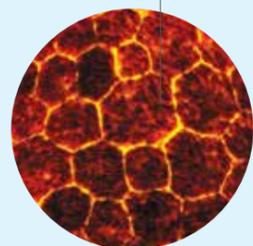


NewYork-Presbyterian

1998 NewYork-Presbyterian is formed, becoming the Ophthalmology Department's partner and the number-one hospital system in New York City.



2004 Opening of the Louis V. Gerstner Jr. Clinical Research Center in Vision, which houses the Russell Berrie Diabetic Retinopathy Research Unit and the Starr Foundation Retina Research Unit.



1980 Charles Koester, MD, develops the first wide-field specular microscope, which proves to be invaluable for studying the corneal endothelium.



4th Department Chair
CHARLES J. CAMPBELL, MD, PHD
1974-1987



5th Department Chair
ANTHONY DONN, MD
1987-1996



6th Department Chair
STANLEY CHANG, MD
1996-2012



1998 The Flanzer Eye Center opens on the Harkness Eye Institute's first floor, and the Low Vision Clinic is established under Dean Hart, OD.

2005 Janet Sparrow, PhD, named Anthony Donn Professor of Ophthalmic Science.



DEPARTMENT MILESTONES

2011 Vision Neuroscientist, Carol Mason, PhD, is elected to the Institute of Medicine.



2013 Steven Brooks, MD, joins the department as Anne S. Cohen Professor of Ophthalmology to direct the pediatric ophthalmology division.



2013 Donald Hood, PhD, elucidates structure-function relationship of glaucomatous damage to the macula.



2016 Basic Science Course in Ophthalmology (BSCO) celebrates 75 years of training residents in the fundamentals of vision science.



2017 Irene Maumenee, MD, joins the department and receives the Laureate award from the American Academy of Ophthalmology for her lifelong contribution in ophthalmic genetics.

2019 Konstantin Petrukhin, PhD, develops tinlarebant, a new drug for Stargardt disease and dry AMD that successfully completes testing in Phase I clinical trials.



2006 Rando Allikmets, PhD, and the AMD Study Group discover factors H and B, genes contributing to age-related macular degeneration.



2012 Stephen Tsang, MD, PhD, is named László Z. Bitó Professor of Ophthalmology.



2014 The Robert Burch Family Eye Center opens at the Lighthouse Guild International on the Upper West Side of Manhattan. The Stephen Ross Pediatric Eye Center opens at Morgan Stanley Children's Hospital.



2015 Jeffrey Liebmann, MD, joins the department as Vice-Chair, Glaucoma Division Director and the Shirlee and Bernard Brown Professor of Ophthalmology.



2017 Brian Marr, MD, is named professor of ophthalmology, leading a relaunch of the Division of Ocular Oncology.



2019 David and Victoria Foley establish the Foley Retina Research Fund and the Foley Clinical Retinal Fellowship Endowment.



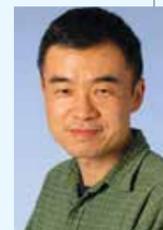
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2005 Mr. and Mrs. Herbert Irving endow the new Florence and Herbert Irving Translational Vision Research Laboratory.



2012 The Jean and Richard Deems Professorship of Ophthalmology & Endowment Fund is established, leading to the recruitment of G.A. (Jack) Cioffi, MD, as the 7th Department Chair.



2014 Xin Zhang, PhD, is named the Jules and Doris Stein Research to Prevent Blindness Associate Professor.



2015 Tongalp Tezel, MD, joins the department as Chang Family Professor of Ophthalmology to lead the retina service.



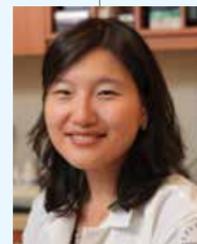
2016 Ronald Silverman, PhD, develops an advanced ultrasound technology to measure ocular blood flow.



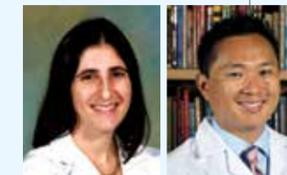
2019 Simon John, PhD, a Howard Hughes investigator in glaucoma and other neurodegenerative diseases, is appointed Robert L. Burch III Professor of Ophthalmic Science.



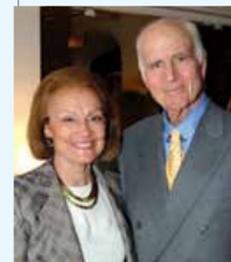
2010 The Columbia Laser Vision Correction Center and the Gloria and Louis Flanzer Vision Care Center open.



2012 Leejee H. Suh, MD, is named Miranda Wong Tang Associate Professor of Ophthalmology and Chief of the Cornea Service.



2017 Royce Chen, MD and Lora Glass, MD are appointed Residency Program and Associate Residency Program Directors.



2019 Applied Genetics at Columbia Ophthalmology is launched.

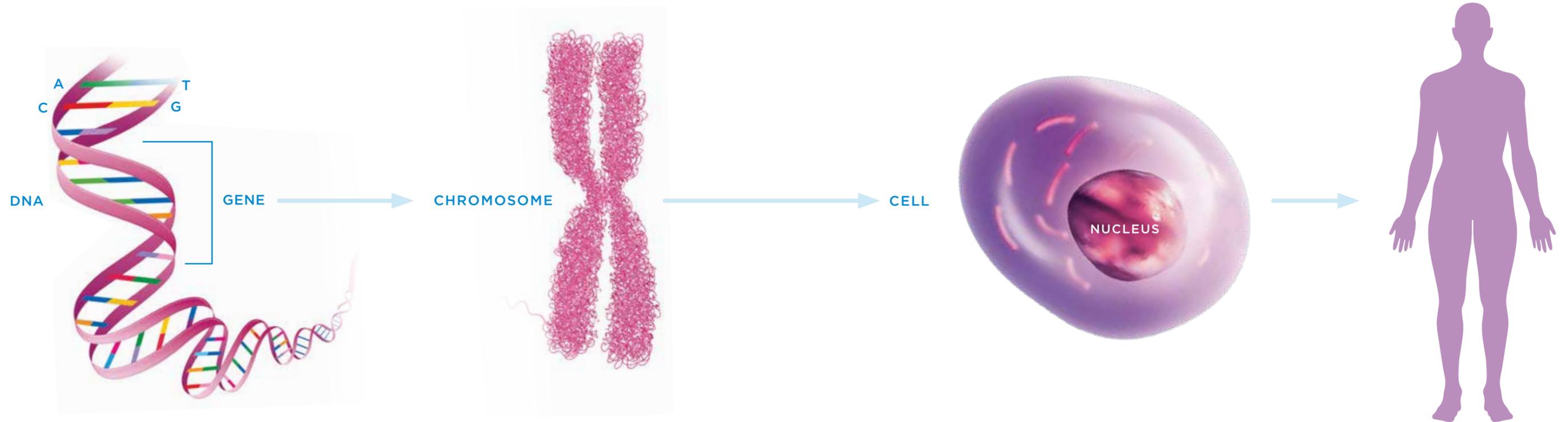


6th Department Chair
STANLEY CHANG, MD
1996-2012



7th Department Chair
G.A. (JACK) CIOFFI, MD
2012-

GENETICS PRIMER



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The blueprint of all human characteristics—everything that makes us who we are—is encoded within **DNA (deoxyribonucleic acid)**. DNA is the basic unit of heredity passed from generation to generation.

Each one of our cells contains the DNA that controls every aspect of cellular health and therefore our overall health. DNA, a complex molecule, is contained within cellular structures called **chromosomes**.

A **gene** is a portion of DNA that contains instructions to build a unique gene product, usually a protein or enzyme, that performs a function in a specific tissue.

Genetic diseases occur when there is a defect in the way a gene is encoded, resulting in a faulty gene product that is absent or dysfunctional.

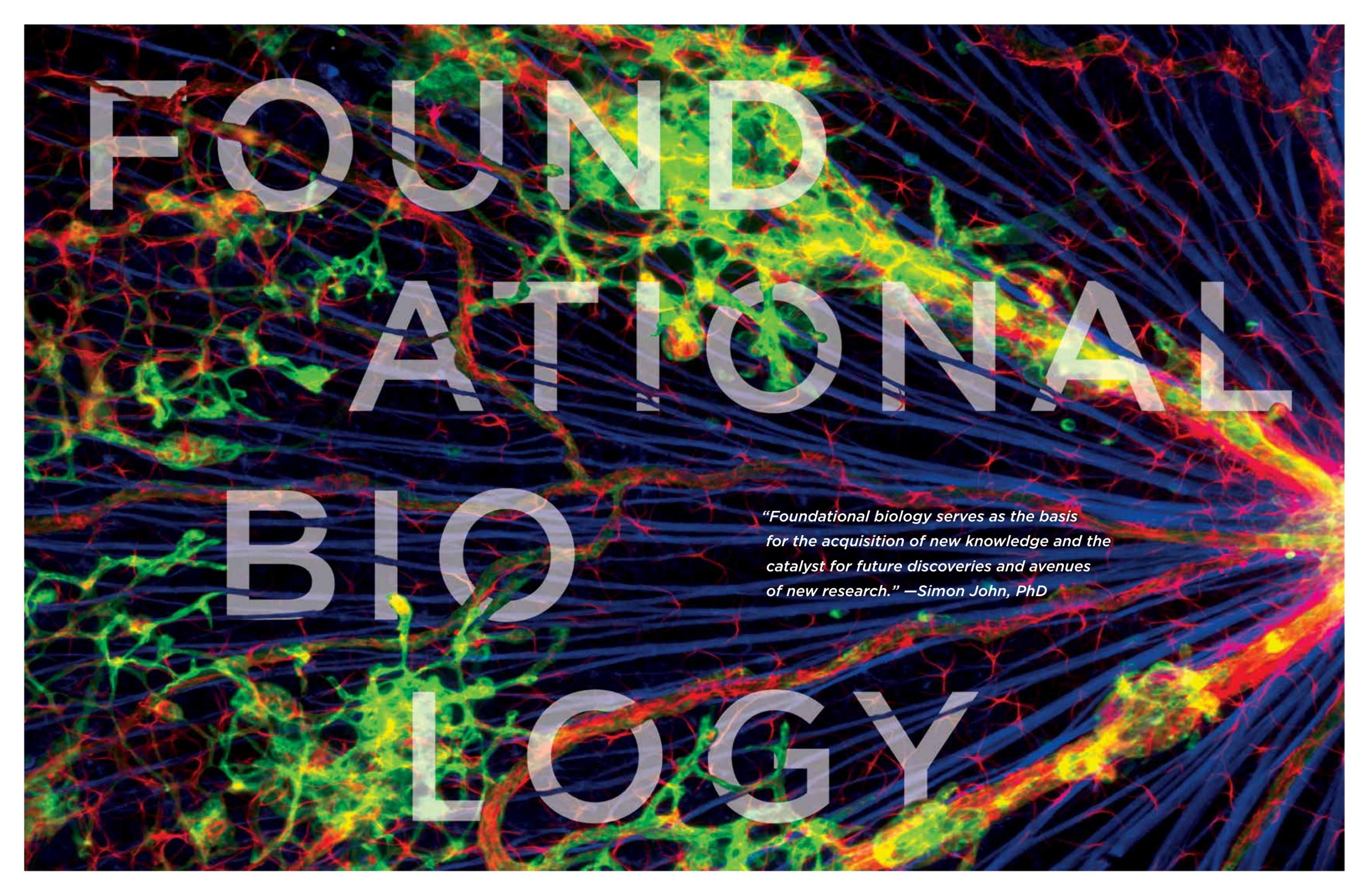
The **genome** is the collection of all genetic information on all of our chromosomes, and **genomics** is the study of the genome to identify causes of disease and their prevalence in the population.

The four bases—adenine, thymine, cytosine and guanine (A, T, C and G)—are the nucleotides found in DNA. Through the technique of DNA sequencing, first developed by Frederick Sanger, scientists can determine the exact order of nucleotides in an organism's genes. Knowing this order is the first step in our efforts to map the DNA sequences of all organisms and thereby connect gene sequence with gene function.

Diagnostic sequencing is the analysis of DNA from a individual person and his or her family to determine which gene is causing a disease.

Genetic counselors help individuals and families uncover inheritance patterns of a specific genetic diseases within a family, which provides important clues for diagnosis. This form of diagnosis is called **Precision Medicine** because it applies genetic information directly to patient care and allows for the development of targeted and individualized treatments.

Gene therapy refers to the delivery of a new, functional gene to replace a nonfunctional inherited gene. This new type of therapy relies heavily on discoveries in basic research laboratories.



FOUNDATIONAL BIOLOGY

“Foundational biology serves as the basis for the acquisition of new knowledge and the catalyst for future discoveries and avenues of new research.” —Simon John, PhD

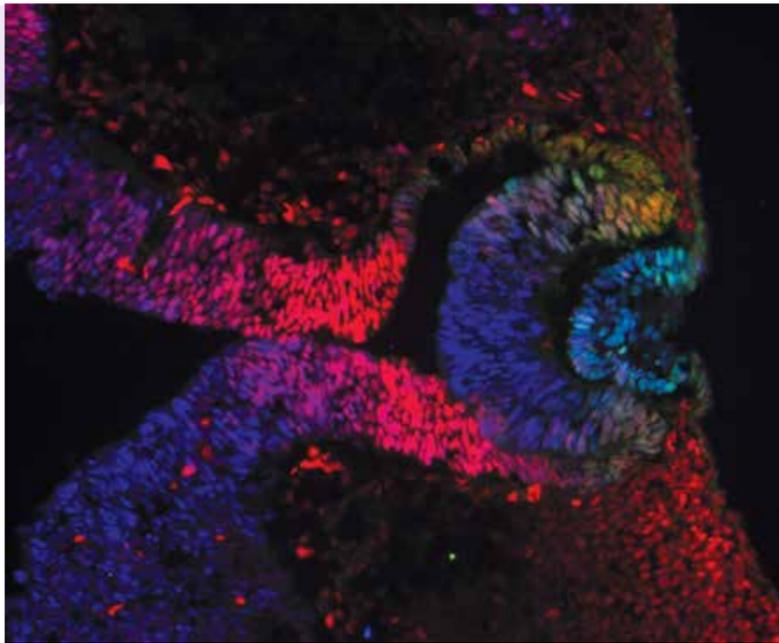


FIGURE 1.a

The early embryonic eye is defined by overlapping expression of regulatory genes. At the early stage of development, all the ocular progenitor cells express Pax6 (blue), without which the entire eye development program is aborted. Pax6 cooperate with additional transcription factors such as Sox2 to precisely specify the different parts of the eye. They also interact with signal Regulated Transcription Factor such as Lef1 (red), a downstream effector of Wnt signaling. Together, these factors regulate the intricate and precise development of the eye.

Xin Zhang, PhD

Causative Genes in Ocular Disease

The recent revolution in genetic studies, based on “next-generation sequencing” technology, has allowed scientists to obtain detailed genetic data on entire genomes in hundreds of thousands of individuals. With this information, we can not only discover disease-causing mutations in single genes but also identify the genetic variation in an individual associated with all observed phenotypes, from benign individual variations to simple and complex diseases. “Phenotype” is the term used to describe the observable characteristics of an individual resulting from the interaction between their genes and the environment. As a result, we can

FIGURE 1.b

make precise molecular diagnoses and plan individualized therapy for hundreds of inherited eye diseases. Emerging technologies also allow us to study individual genetic variants in disease models and, eventually, correct genetic errors in patients.

At Columbia Ophthalmology, we are applying state-of-the-art genetic methods to diagnose and treat specific eye diseases. By sequencing genomes and their protein-coding parts, exomes, in thousands of patients with eye diseases, we have been able to identify genetic variations causing single-gene diseases, such as Stargardt disease and retinitis pigmentosa, and

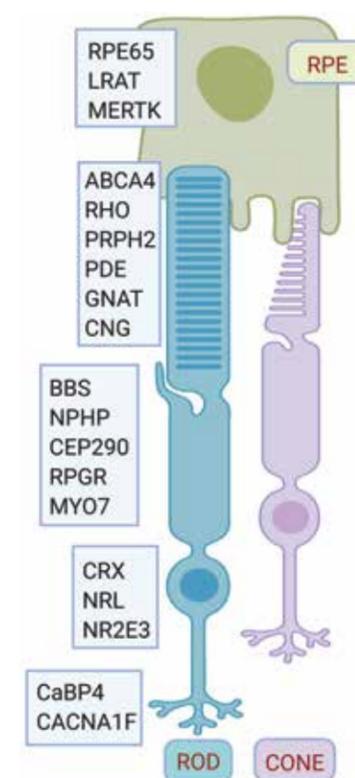
Development of the Eye

Just as the tectonic movement of the earth created the continents, the immense complexity and structural diversity of the eye arises from the collision of two tissues: the optic cup and the lens vesicle. The optic cup traces its origin to the central nervous system, and the lens vesicle shares its pedigree with the skin. As the pro-neural optic cup wraps around the epidermal-like lens vesicle, these two tissues send signals back and forth by releasing small molecules that can activate intracellular pathways. These cross talks are crucial for guiding the development of the optic vesicle into the light-sensing retina and the lens vesicle into the light-focusing lens, while maintaining the perfect symmetry and proportions of the eye structures. Helping to interpret these signals within the cells are transcription factors (proteins that

control gene expression), which translate the developmental program into changes in gene expression, dictating the identity and function of each ocular tissue. Through the combined activity of signaling pathways and transcription factors, vast number of ocular cells are specified to perform the necessary function of the eye.

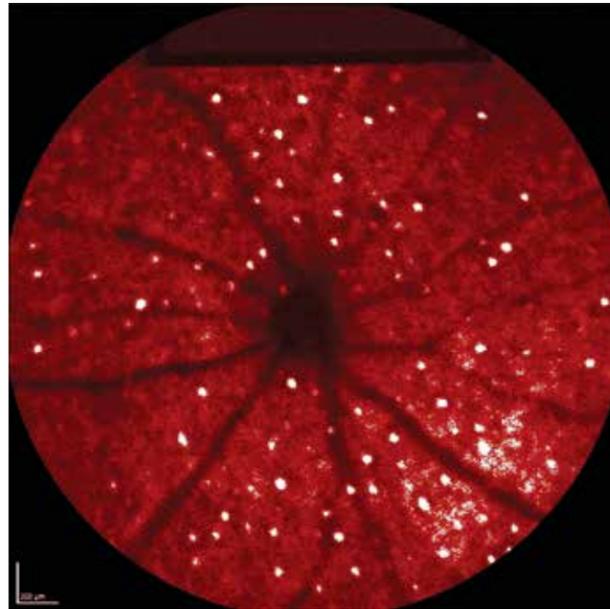
Localization of genes and proteins involved in retinal diseases is shown in the retinal pigment epithelium (RPE), rod and cone outer and inner segments, in the nucleus and synaptic body. Genetic testing identifies mutations in these genes, which cause a spectrum of retinal diseases.

Rando Allikmets, PhD



complex, multifactorial diseases such as age-related macular degeneration and myopia. We have introduced these variants in mouse and cell-based models, enabling the development of precisely defined, genetics-based therapeutic approaches based on small molecules, stem cells, gene therapy and gene correction therapy. We call this Precision Ophthalmology™: comprehensive, interactive patient care, integrating state-of-the-art clinical characterization and an unprecedented depth of genetic analyses, to achieve personalized treatment of eye diseases.

Overleaf: In a mouse model of retinopathy of prematurity, new blood vessels (red) grow to occupy the surface of the retina overlaid with the neural fibers (blue) and astrocytes (red).
Xin Zhang, PhD



A stylized image of fundus autofluorescence in the Abca4^{-/-} mouse, a model of recessive Stargardt disease. Fundus autofluorescence originates in bisretinoid molecules that accumulate in retinal pigment epithelium. This autofluorescence is amplified in patients presenting with ABCA4-disease. This disease feature is replicated in the mouse model. The spots (white) are also a feature of the disease in mice.

Janet Sparrow, PhD

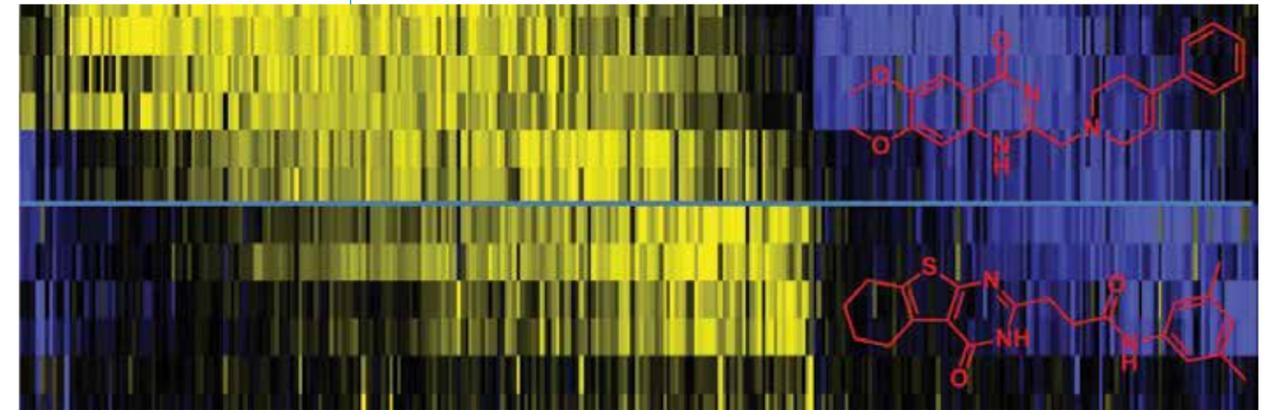
FIGURE 1.c

Use of Models in Ocular Genetic Research

Stem-cell-based disease models, sometimes referred to as a “disease in a dish,” can recapitulate key aspects of ocular and other health disorders. This is particularly true if the induced pluripotent stem (ipS) cells are specific to a patient and the patient’s cells are grown in the laboratory. Combining ipS technology with recent advances in gene editing and in the construction of three-dimensional cell culture systems further increases the value of bioengineered models of eye disease. These cell culture systems can be clinically relevant and can help to bridge the gap between

the clinical presentation of ocular disorders and an understanding of the genetic cellular and molecular mechanisms that cause tissues to malfunction. Cell culture systems also provide a platform for testing novel therapeutics and for serving as the essence of regenerative medicine. Breakthroughs in understanding retinal disease have also relied heavily on animal models, beginning with the fruit fly and zebrafish. The importance of these models lies in their ability to aid in the identification of causative genes and gene products. They also assist in unveiling disease mechanisms. Preclinical testing in animal models is essential to the discovery of novel disease mechanisms and to the advancement of treatments for humans.

FIGURE 1.d



*Expression changes in the mouse retina associated with different levels of activity of the retina-specific nuclear receptor NR2E3. Disease mutations in the photoreceptor-specific nuclear receptor NR2E3 are responsible for the enhanced S-cone phenotype in humans. Transcriptome analysis reveals a photoreceptor survival signature associated with certain levels of NR2E3 activity. Small-molecule NR2E3 modulators may promote photoreceptor survival in patients with degenerating retina. **Konstantin Petrukhin, PhD***

Using Genes to Create Therapies

To discover gene-related drug targets that can be modulated with therapeutic interventions, we must first define the genetic mechanisms responsible for disease. In recent years, scientists at Columbia Ophthalmology have made significant progress toward understanding the causes of relatively rare, single-gene ophthalmic disorders such as Stargardt disease, Best vitelliform macular dystrophy and juvenile glaucoma. By applying modern genomic technologies, we also have been able to identify predisposing genetic factors that contribute to more common ophthalmic diseases such as age-related macular degeneration, myopia and primary open-angle glaucoma. The explosion of genetic information about

pathways and potential drug targets allows pharmaceutical researchers to develop new therapies for currently untreatable ophthalmic disorders. Pharmacology and medicinal chemistry, combined with the power of current genomic technologies, will play an essential role in developing novel drug treatments in years to come.

TT 20 ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTT CGGTAGCATCAT TCTATTCGGTTTACACGGCGGTAACCTTAACA 21CTC

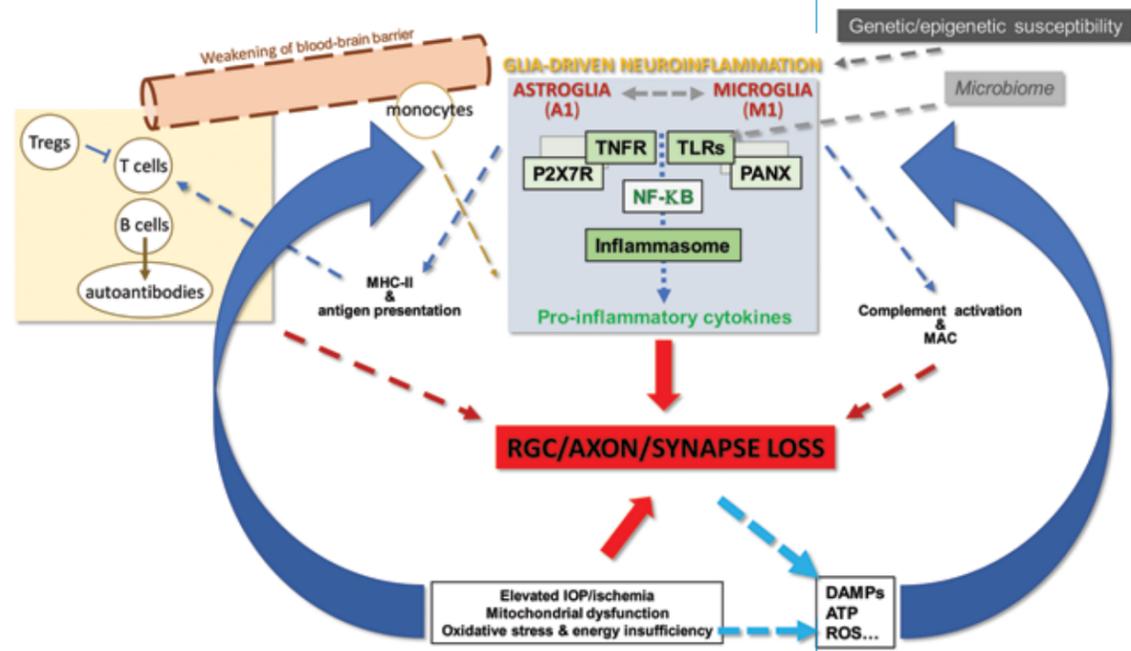


FIGURE 1.e

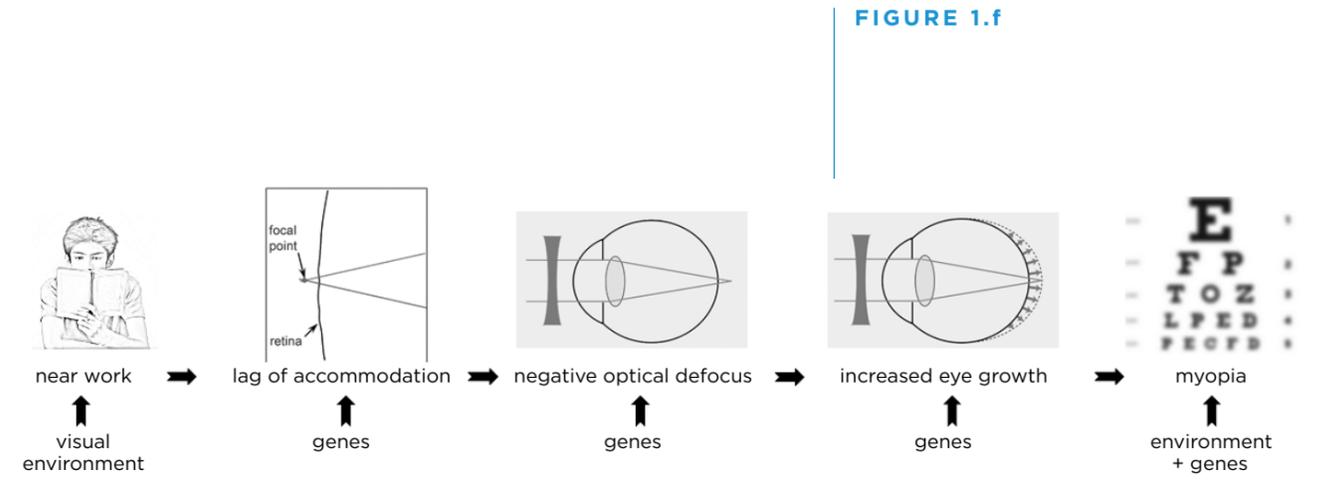


FIGURE 1.f



This figure shows a chain of events leading to the development of myopia. The main environmental factor causing myopia is near work, such as reading, which is associated with the accommodative effort required to focus the image on the retina. This results in negative optical defocus, which stimulates excessive eye growth and ultimately leads to myopia (top panel). The contribution of environmental factors in the development of myopia has been estimated at 30%, while the contribution of genetic factors has been estimated to be close to 70%. **Andrei Tkatchenko, MD, PhD**

Neurodegeneration

Improved understanding of cellular and molecular mechanisms of neuroinflammation will allow us to test immunomodulation as a neuroprotective treatment strategy for glaucomatous neurodegeneration.

Gülgün Tezel, MD

Many of the cells within the eye are nerve cells, also known as neurons. Degeneration of neurons, termed “neurodegeneration,” is a feature of many ocular diseases, including glaucoma, age-related macular degeneration, diabetic retinopathy, optic neuropathies and some inherited disorders of the retina. Through studies of human donor tissues and experimental models, departmental researchers are seeking to uncover new therapeutic approaches to protect, rescue and regenerate neurons in these blinding conditions. Research in this field seeks to pinpoint molecular mechanisms of neurodegeneration and identify novel neuroprotective treatments. A growing body of research suggests that chronic tissue stress, neuronal injury, glial and systemic immune responses,

combined with sustained release of neurotoxic mediators, create a vicious cycle that promotes further injury to neurons within different compartments from the retina to the brain. Therapeutic modulation of neuroinflammation therefore offers a promising treatment strategy for widespread neuroprotection. Recent studies have revealed a promising target for this treatment approach: NF-KB, the key transcriptional activator of inflammatory mediators. By profiling cell-type-specific proteomic alterations and conducting functional testing of outcome molecules through cell-type-targeting transgenic strategies, it is possible to inhibit NF-KB to provide neuroprotection through immunomodulation in glaucoma and possibly in other ocular diseases.

Gene-Environmental Interactions

Myopia, better known as near-sightedness, is a complex genetic disease. It results from the interaction between environmental and genetic factors, which shape the geometry of the eye and determine its refractive state and need for eyeglasses. The leading environmental factor causing myopia is near work (looking at close objects for extended periods of time); however, several other environmental factors, such as light intensity, day-night light cycles, and exposure to outdoor activities, have also been implicated. Although environmental factors play a very important role in its development, genetic factors account for about 60-80% of the propensity for myopia. At Columbia Ophthalmology, it was recently discovered that as many as 3,500 retinal genes and over 80 retinal pathways are involved in

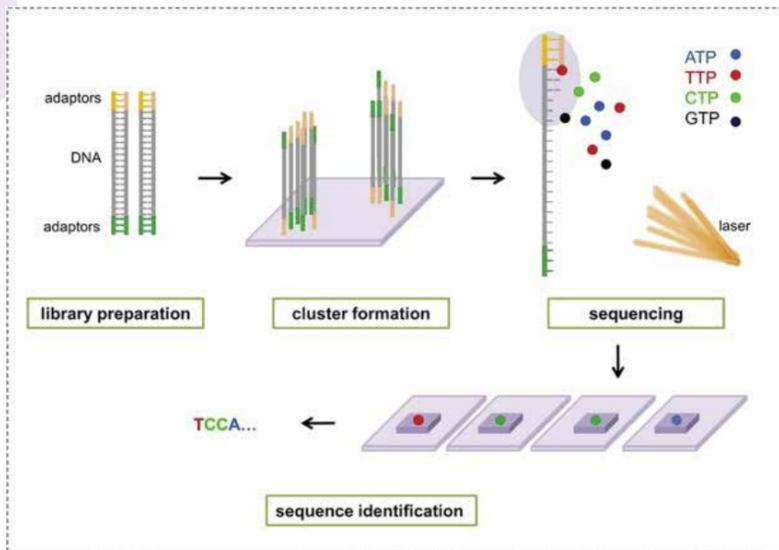
the development and progression of myopia in humans. Many of these genes were found to be involved in the gene-environment interactions underlying refractive eye development. One such gene, APLP2, was found to be involved in gene-environment interaction underlying the development of myopia in children. Children who carry a “myopic” version of the APLP2 gene are five times more likely to develop myopia if they engage in prolonged close work, thus confirming an important role of gene-environment interaction in myopia development.

TT 22ATTTCGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGGCGGTAACCTTAACA23CT

“The field of vision research is benefitting from advances in non-invasive ocular imaging, DNA sequencing technology, animal modeling, stem cell generation and gene therapy.”

— Carol Mason, PhD

VISION SCIENCE TODAY



Chapter 2: Techniques for Oral Microbiology." Atlas of Oral Microbiology: from Healthy Microflora to Disease, by Xuedong Zhou and Yuqing Li, Academic Press, an Imprint of Elsevier, 2015, pp. 15–40. Figure 2.39: Illumina Sequencing

FIGURE 2.a

*High-throughput sequencing: Each of the nucleotides (A,T,C,G) is fluorescently labeled with a different color, allowing their specific identification. The DNA is first fragmented into smaller pieces—known as library preparation. The specific fragments are fixed to a glass substrate in high-density clusters. During sequencing, the fragments in each cluster are copied by synthesizing new DNA strands. As specific bases are added to the DNA strands, the clusters are repeatedly imaged with a laser, allowing determination of the unique DNA sequence in each cluster based on the color of the sequentially attached fluorescent tags. **Simon John, PhD***

FIGURE 2.b



TT 26 ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTCGGTTTACACCGCGGGTAACCTTAACA 27 CT

Building Genetic Models

Animal models are vital for understanding the molecular processes underlying eye diseases and for testing potential therapies before human clinical trials. Due to similarities in anatomy and physiology, the mouse is a widely used animal model for studying the human eye. In one approach, mouse genes are systematically altered to pinpoint their exact functions in development and disease progression. At Columbia Ophthalmology, we utilize sophisticated methods including conditional disruptions of genes in tissue- and stage-specific manners and point mutations (changing a single base pair in the DNA sequence) to alter proteins. A complementary approach utilizes data from the general population to identify unknown genes involved in development and disease.

CRISPR-Cas9 gene editing technology allows us to target the mammalian genome more directly and rapidly, providing a versatile means to generate next-generation models in mice and other species. These advances have opened a golden era of genetics for the study of complex ocular diseases, fueling research to identify novel mechanisms and treatments. Some of our ongoing studies are focused on the development of key ocular tissues (including Schlemm’s canal, ciliary body, optic nerve and retina) as well as a variety of retinal diseases, such as Stargardt disease and age-related macular degeneration. We are also modeling genes associated with glaucoma in order to generate improved models and to assess metabolism and metabolism-protecting treatments.

Phenotyping

When we talk about an individual’s phenotype, we are referring to the sum total of their observable traits—everything from hair color and eye color to manifestations of disease. A person’s phenotype is the product of the interaction of their genotype (their total genetic inheritance) with the environment. In Precision Ophthalmology™, phenotyping describes the effort made to observe the features of a healthy eye or the characteristic changes due to disease. Phenotyping is important as it can direct our efforts to discover new genes associated with eye disease, and aids in gene discovery. For the patient in the physician’s office, accurate phenotyping helps us establish a connection between eye disease and an underlying gene defect, and may link the gene defect to a specific, individualized treatment for the patient and affected family members.

*“Phenotype” is the term used for observable features (such as eye color, eyelid configuration and eyebrow size) that results from the combined effects of environmental and genetic factors. **G.A. (Jack) Cioffi, MD***

FIGURE 2.c

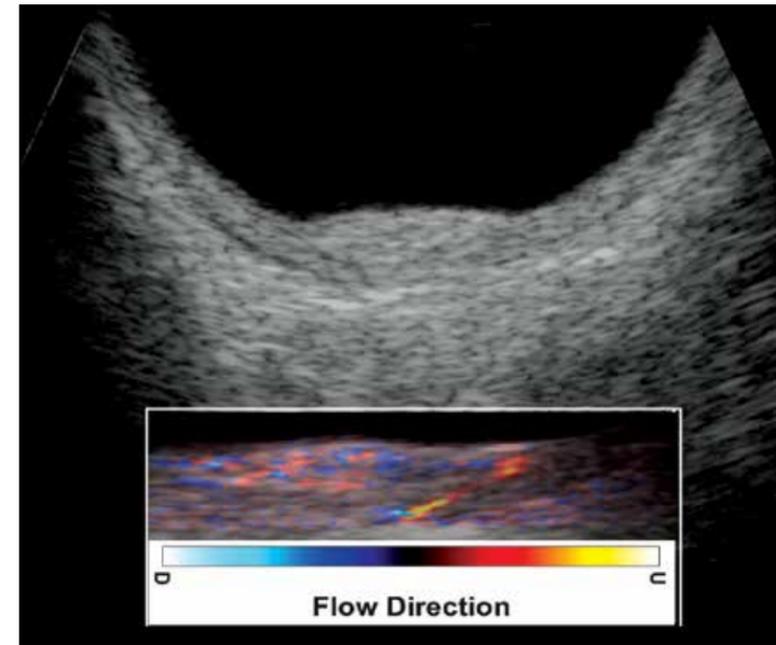
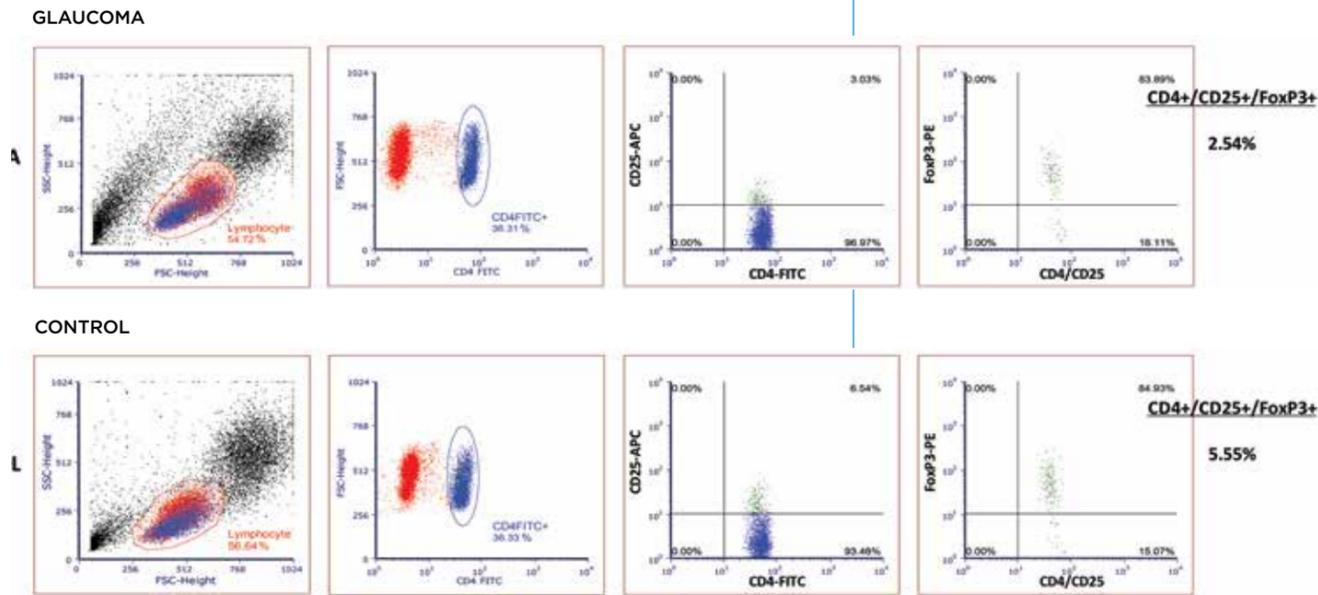


FIGURE 2.d

Mode image of treated choroidal malignant melanoma located inferiorly in the right eye of a 47-year-old woman. Although the tumor was treated 17 years ago and shows no growth in recent exams, color-flow Doppler (insert) derived from plane-wave ultrasound techniques developed at Columbia demonstrate blood flow, primarily in the anterior aspects of the lesion. Visualization and measurement of blood flow in ocular tumors may provide a novel means for assessing metastatic potential and responsiveness to treatment. **D. Jackson Coleman, MD**

Ultrasonic Imaging of Phenotype

Intraocular tumors are often highly pigmented, which severely limits the usefulness of optical methods such as optical coherence tomography in their capacity to provide diagnostic information. Because ultrasound is less subject to scattering and absorption by pigment than is light, it has long been of crucial importance in assessment of tumor thickness pre- and post-treatment by brachytherapy. Conventional B-scans, however, only provide information on tumor position and thickness. Recently developed Doppler techniques can assess both tumor anatomy and blood flow within the tumor and in feeder vessels.



Biomarkers of Disease

Biomarkers are surrogate measurements that can be used to detect or monitor a condition or disease. Molecular biomarkers can improve clinical prediction, early diagnosis and monitoring of diseases. This can be facilitated by the study of proteins (proteomics and immunoproteomics) to identify candidate molecules for validation in the clinical testing of ocular diseases. Since many eye diseases are complex and variable among patients, analysis of a set of biomarkers—including some specific molecules, oxidative stress-related candidates and T lymphocyte profiling being evaluated in our laboratories—may allow us to develop a blood testing panel that can improve our clinical prediction of disease and facilitate follow-up of treatment responses.

*Multicolor flow cytometry-based analysis of T lymphocyte subset distribution shows a decreased percentage of T-regulatory cells (CD4+/CD25+/FoxP3+ fractions of isolated T lymphocytes) in blood samples of patients with glaucoma compared to normal controls. **Gülgün Tezel, MD***

TT28ATTTCGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGGCGGGTAACCTTAACA29CT

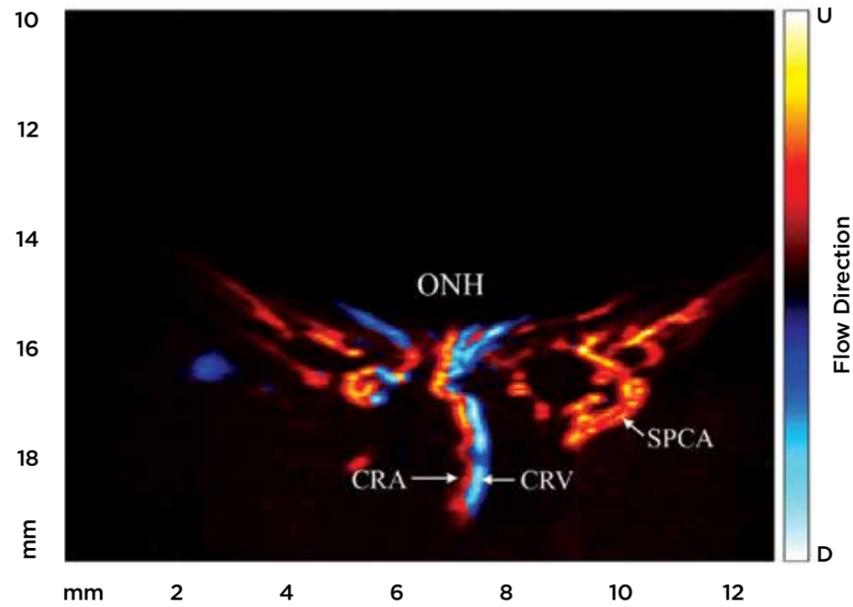


FIGURE 2.e

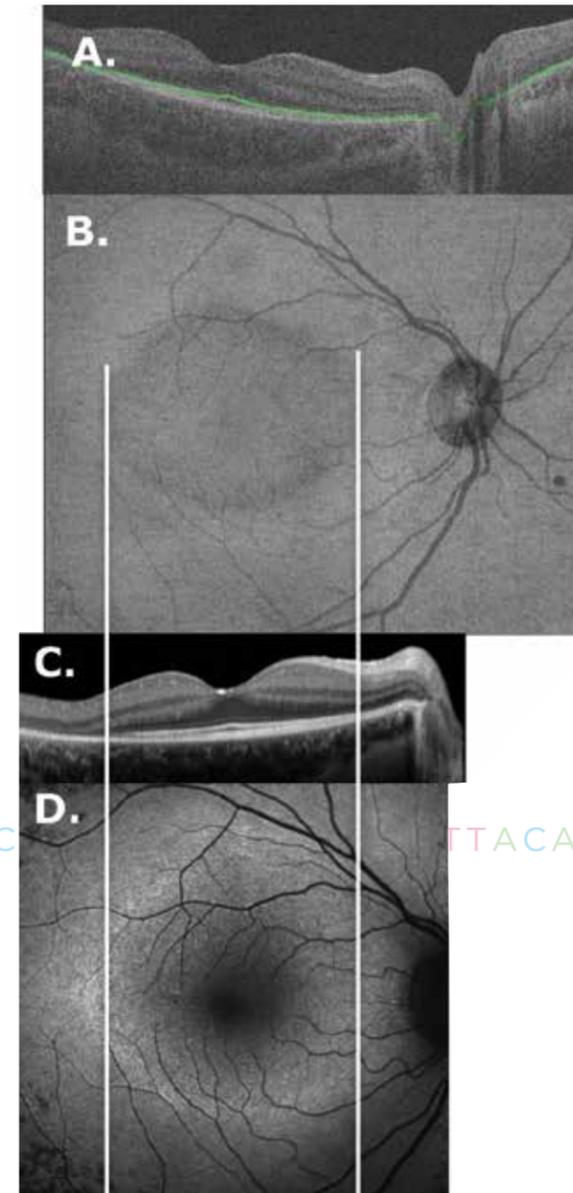
This photomicrograph demonstrates color-flow Doppler images of a pre-term neonate obtained using plane-wave ultrasound techniques developed in our labs. The project is supported by a Jonas grant and aims to find markers representing retinopathy of prematurity risk factors. The images depict vessels in the region of the optic nerve: red colors depict arteries, and blue depicts veins. The central retinal artery and vein are seen, as is the short posterior ciliary artery, retina and choroid.
Ronald Silverman, PhD

Imaging as a Biomarker

In the last decade, a novel approach to Doppler imaging called “plane-wave” ultrasound was developed. With this technique, unfocused ultrasound is transmitted and focusing is achieved by computer post-processing. Plane-wave enables acquisition of many thousands of B-scans per second, which facilitates identification of tissue motions, including flowing blood. Columbia researchers in the Silverman Lab have developed this technology for imaging the eye. Not only does it provide high-resolution color-flow images but it does so at intensities compliant with strict regulatory standards. Clinical studies of ocular blood flow in glaucoma, preeclampsia and in low-birthweight neonates at risk for retinopathy of

prematurity are now underway. The application of plane-wave ultrasound Doppler offers an exciting new avenue for functional and structural imaging of the eye in health and disease.

Imaging for Diagnosis



OCT and FAF images for a patient with retinitis pigmentosa..
A. Image depicting a cross section of macula and optic nerve anatomy.
B. En-face image with EZ band as the reference showing the boundary of the intact EZ band.
C. Averaged B-scan.
D. FAF image showing ring of hyper autofluorescence.
Vivienne Greenstein, PhD

FIGURE 2.f

Optical coherence tomography (OCT) and fundus autofluorescence (FAF) are noninvasive imaging methods that play a key role in the diagnosis and management of inherited retinal degenerations (IRDs). The results contribute to our understanding of the pathophysiology of IRDs and to correlations between genotype and phenotype (the set of observable characteristics resulting from interaction between genotype and environment). Using OCT, we can evaluate the integrity of the outer and inner retinal layers both qualitatively and quantitatively. For example, in patients with retinitis pigmentosa, we can use OCT to visualize damage or disruption of the photoreceptor layers and to observe any loss of integrity of the external limiting membrane

(ELM) and ellipsoid zone (EZ) band. Quantitative assessments of EZ width and outer segment (OS) layer thickness can be used as markers of disease progression. We can also generate en-face OCT images of the retinal layers at any specified depth, providing morphologic information that we can then compare to changes observed on FAF images. Novel techniques for wide-field and swept-source (SS) OCTs and wide-field fundus autofluorescence now permit us to evaluate regions outside the central retina—regions that are affected in IRDs such as Stargardt disease and retinitis pigmentosa. These techniques will make it possible to study cohorts of patients with specific gene mutations, identifying relationships among measures and documenting disease progression.





"Hereditary risk assessment necessitates genetic testing to allow families to understand their familial risk and answer the question: Will my children get my disease?" — Irene Maumenee, MD

THE HERITANCE QUESTION

THE INHERITANCE QUESTION

FIGURE 3.a

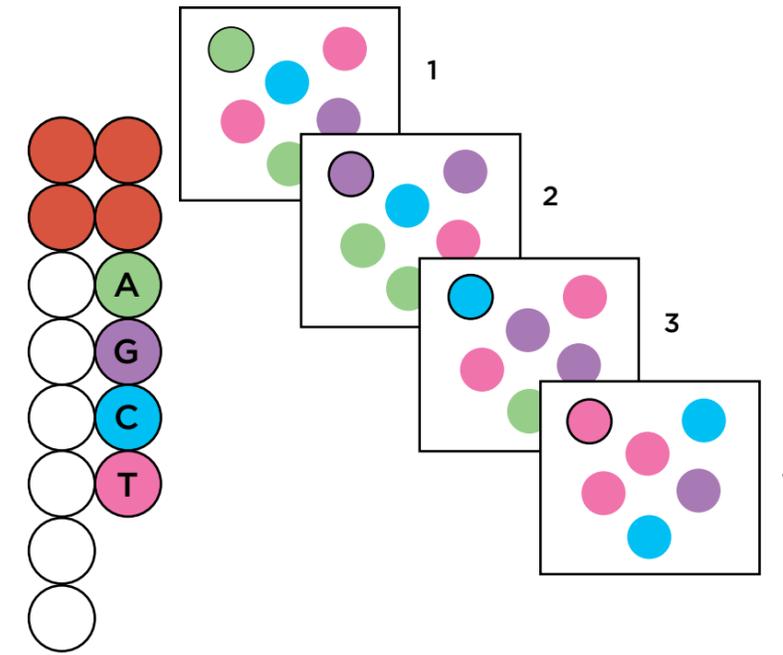
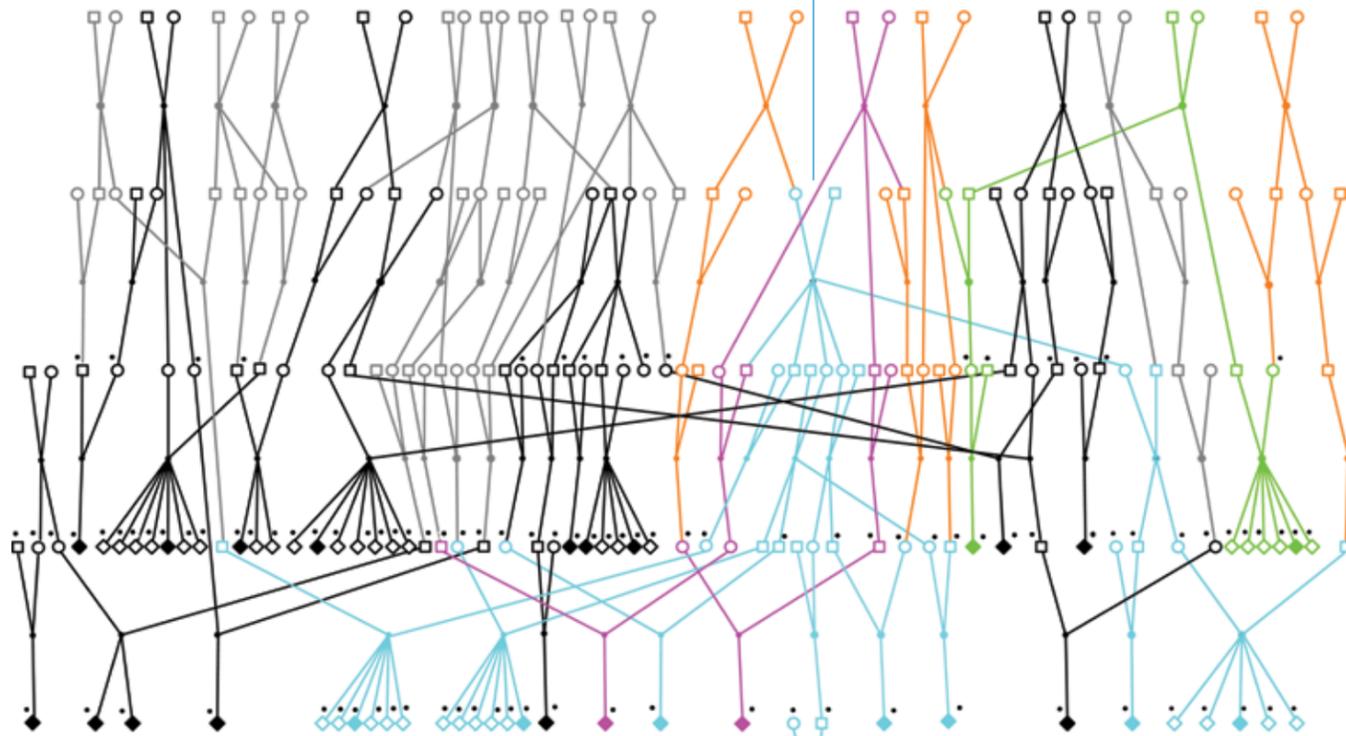


FIGURE 3.b

Sequencing is the basis of modern genetic testing. Each of the nucleotides (A,T,C,G) is fluorescently labeled with a different color. A representation of fluorescent signal from a single cluster is on the left.

Simon John, PhD

TT 34 ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTT CGGTAGCATCATTCTATTTCGGTTTACACGGCGGTAACCTTAACA 35CT

Will My Children Inherit My Disease?

The interplay of a person's genetic information with environmental factors is often a major force in disease development. Alternatively, a person's genes can be the primary driving factor in the development of a disease, regardless of environmental exposures. A mutation of a single gene can cause disease at a discrete level (just in one tissue or organ, such as the eye) or throughout the body, depending on how developmentally critical the mutated gene is. Each of us is supplied with two sets of genes from our parents (one from Mom and one from Dad). If you have a disease that results from a genetic mutation, your children have a risk of inheriting that disease, but the level of risk is dependent on several factors. Are both copies of the gene required in order to be healthy? Is the mutation in a location that is defined

- by gender, without other copies?
- Is there a role for environment or other factors to lessen or exacerbate the impact of the mutation? The genome of each individual is unique and varies from person to person. This complexity and diversity among individuals with and without disease is why genetic testing and counseling is critical.

Genetic Testing in the Modern Society

Each of us knows that many diseases have some component of heritability, whether it be within our own families or others. The fundamental underpinning of modern genetics began with the discovery of DNA. In the past two decades, our ability to analyze the human genome has swiftly become routine, much more widely available and less costly. This has led to its increasingly common use in daily medical practice in such diverse fields as maternal-fetal medicine, oncology, pediatrics and ophthalmology. Commercially available gene testing kits are increasingly common but do not yet offer the precise diagnostic capabilities found in the scientific and medical communities. Our existing database of genetically determined ocular diseases is rapidly expanding while at the same time our ability to

manipulate the genome has emerged. This empowers each of us to better understand our own disease risks, tendency for familial inheritance, prognosis and potential therapies.

FIGURE 3.c



A Family's Perspective

Celebrating the launch of Jonas Children's Vision Care with the Jonas family, made possible by the generosity of Barbara and Donald Jonas. G.A. (Jack) Cioffi, MD

Applied ophthalmic genetics integrates many facets of eye care and vision research and offers us the potential to reach new goals that previously would have been considered impossible. These include novel discoveries, innovative therapies and the delivery of state-of-the-art, personalized care for each patient. We can only achieve these lofty aims through partnerships between dedicated medical teams on the one hand, and philanthropists with a commitment to curing disease on the other. The Jonas Initiative, created with a generous gift from Jonas Philanthropies, is an example of such a partnership. The funding from this gift has allowed the expansion of pediatric eye care and research, as well as a substantial investment in Applied Genetics, at Columbia Ophthalmology. It has paved the

way for families and children with sight-threatening conditions such as congenital cataract and glaucoma to get the advanced testing and treatment they need to save their vision. Applied Genetics also allows children with syndromes that can affect multiple organs and tissues, such as Marfan syndrome or Usher syndrome, to be evaluated and treated for vision-threatening complications, as well as helping to guide genetic testing and referrals to other pediatric specialties. Applied Genetics at Columbia Ophthalmology, and its partnership with philanthropy, has virtually limitless promise to transform the lives of children and families with complex medical conditions.

FIGURE 3.d



Genetic counselors educate patients about their genetic testing results. This allows patients to make informed decisions about their medical management. Megan Soucy, MS, CGC

Genetic Counseling

“Genetic counselors are professionals who have specialized education in genetics and counseling to provide personalized help that patients may need as they make decisions about their genetic health.” —The National Society of Genetic Counselors (2019)

Genetic test results affect families—not just individuals. In order to accurately interpret the results of genetic tests, we often need to include information from other family members. Individuals undergoing genetic testing can feel a myriad of emotions, such as guilt, shame, anxiety and relief—feelings that are made even more complex by family dynamics. Family secrets such as nonpaternity can be discovered; individuals might need to communicate with estranged family members; and sometimes an individual has

no biological relatives available, but family member testing is needed to interpret results. Genetic counseling addresses these concerns while guiding individuals through the testing process and interpretation of results. While genetic counseling can be performed by a physician, oftentimes the use of a genetic counselor is beneficial. The genetic counseling process allows for more time to devote to these conversations, allowing individuals undergoing testing to feel confident and empowered by their genetic health information. At Columbia Ophthalmology, we have genetic counselors who have been specifically trained in ophthalmic diseases to assist patients and families.

CLINICAL GENETIC TESTING & THERAPIES



“Understanding the genetic basis of a disease will aid in the hunt for new therapies and allow clinicians to select specific therapies for specific patients.”

— Janet Sparrow, PhD



Why We Do Genetics Testing

A young blind Pingelapese man sitting in his boat but unable to identify the low-lying "Island of the Colorblind" in the distance. The gene mutation that results in 1 in 20 islanders being severely color blind took almost three decades to identify before modern sequencing technology.
Irene Maumenee, MD

We conduct genetic testing on individual patients for three main reasons: to improve understanding of a patient's disease, to understand the risk of disease recurrence in a family and to foster patients' participation in their own care and search for knowledge.

Identifying gene mutations and better understanding a patient's disease helps us to better manage that disease. The clinical presentation of a patient's disease, or phenotype, depends upon the underlying gene mutation as well as the overall genetic makeup and the environment. Depending on the disease, each of these factors may have different impacts on the symptoms and severity of a disease. Also, more than one gene may produce the same

FIGURE 4.a

disease phenotype, or a similar one—but managing the disease may differ based on which genes are involved.

When a genetically linked disease occurs in a family, the risk of that disease recurring in other family members can vary from zero to 50%. When DNA analysis finds a previously identified genetic mutation that is compatible with an observed disease phenotype, our counseling changes from an estimated risk of recurrence to a confirmed probability, or even 100% certainty. Understanding the genetic underpinnings of a particular condition allows us to provide diagnosis and counseling at many stages: prenatal diagnosis, preimplantation diagnosis, pre-symptomatic diagnosis and early management. We can also confirm

that a person is healthy and will not develop a particular disease. Counseling should be provided by certified genetic counselors, medical geneticists or, ideally, double-board-certified genetic ophthalmic geneticists.

Patients will benefit most from the scientific revolution that is occurring in the diagnosis, gene and mutation identification, and gene therapy of hereditary diseases, if they develop knowledge of the possibilities for others as well as their disease. Our department, along with foundations created and directed by patients, has been very successful in promoting ongoing research progress through advocacy and financial support.

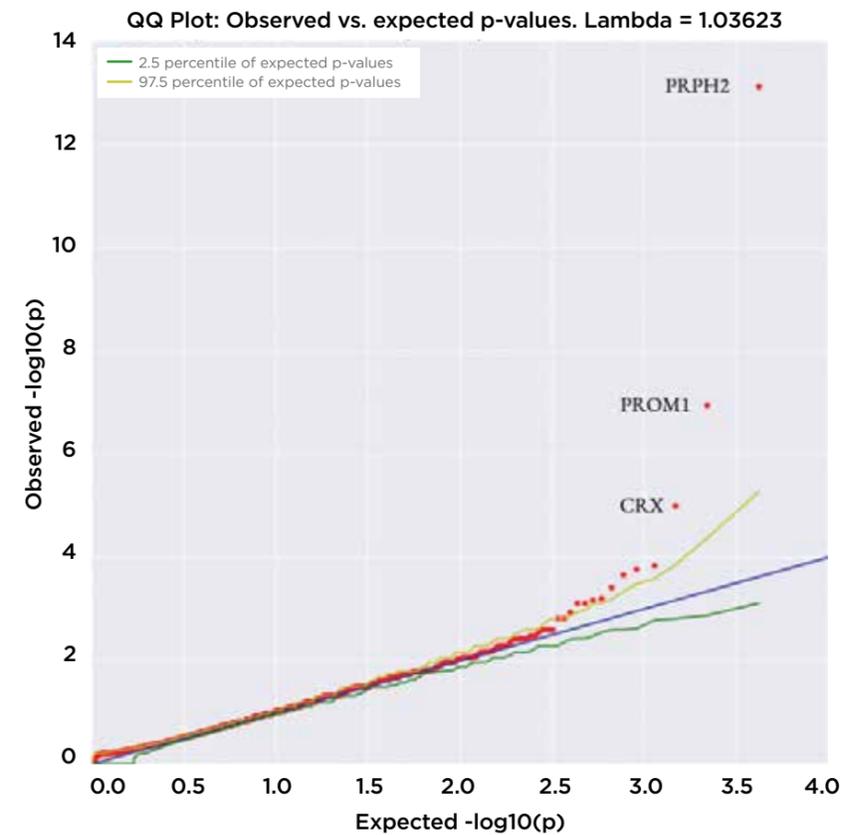


FIGURE 4.b

Quantile-quantile (QQ) plot for exome-wide gene-based collapsing analysis under the dominant genetic model in a cohort of patients who clinically presented with Stargardt disease but had no mutations in ABCA4. The analysis identified the top three genes, PRPH2, PROM1 and CRX, that reached genome-wide significance. These genes are the primary candidates for causality in macular diseases mimicking Stargardt, allowing for precise genetic diagnosis.

David Goldstein, PhD
Rando Allikmets, PhD

Advances in next-generation sequencing have revolutionized both gene discovery and the diagnostic analysis of patients with rare diseases. Our Institute for Genomic Medicine (IGM), directed by Dr. David Goldstein, has been instrumental in using these advances and related statistic genetic approaches to help make Precision Medicine a reality across the medical center. In partnership with several clinical departments, the IGM is breaking new ground not only to understand the clinical applications of genomics across the life span of an individual, but also to determine how mutations can be studied in the laboratory to help develop personalized medicine strategies for the treatment of patients.

Collaborators from IGM and Ophthalmology seek to identify individuals with specific phenotypes, such as macular telangiectasia, age-related macular degeneration and Stargardt-like retinal dystrophies, to participate in research aimed at identifying new genes and enhancing precision diagnosis. Our analysis, aimed at finding genes with a high burden of rare variants, has found a significant signal in retinal dystrophy genes among the Stargardt-like patients (see plot above). We continue to explore other eye disease phenotypes, including nystagmus. The IGM will continue to provide essential intellectual, technical and bioinformatics infrastructure to advance Precision Ophthalmology™.



CLINICAL GENETIC TESTING & THERAPIES



FIGURE 4.c

With the advancements of genetic testing and diagnosis, it is now possible to perform prenatal genetic analysis at the earliest stages of pregnancy or even before conception. **Jeffrey Liebmann, MD**

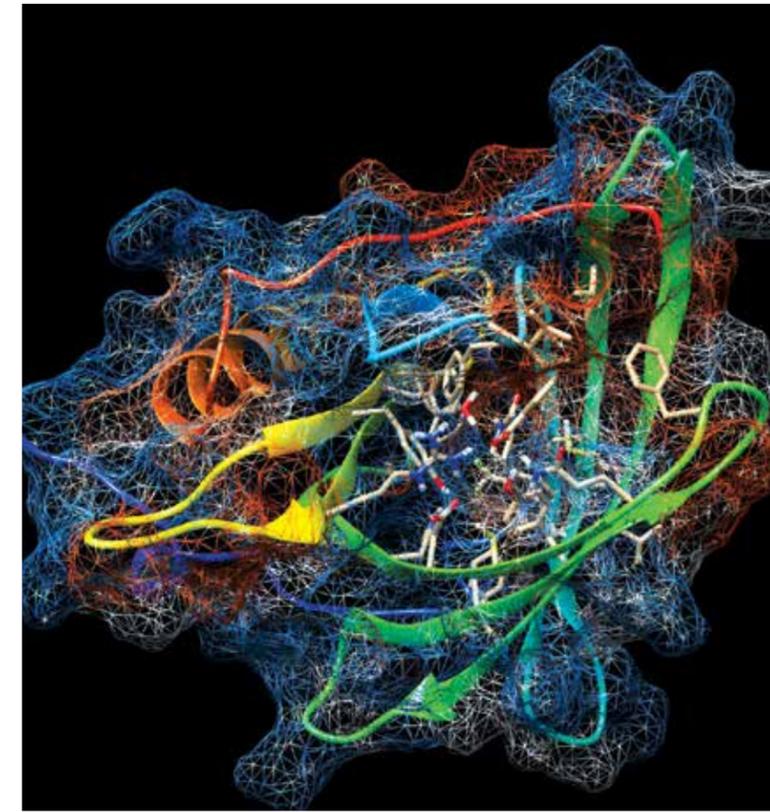


FIGURE 4.d

Pharmacological modulation of vitamin A traffic to the retina is one approach to treating retinal diseases. Toxins called lipofuscin bisretinoids, byproducts of the eye's visual cycle produced from vitamin A, cause Stargardt disease and contribute to dry AMD. Tinalarebant is a first-in-class oral therapy that prevents the buildup of these toxins. It works by binding to the vitamin-A-binding pocket on a carrier protein, Retinol-Binding Protein 4 (shown in the figure), that delivers vitamin A to the eye. This partially restricts traffic of retinol to the eye and inhibits production of these toxic bisretinoids.

Konstantin Petrukhin, PhD

TT 42 ATT CGG TTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTT CGGTAGCATCATTCTATT CCGGTTTACACCGCGGTAACCTTAACA 43 CT

Family Planning/ Genetic Counseling

People who are planning a family seek genetic testing for a variety of reasons, including hereditary ocular conditions. Parents hope to better understand the risks of their children developing a condition. Hereditary ocular conditions follow many different inheritance patterns, and identifying the underlying genetic cause is often the only way to accurately inform couples of their child's risk. Many times, both parents (the parent with disease and the unaffected partner) may need specialized genetic testing for the risk to be accurately assessed. Proper genetic counseling can inform couples about what type of testing is best.

For certain conditions, identification of a genetic mutation before pregnancy can allow for preimplantation genetic testing (PGT). Through in vitro fertilization (IVF), couples can test embryos for the condition of concern and then transfer the unaffected embryos for implantation. This greatly reduces the chance of the condition being passed on. In addition, during pregnancy, genetic testing may be used to determine if the child may have or will develop the condition. As we learn more about gene-based therapies, early identification and early treatment of these conditions can improve quality of life and decrease vision-related disability.

Small Molecule Treatments

Both young and old individuals can suffer from vision loss from macular dysfunction. Dry (atrophic) age-related macular degeneration (AMD) affects millions of older individuals worldwide. Stargardt disease is the most common form of inherited juvenile-onset macular dystrophy. Despite the huge unmet medical need, there is no FDA-approved pharmacological therapy for dry AMD and Stargardt disease.

Dry AMD is a multifactorial disorder with several different pathways contributing to its pathogenesis. Age-dependent accumulation of cytotoxic lipofuscin pigment in the retina matches the age-dependent increase in dry AMD prevalence and thus is frequently cited as one of the critical pathogenic factors contributing to the disease progression. Excessive formation of cytotoxic lipofuscin

bisretinoids seems to be the primary biochemical defect in Stargardt disease. Our work in recent years led to identification of the novel drug tinalarebant, which inhibits biosynthesis of cytotoxic lipofuscin retinoids in animal models that mimic significant aspects of dry AMD and Stargardt disease.

After successfully passing all hurdles of pre-clinical development, tinalarebant has been advanced to human clinical trials. Recently completed first-in-human single and multiple ascending dose studies evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of oral, once-a-day tinalarebant in healthy adult subjects. Tinalarebant was well tolerated and highly effective against the serum biomarker in these Phase 1 clinical trials.

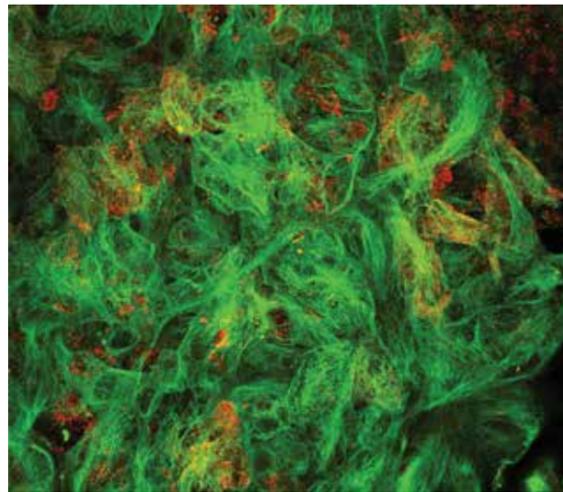
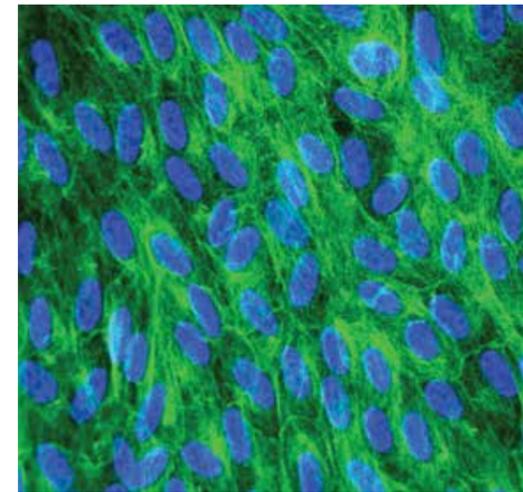


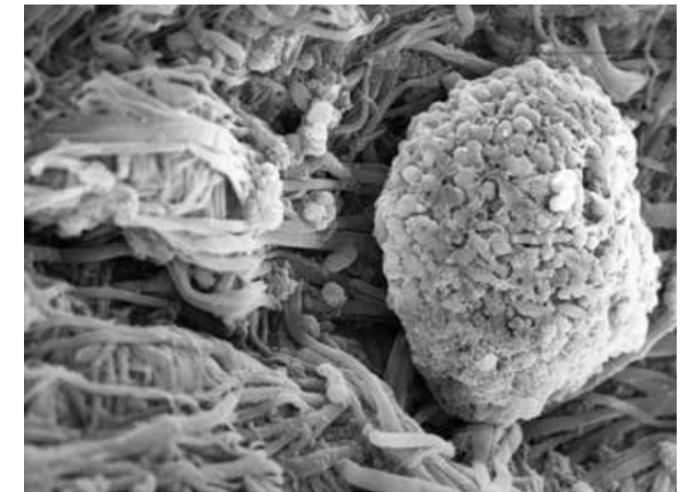
FIGURE 4.e

Behavior and function of the grafted cells depends on the host's subretinal milieu. We have demonstrated that the stiffness and vertical stabilization of the scaffold carrying the grafted retinal cells plays a major role in their subsequent behavior. Failure to optimize the host subretinal environment results in loss of epithelial morphology and specific functions of the grafted cells required to restore sight—a process known as epithelial mesenchymal transition.
Tongalp Tezel, MD

Human retinal pigment epithelial cell generated from induced pluripotent stem cells can be generated from patients suffering from age-related macular degeneration. After the correction of the genetic defects with gene surgery, monolayers of these cells can be transplanted into the patient's subretinal space to replenish the cellular defects and restore the central sight.
Tongalp Tezel, MD



Scanning electron microscopy of a retinal pigment epithelial cell seeded on inner collagenous layer of human Bruch's membrane. Ex vivo models of human macular degeneration allow us to study the biology of retinal cell transplantation and optimize the conditions for grafted cells to survive and function in the host subretinal space.
Tongalp Tezel, MD



TT 44 ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGGCGGTAACCTTAACA45CT

Therapeutic Developments

Several blinding disorders, such as macular degeneration, develop as a result of the complex interactions of multiple genetic, environmental and constitutional factors. Meaningful and reproducible treatment outcomes for restoring sight can only be achieved if each of these factors are addressed before planning human surgeries. At the Edward S. Harkness Eye Institute, we have developed a new comprehensive treatment strategy to restore the sight of the patients suffering from macular degeneration and hereditary retinal diseases. This approach involves replenishing the cellular defects of the retina with stem-cell-derived retinal cells and repairing the defects of the extracellular matrices to create an

ideal environment for the grafted cells to survive and function. We call this novel concept “maculoplasty.”

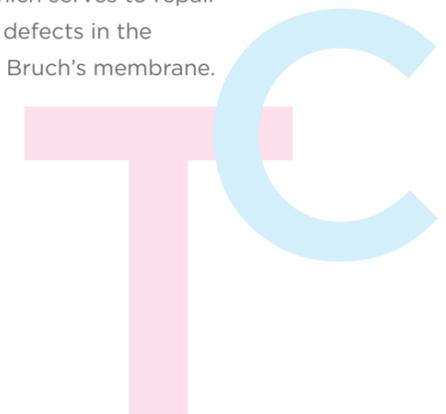
Our researchers are able to generate retinal pigment epithelial and photoreceptor cells by reprogramming somatic cells taken from the patient's skin or blood. Using the patient's own cells prevents the immune response or inflammation that occurs with donor cells. Next-generation sequencing identifies the underlying genetic defects in these cells, which can subsequently be corrected with “gene surgery” using the CRISPR-Cas9 system. The result is autologous retinal cells ready to replenish the cellular defects in the patient's eye. These retinal cells then must be prepared under current good manufacturing practice standards

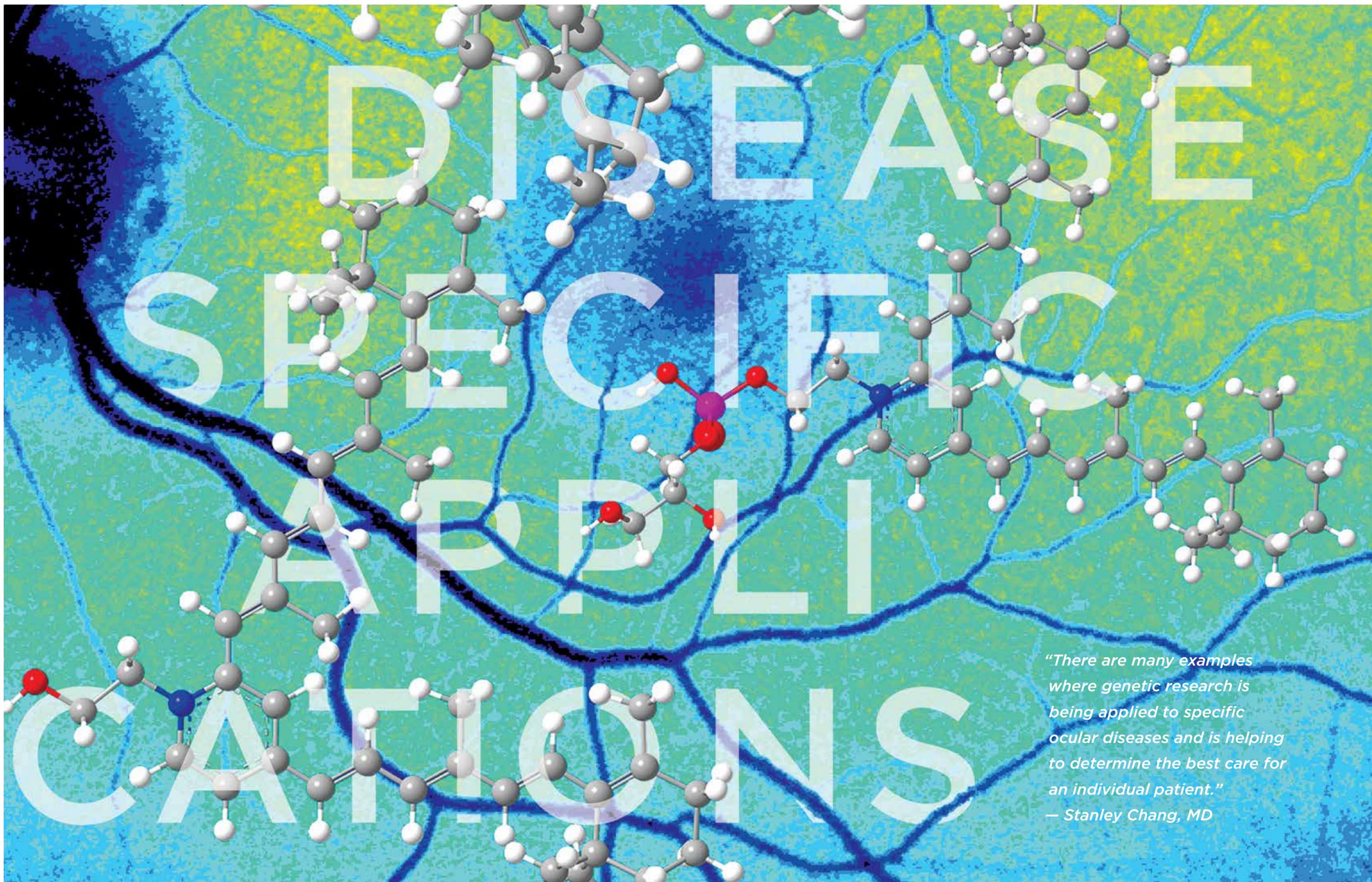
and undergo vigorous testing to detect any residual genetic defect and functional deficiency.

The success of the retinal cell transplantation depends on the engineering of the patient's subretinal space to create a suitable environment for the grafted cells to survive and function properly. The signals that tell retinal pigment epithelium (RPE) to either remain differentiated and function as intended, or turn into mesenchymal, scar-forming cells, comes from the matrix they rest on. In patients with macular degeneration, the Bruch's membrane, the natural substrate for the retinal pigment epithelium, is structurally altered by age and environmental damage, resulting in

poor survival for the RPE.

Our researchers have developed in vitro models to study the fate of the grafted retinal cells in the host subretinal space, which allowed them to develop technologies to rejuvenate the aged Bruch's membrane and patch-graft it with natural and synthetic matrices that mimic the retinal anatomy and offer 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.





“There are many examples where genetic research is being applied to specific ocular diseases and is helping to determine the best care for an individual patient.”
— Stanley Chang, MD

DISEASE-SPECIFIC APPLICATIONS

1861: The indirect ophthalmoscope is invented

1865: Gregor Mendel presents his work on inheritance

2003: Human Genome Project declared complete

2019: The illuminate trial begins

1869: Theodore Leber describes what is now generally known as LCA

1953: Watson and Crick describe the double helix structure of DNA

2017: The first in vivo gene therapy is approved by the FDA

150 Years

Over the past 150 years, we have moved from the earliest descriptions of inheritance to the testing of human genetic therapies.
Steven Brooks, MD

FIGURE 5.a



FIGURE 5.b

This toddler has type I Peters anomaly of the left eye, caused by adhesions from the iris to the cornea. The result is a poorly formed Descemet's membrane (a layer deep within the cornea) and a congenital corneal opacity. The girl's right eye

is normal. Peters anomaly can be caused by mutations in the PAX6 gene (11p13), the PITX2 gene (4q25-26), the CYP1B1 gene (2p22-21), and the FOXC1 gene (6p25).
Danielle Trief, MD, MSc

TT 48 ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTCGGTTTACACCGCGGGTAACCTTAACA 49CT

Genetic Therapeutic Applications

The loss of function of a gene that is critical to the health of the retina can be devastating, resulting in severe vision loss or blindness. Gene therapies now offer hope for previously untreatable conditions. One of the most extensively investigated applications of gene therapy has been in early-onset retinal degenerations. This research has been so successful that the FDA recently approved one such agent, Luxturna (voretigene neparvovec), for use in a specific form of childhood retinitis pigmentosa (RP).

Several promising strategies can be employed to restore the function of the damaged gene in the eye. Viruses, also known as viral vectors, can be engineered to deliver a normal copy of the gene to affected cells, as with Luxturna. Specifically, small

pieces of the genetic material (RNA oligonucleotides) can be inserted into the retinal cells to correct an aberration in gene processing. There is even hope that gene editing at a molecular level can be used to correct the underlying mutation itself.

At the Edward S. Harkness Eye Institute, all of these approaches are under laboratory investigation, and some are being studied in clinical trials. The application of these cutting-edge therapies requires genetic testing, the design of precise and personalized therapeutic agents, and a team of clinical specialists capable of delivering the agents to the eye.

Pediatric Corneal Disease

Disorders of the cornea in children can be either congenital or acquired, and many of these diseases stem from genetic causes. Some conditions, like congenital hereditary endothelial dystrophy (CHED), which causes corneal clouding at birth, are caused by a mutation in a single gene. Other congenital corneal conditions, like Peters anomaly, are associated with mutations in multiple genes.

Today, we are making rapid advances in our understanding of pediatric corneal disease. While we are able to link some conditions directly to their genotypes, we understand that others are likely the result of an interplay between genetic and environmental factors. Keratoconus, for instance, which often begins to manifest in puberty, can be seen in

higher frequency in certain families and among children with allergies and eye rubbing.

We now have a dedicated monthly clinic for children with corneal disorders. Many of these children also have other ophthalmological or systemic diseases. Care of these children is always interdisciplinary, whether that means working with an ophthalmologist in the field of glaucoma or retina, or a pediatrician with an entirely different medical specialty. By understanding the genetic origins of these complex diseases, we will be able to develop more targeted therapies.

Overleaf: Color-coded quantitative autofluorescence image overlaid by structures of some of the bisretinoids that are the source of short-wavelength fundus autofluorescence
Janet Sparrow, PhD

DISEASE-SPECIFIC APPLICATIONS

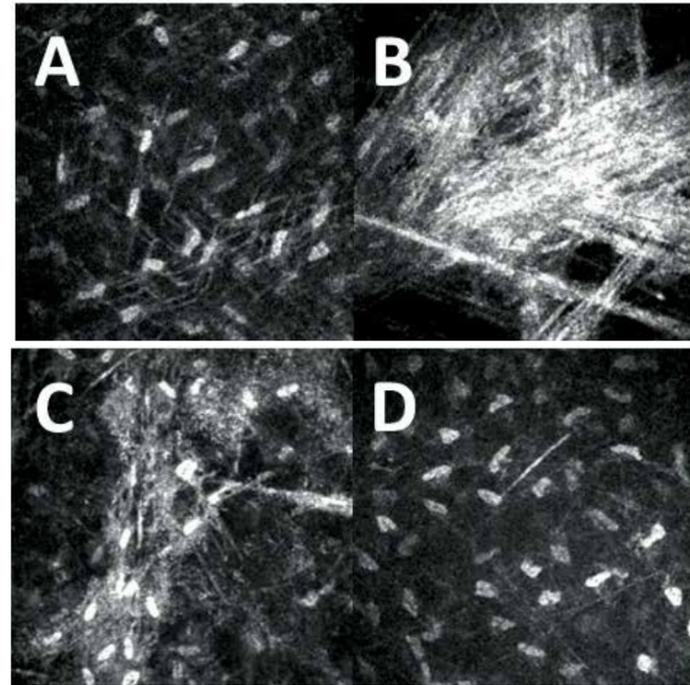


FIGURE 5.c

Real-time confocal microscopy images of the corneal stroma following topical cross-linking, with progressive keratocyte changes over 2 months. The normal keratocytes (bright white oval nuclei in panel A) initially undergo cell death followed by repopulation and activation with various degrees of cytoplasmic and extracellular matrix hyper-reflectivity as shown in panel B (1 week) and panel C (1 month). By 2 months (panel D), the keratocyte repopulation and normalization is complete.

David Paik, MD
Leejee Suh, MD

Keratoconus

Keratoconus, a progressive eye disease in which the cornea thins and begins to bulge into a cone-like shape, typically develops in a person's late teens or early twenties, and results in high degrees of astigmatism and inability to correct a person's vision despite glasses and contacts.

With the help of a grant from the National Eye Institute, scientists at Columbia Ophthalmology are developing a topical tissue-strengthening treatment for keratoconus that involves the application of cross-linking agents to the corneal surface. This cross-linking solution could have far-

ranging treatment applications beyond keratoconus, including the progressive myopia resulting from anesthesia injection in the sub-Tenon's space, and difficult-to-treat corneal infections involving multi-drug-resistant organisms.

A
G
T
C

Congenital & Juvenile Glaucoma

Although more commonly seen among adults, glaucoma can also affect newborns and infants, leading to lifelong visual impairment. Primary congenital glaucoma affects children between birth and 3 years of age in the absence of other abnormalities; developmental glaucoma is accompanied by abnormalities of the iris and/or the eye's drainage system, and sometimes also by systemic conditions such as dental abnormalities, intellectual disability, and musculoskeletal malformation.

Genetic testing plays an important role in the prompt identification

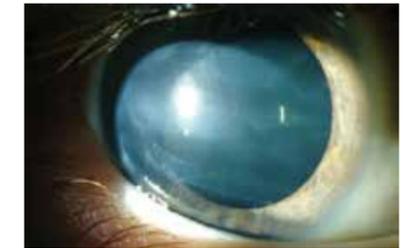
and treatment of these types of glaucoma. For instance, more than 50% of children with ocular abnormalities caused by either PITX2 or FOXC1 mutations have glaucoma characterized by high eye pressure. These are genes that in healthy individuals help regulate cell division. Another important gene with a similar role is called PAX6, and its mutation can cause a severe form of glaucoma associated with a rare type of kidney cancer.

Juvenile open-angle glaucoma is a highly inheritable form of the disease that also affects individuals at an early age—typically between 4 and 35. Patients often have multiple family members with early-onset, severe forms of glaucoma. One of the first glaucoma-associated genes to be

FIGURE 5.d

A photograph of the eye of an infant with congenital glaucoma showing a hazy cornea (the front window of the eye) with linear streaks (Haab's striae) from the high intraocular pressure that stretches and damages the eye.

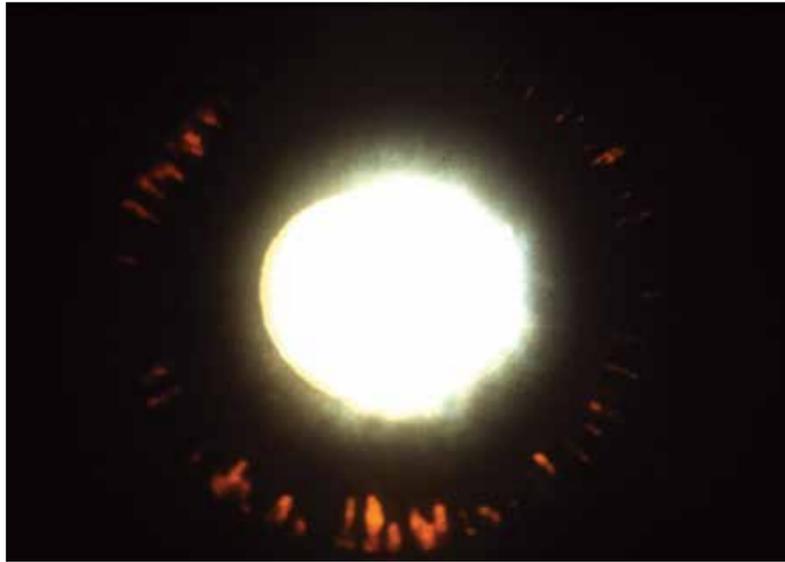
Steven Brooks, MD
C. Gustavo De Moraes, MD, MPH, PhD



described, myocilin gene (MYOC), is highly prevalent among patients with juvenile glaucoma. An estimated 8%-63% of unrelated juvenile glaucoma patients have MYOC mutations. New evidence suggests genetic testing of family members of patients with juvenile glaucoma can lead to earlier detection of milder forms of the disease. Moreover, new genetic therapies, namely gene editing (CRISPR), have shown promising therapeutic outcomes in mice and could potentially be tested in humans in the near future.

TT 50 ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTCGGTTTACACGGCGGGTAACCTTAACA51CTC

DISEASE-SPECIFIC APPLICATIONS



Pigmentary Glaucoma

Pigmentary glaucoma (PG) accounts for 1-2% of all open-angle glaucomas, and typically affects nearsighted individuals between the ages of 20 and 50 years. Although the phenotype of PG has been well understood since its first description in 1940, we know very little about its genetic predisposition.

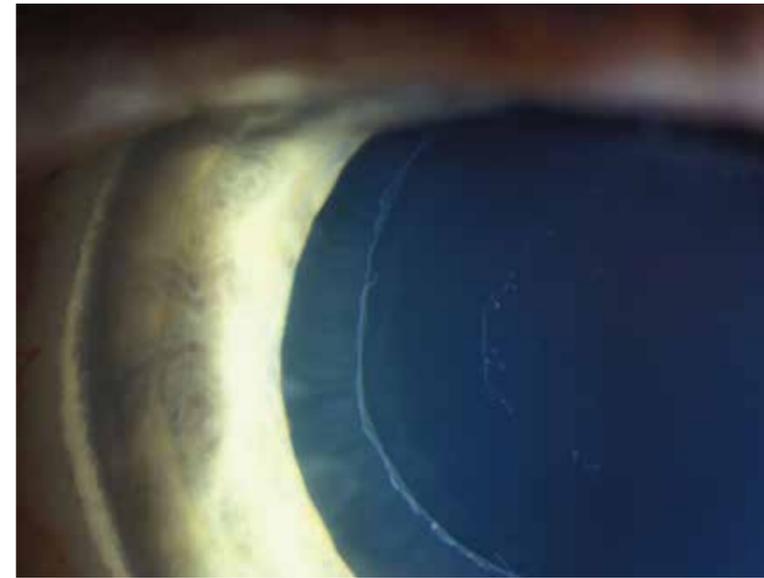
Pigment dispersion syndrome (PDS), which involves the release of pigment from the back part of the iris into the eye's anterior segment, is a secondary cause of elevated intraocular pressure. Individuals with PDS have a 35-50% lifetime risk of developing pigmentary glaucoma. Studies have suggested that PDS may result from a combination of mutations in multiple genes.

FIGURE 5.e

Pigment dispersion syndrome is characterized by release of pigment from the iris pigment epithelium, which is the posterior-most layer of the iris. This results in the characteristic, midperipheral, radial, iris transillumination defects pictured here. The pigment that is released can clog the eye's drainage system, leading to a buildup of ocular pressure and causing pigmentary glaucoma in approximately 30-35% of patients. While clustering in families occurs, the specific gene defect remains unknown and is the focus of an ongoing research program.

Dana Blumberg, MD, MPH
Y. Shira Kresch, OD

Here at Columbia, we have led many of the recent studies that have used next-generation sequencing to identify the genes involved with similar complex disorders of the eye, and we are now applying the same techniques to search for the genes that underlie PDS and PG. Our large database featuring state-of-the-art imaging of patients with PDS and PG, along with a newly established collaboration with the Columbia Institute of Genomic Medicine, will help us shed light on the genetic origins of these conditions and customize care for those at risk.



Exfoliation Syndrome

Exfoliation syndrome (XFS) is the most common identifiable of secondary open-angle glaucoma, accounting for up to 25% of open-angle glaucoma worldwide and posing a greater risk of visual impairment than other forms of open-angle glaucoma.

Exfoliation material appears as white, flaky material in the anterior segment of the eye. This material accumulates within the eye's drainage system, obstructing its flow and causing an increase of intraocular pressure, resulting in glaucomatous damage of the optic nerve. This process causes telltale pigmentary changes in the eye and notoriously weakens intraocular structures. This creates a high-risk environment for intraocular procedures, such as cataract surgery, requiring highly skilled surgeons.

FIGURE 5.f

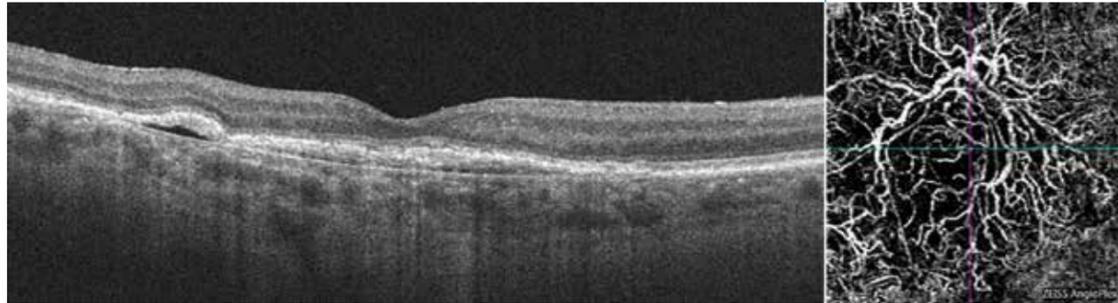
Exfoliation material consists of fibrillo-granular deposits that appear clinically as a white, snowflake-like material on the surface of the lens and other structures of the anterior segment, such as the ciliary body, iris and zonules. A lysyl oxidase-like 1 (LOXL1) gene defect is necessary for the development of the disease, but a gene-environment interaction is thought to be responsible for the differences in worldwide prevalence of the disease across continents and latitudes.

Jeffrey Liebmann, MD

Over a decade ago, genome-wide association studies identified the first variants associated with exfoliation syndrome on the gene LOXL1. More recently, at least six other genetic loci (CACNA1A, FLT1-POMP, TMEM136-ARHGEF12, AGPAT1, RBMS3 and SEMA6A) have been pinpointed as associated with a high risk for XFS. Columbia University's Glaucoma Division is at the forefront of the genetic study of XFS, managing some of the most complicated patients with this condition and working to help identify family members at high risk of developing glaucoma and provide tailored treatment.



DISEASE-SPECIFIC APPLICATIONS



Spectral-domain optical coherence tomography (SDOCT, left), and optical coherence tomography angiography (OCT-A, right) of a patient with neovascular age-related macular degeneration. The SDOCT shows elevation of the retinal pigment epithelium, and the corresponding

FIGURE 5.g

OCT-A image strikingly demonstrates a mature choroidal neovascular membrane. Precise genetic analysis coupled with high-resolution retinal imaging may allow us to develop molecularly targeted therapies.
Royce Chen, MD

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a leading cause of blindness in individuals over the age of 60 around the world. It is an acquired degeneration that specifically affects the macula, the part of the retina responsible for central vision. AMD is classified as non-neovascular, characterized by drusen (subretinal deposits) and geographic atrophy, or neovascular, characterized by the formation of new vessels that may leak into the retina, bleed, and eventually cause irreversible scarring. In recent years, therapies have been introduced that have improved our care of individuals with AMD.

Although there is no simple genetic inheritance pattern for the development of AMD, the disease certainly runs in families, as a family member of a patient with AMD is at least three times more likely to develop AMD. Of the multiple genetic alterations that have been found to confer a greater risk for the development of AMD, the polymorphisms Tyr402His at 10q26 (Complement factor H locus), and A1s69Ser (LOC387715) may be responsible for the majority of the genetic risk of AMD. Columbia Ophthalmology is a world leader in discovering genetic variants responsible for AMD, developing novel imaging techniques for earlier disease diagnosis, and providing vision-saving treatment to thousands of patients.

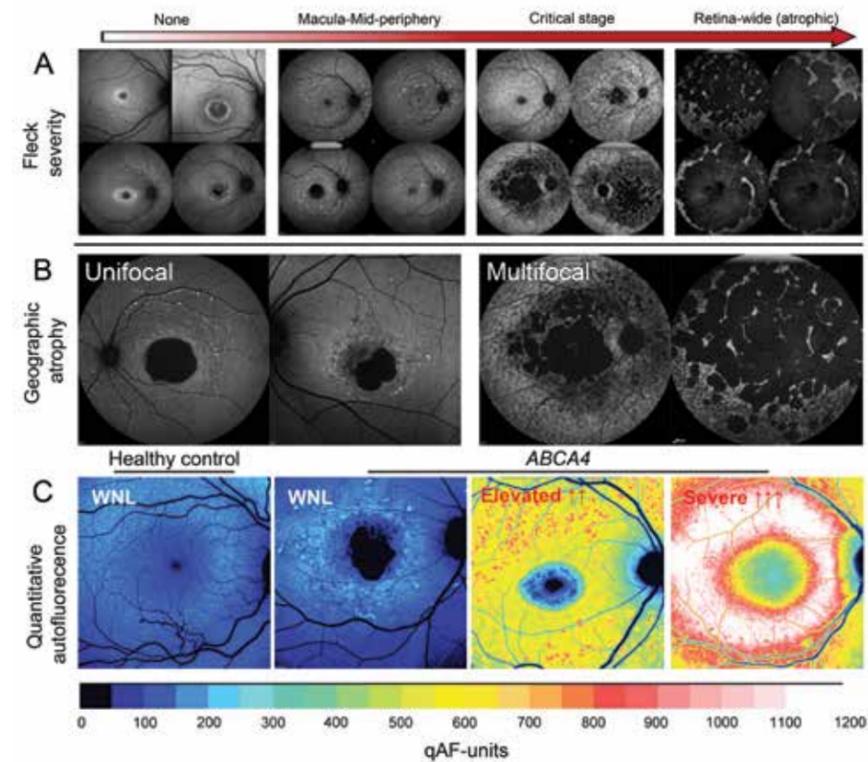


FIGURE 5.h

Disease severity in ABCA4 associated macular degeneration: (A) The spatial distribution of flecks as a function of age is a reflection of lipofuscin accumulation. Confluence of flecks in the retina marks a critical transition stage culminating with retina-wide involvement. (B) Geographic atrophy (black lesions) is defined by the simultaneous loss of RPE and photoreceptor cells. (C) Quantitative autofluorescence (qAF) is an indirect measure of RPE and photoreceptor outer segment lipofuscin, which progressively accumulates due to ABCA4 dysfunction in accordance with disease severity.

Rando Allikmets, PhD
Janet Sparrow, PhD
Stephen Tsang, MD, PhD

Retinal Degenerations

More than 300 genes have been associated with inherited retinal dystrophies, which affect vision in approximately 1 in 2,000 people. One of these genes is the ABCA4 gene and was first identified at Columbia Ophthalmology. More than 1,000 disease-associated variants in ABCA4 have since been described.

Certain ABCA4 mutations cause autosomal recessive Stargardt disease (STGD1), the most frequent form of inherited juvenile macular degeneration. People with STGD1 experience slowly progressing central vision loss, usually beginning in their teens. Almost all people with STGD1 will become legally blind. Other phenotypes caused by ABCA4 mutations range from late-onset, mild cases of central atrophy to very early-onset degeneration throughout the retina.

At Columbia Ophthalmology, we have made significant progress in understanding the disease-causing genetic variation in ABCA4, which has substantially improved diagnostic screening. Thanks to vast improvements in imaging methods, such as optical coherence tomography, autofluorescence (AF) and adaptive optics, we can precisely categorize ABCA4 disease and quantitatively measure its progress. The ABCA4 locus serves as a model of complex genotype/phenotype associations not only for Mendelian eye diseases but for the entire genetic research field. When we know the exact genetic cause of a disease and its clinical phenotype, we can make a proper diagnosis, which is crucial for genetic counseling, predicting disease progression and selecting patients for clinical trials.

TT 54ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTT CGGTAGCATCATTCTATTCGGTTTACACCGCGGGTAACCTTAACA 55CT



FIGURE 5.i

Color fundus photograph from a retinitis pigmentosa patient with mutations in the gene encoding Cytochrome P450, Family 4, Subfamily V, Polypeptide 2 (CYP4V2).

Stephen Tsang, MD, PhD

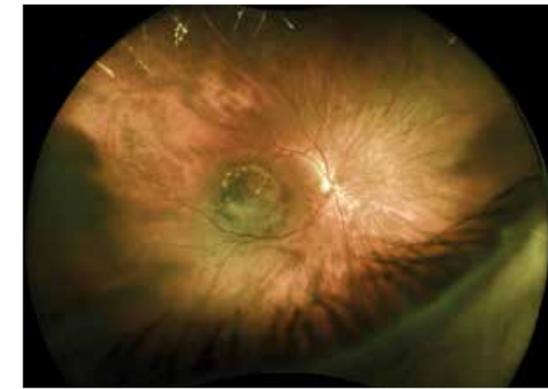
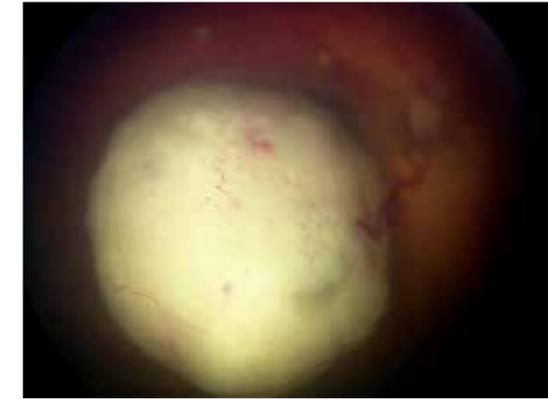


FIGURE 5.j

Retinoblastoma was the first disease in which an abnormal gene was found to be associated with cancer. Genetic testing can be performed to determine if a mutation is inheritable. This information helps to assess risks for second cancers and is used in family planning.

Choroidal melanoma can be evaluated genetically to gain prognostic information. Before treatment, a fine-needle biopsy provides the samples needed for gene profiling and to assess the patient's risk for metastatic disease.

Brian Marr, MD

TT 56 ATT CGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTTCGGTTTACACCGCGGGTAACCTTAACA 57 CT

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a group of hereditary disorders that cause progressive degeneration of the photoreceptors and retinal pigment epithelium (RPE), resulting from mutations in any one of more than 50 genes. These disorders typically first appear in childhood and, because of the many genes involved, can have a widely varying course.

Mutations in the RPE65 gene account for a number of cases of early-onset retinal dystrophy, and positive results from gene therapy trials for RPE63-mediated retinal dystrophy led to the 2018 approval of voretigene neparvovec-rzyl (Luxturna), the first gene therapy for any disease to be approved in the United States. But autosomal dominant forms of RP pose a more difficult challenge for gene therapy, because the defective

gene must be replaced without altering the healthy one. Columbia Ophthalmology is pioneering genetic surgery and has developed a novel technique for the gene editing tool CRISPR, which has successfully restored retinal function in mice afflicted by autosomal dominant RP.

There are now at least six clinical trials underway studying gene therapy as a treatment for RP, with two of those trials headquartered at Columbia Ophthalmology. These trials focus on X-linked RP, an inherited condition caused by mutations in the RPGR gene that causes progressive vision loss in boys and young men. Another precision stem cell trial is in the planning phase, focused on patients with RP associated with mutations in the MERTK gene.

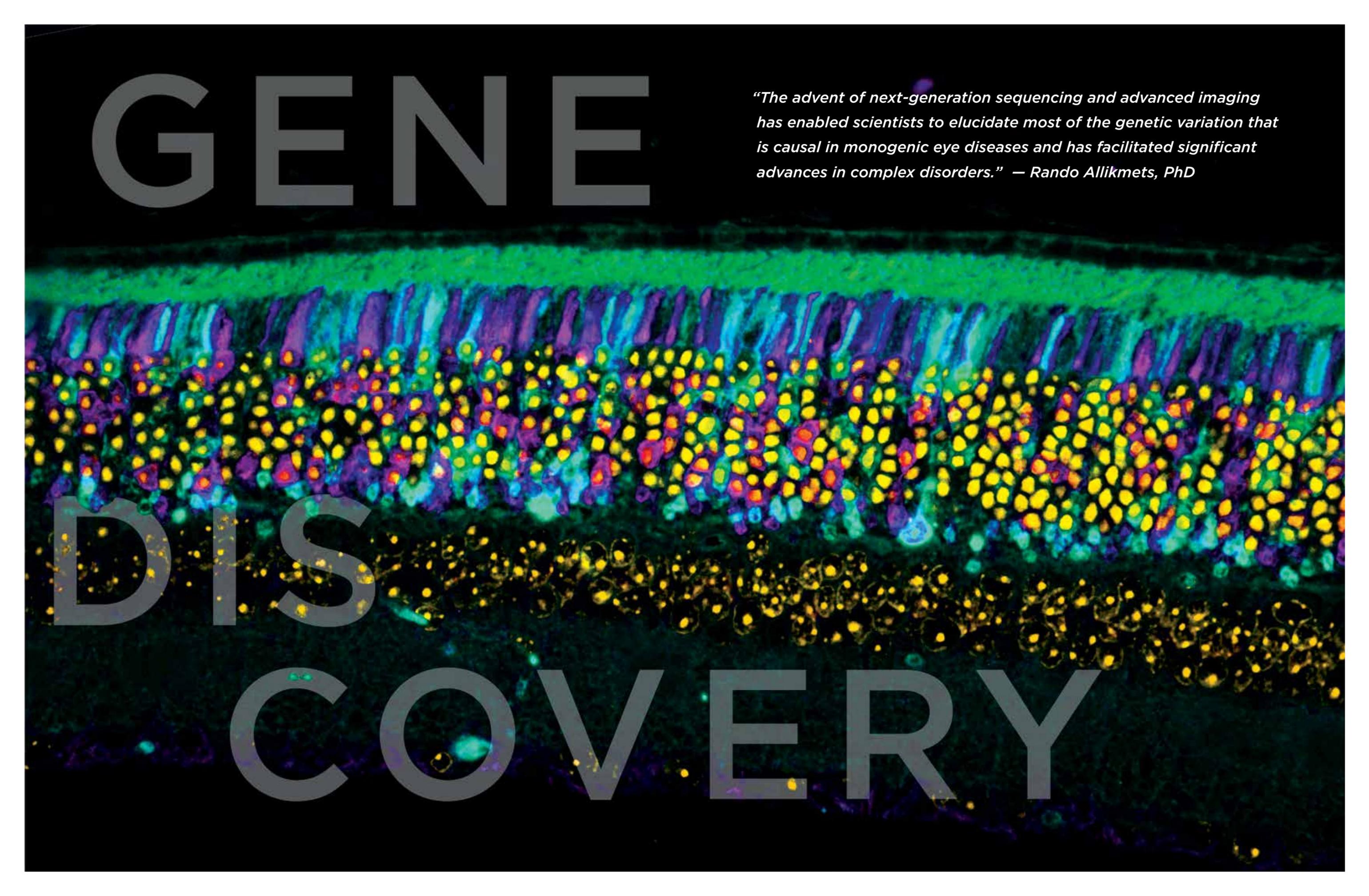
Ocular Oncology

Ocular oncology has a long and storied history at Columbia Ophthalmology. Of eye cancers, retinoblastoma is the most common primary intraocular tumor in children, with approximately 350 new cases occurring in the United States yearly. The retinoblastoma gene found on chromosome 13 occurs sporadically or can be passed down from affected parents. This gene was the first discovered oncogene linking genetic mutation with cancer. Genetic testing can be done on affected individuals and family members that can help predict risks for disease and risk for second cancers. If a germline mutation is found in an individual, then the risk for second cancer and transmission of the gene to offspring is known, and patients can be counseled, managed and screened to achieve the best outcomes with the disease and its sequelae.

The uveal tract consists of the iris, ciliary body and choroid. Uveal melanoma is the second most common type of melanoma, affecting six per million people in the United States. Currently, it can be managed locally with radiation or surgical treatment. Despite high success with control of the primary tumor, metastatic disease can occur in up to 50% of patients. Genetic analysis of uveal melanoma has revealed certain mutations that are predictive of developing metastatic disease. Fine-needle aspiration biopsy at time of primary tumor treatment can be used to obtain the genetic information from the tumor and predict this risk. The genetic information can be used to adjust systemic screening schedules and permit eligibility into adjuvant clinical trials.



GENE

A fluorescence microscopy image of a retina cross-section. The image shows multiple layers of cells. The outermost layer is a thin, bright green line. Below it is a layer of photoreceptors, with rods appearing as purple and blue vertical structures and cones as yellow and orange dots. The inner layers consist of various cell bodies and fibers, appearing in shades of blue, green, and yellow. The overall appearance is a dense, multi-layered structure with a dark background.

“The advent of next-generation sequencing and advanced imaging has enabled scientists to elucidate most of the genetic variation that is causal in monogenic eye diseases and has facilitated significant advances in complex disorders.” — Rando Allikmets, PhD

DISCOVERY

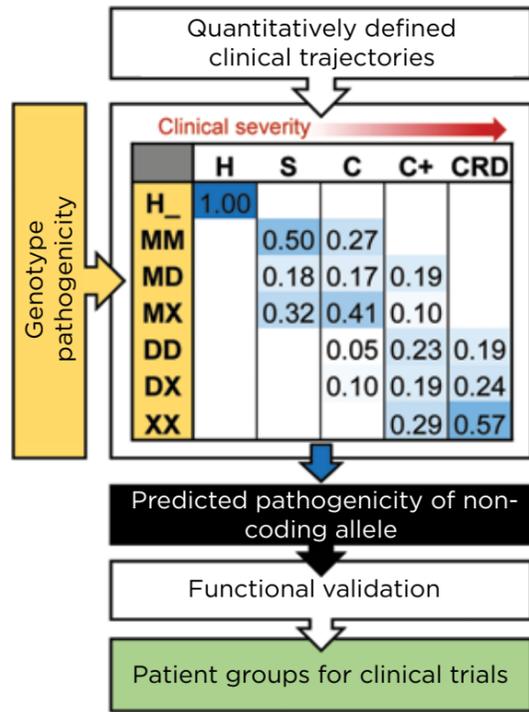
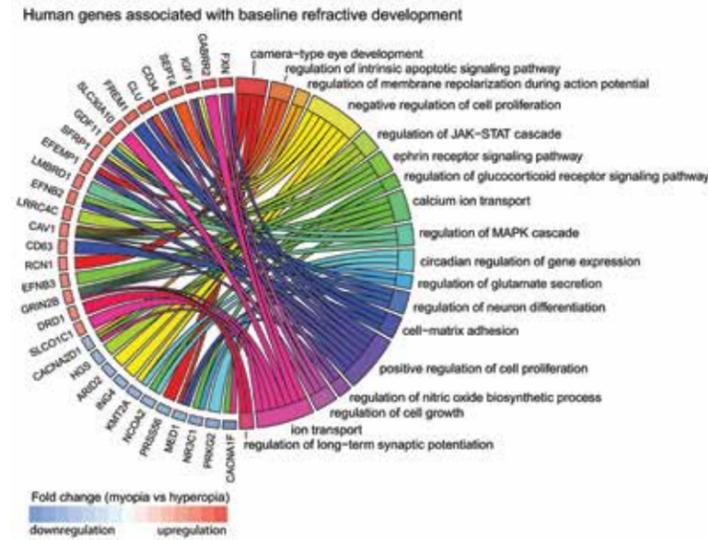


FIGURE 6.a

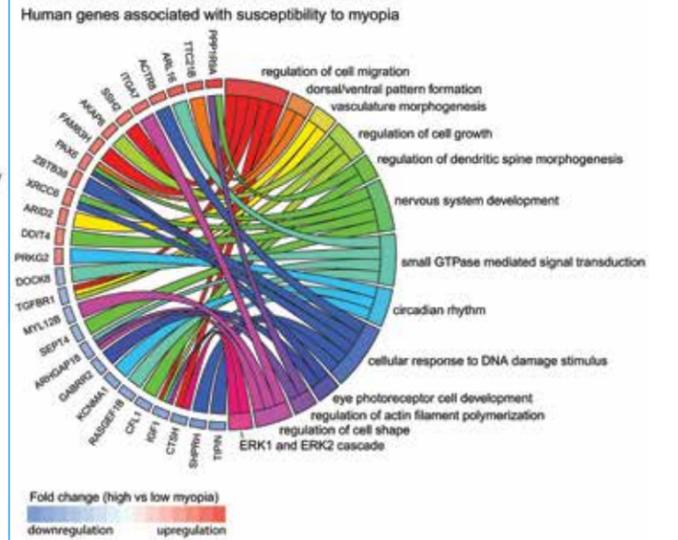
Study scheme for integrated phenotype/genotype correlation studies. Phenotype/genotype correlation matrix for patients with a ABCA4 mutation based on preliminary genetic and clinical data is presented in the center. Quantified clinical data obtained will be correlated with genetic data obtained and analyzed. Integrated data analysis will result in deducing the variant class and relative pathogenicity of DI variants, which are then functionally tested.

Rando Allikmets, PhD



Recent evidence suggests that refractive eye development and the development of myopia are controlled by two overlapping gene sets. This figure shows key genes and top biological processes involved in refractive eye development. The first

FIGURE 6.b



gene set (left panel) is mostly involved in the regulation of baseline refractive development and determines the overall trajectory of refractive eye development. The second gene set (right panel) is chiefly responsible for the gene-environment integration underlying refractive error.

Andrei Tkatchenko, MD, PhD

TT 60ATTTCGGTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGAGTGAGTTCTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGGCGGTAACCTTAACA61CTC

Intersection of Clinical & Research Genetics

Genetic testing is performed on a patient's DNA to reveal known mutations in established disease genes. Those data come from basic and clinical genetic research, which is constantly adding to our knowledge of genetic causality of not only monogenic, Mendelian diseases but also complex disorders such as age-related macular degeneration and glaucoma. While genetic testing of single-gene diseases is established reasonably well, the necessity of testing complex disorders is still under serious discussion. The main arguments against testing late-onset, complex traits are ambiguity of results and lack of treatment options. However, the development of genetic research is constantly adding to our knowledge of causality and also provides ample targets for developing treatment options,

whether directly based on genes or the functional pathways they direct. Direct application of genetic research data is not always straightforward even for monogenic disorders, such as Stargardt/ABCA4 disease, where resulting clinical complexity takes time to be approved by certified labs performing genetic testing. But the real revolution ongoing in genetic research and gene-based therapies allows optimism for substantial advances also in the genetic testing field.

Myopia

Genetic factors modulate the impact of the visual environment on refractive eye development and play an important role in the development of myopia (nearsightedness). We have recently found that over 900 retinal genes, initially identified in the mouse model of myopia, are subjected to genetic variation causing myopia in humans. These genes are associated with over 50 signaling pathways, many of which are involved in the processing of positive and negative optical defocus known to regulate refractive eye development.

Importantly, these signaling pathways were found to be highly conserved across distant vertebrate species, including chickens, mice, marmoset monkeys and humans—suggesting that systems genetics studies in animal models can identify genetic

networks and signaling pathways underlying the development of human myopia.

Combining systems genetic studies in animal models and humans, Columbia Ophthalmology has characterized the genetic networks and signaling pathways involved in refractive eye development. Using that information, we have developed a pharmacogenomic pipeline for anti-myopia drug development. This approach already has produced several promising candidates, which are currently being studied in the laboratory.

Overleaf: AAV-based CRISPR therapy in a rhodopsin mutant mouse. The mouse model was crossed with Brainbow 2.1 reporter mouse in order to evaluate the transduction efficiency. Stephen Tsang, MD, PhD

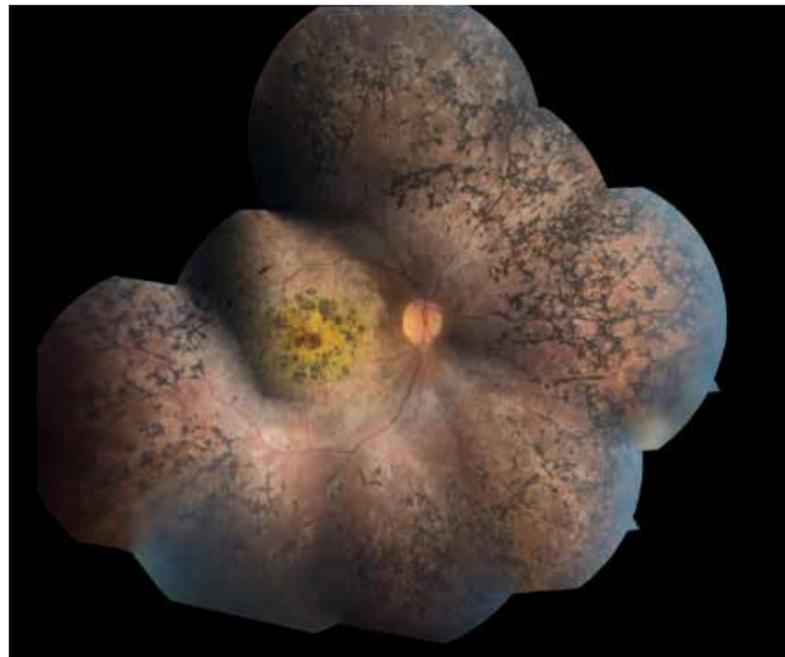


FIGURE 6.c

A retinal photograph demonstrating characteristic findings seen in patients with retinitis pigmentosa, including "bone spiculating" in peripheral retina, which are the fine, lacey black changes. In addition, the retinal blood vessels are attenuated, and the optic nerve is slightly pale.

Stephen Tsang, MD, PhD

A
G

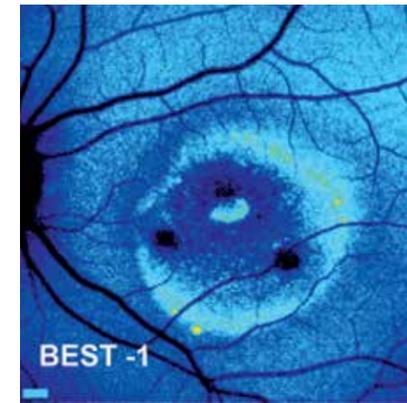
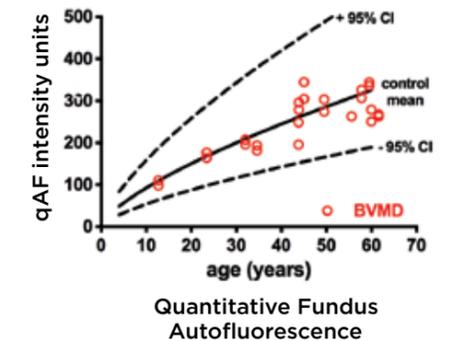


FIGURE 6.d



Best Disease

T
C

Best disease is caused by mutations in the gene BEST1. Deficiency in the BEST1 protein leads to fluid accumulation in the subretinal space leading to a dome-shaped lesion separating neural retina from retinal pigment epithelium. Scientists at Columbia have determined how mutations can cause the protein to malfunction. The scientists have also demonstrated that, contrary to what had been assumed, a retina-wide increase in lipofuscin does not occur. Instead the central egg-yolk-like lesion acquires autofluorescence secondary to photoreceptor cell damage.

Color-coded quantitative fundus autofluorescence (qAF) images. In the image acquired from the patient diagnosed with Best disease, the central lesion is a paler blue, indicating higher-intensity fundus autofluorescence. Outside the lesion, the levels are not different than in the healthy eye. The graph above shows that qAF values for Best patients (red circles) are within the range of healthy eyes (black lines).

Janet Sparrow, PhD
Stephen Tsang, MD, PhD

Retinitis Pigmentosa

Associated with more than 80 genes, retinitis pigmentosa (RP) is a heterogenous condition characterized by the breakdown and loss of rods, the photoreceptors in the retina that enable peripheral and night vision. Over time, the deterioration of rods compromises the function of cones, the color-sensing photoreceptors, leading to night blindness, tunnel vision and, eventually, complete blindness.

Although gene therapy has shown promise in RP, it is complicated by the fact that defects in at least 80 genes have been linked to the disorder, and each genetic defect would require a different therapy. As of 2020, there are about 20 clinical trials underway studying different gene supplementation approaches

for the treatment of RP. Because rods are among the most metabolically active cells in the body, burning glucose to release energy, it is possible that diseased rods could be restored by reprogramming their sugar metabolism. At Columbia, we have shown that this precision metabolic reprogramming can improve the survival and function of affected rods and cones in at least one type of RP. Since many forms of the disorder have the same metabolic error, precision reprogramming could conceivably be applied to a wide range of RP patients.

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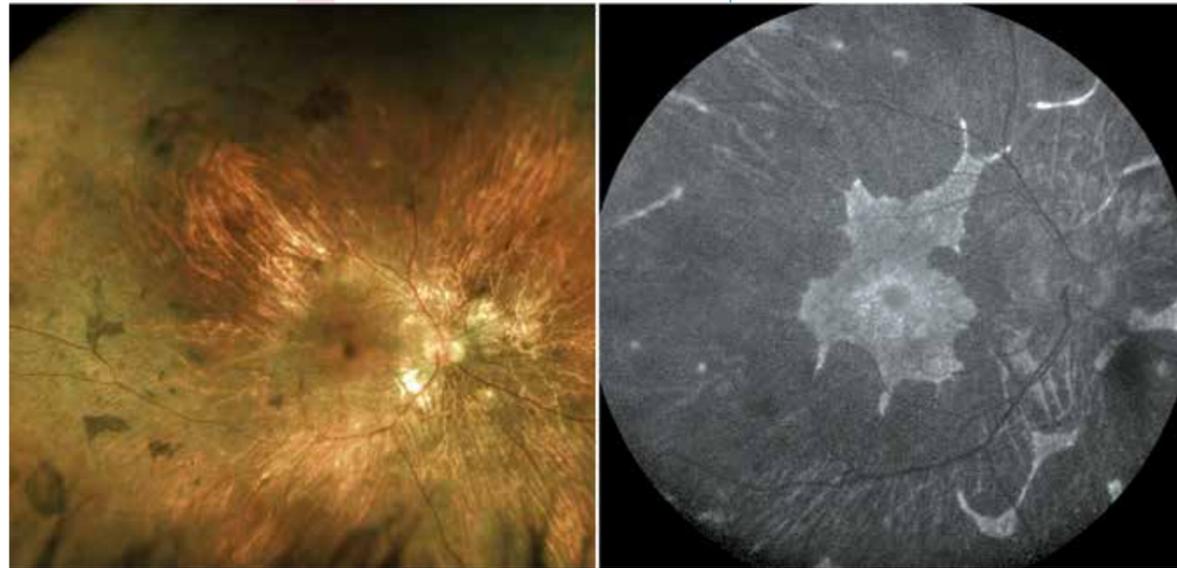
CLINICAL TRIALS

“Clinical trials are designed to test new approaches to the treatment of patients with eye disease. The trials are conducted in phases that build on one another, the goal being to establish the safety and effectiveness of the interventions.”

— Stephen Tsang, MD, PhD



FIGURE 7.a



Choroideremia

Choroideremia is an example of an ocular disease that is currently being investigated by both clinicians and scientists within Columbia Ophthalmology. Choroideremia is an X-linked recessive disorder affecting approximately 1 in 50,000 males with disease onset in affected males occurring in childhood. Loss of sight progresses to legal blindness by the fourth decade. Our investigators have discovered a phenotype of choroideremia that is also expressed in some carriers of the disease gene. This means that characteristic findings associated with the disease are seen not only in confirmed patients but also in women that are “carriers” of the genetic mutations but never develop the disease themselves.

The Columbia Department of Ophthalmology has participated

Choroideremia-affected males present with progressive degeneration of retinal cells and underlying choroid (left). Preserved cells in the center of the retina are visible as speckled islands in fundus autofluorescence images (right).

Janet Sparrow, PhD

in two multicentered, clinical trials focused on choroideremia. One of these studies’ aims is to collect information on the natural history of the disease so as to establish diagnostic measures that can be used to measure treatment outcomes during the development of novel therapies. The objective of the second clinical trial is to evaluate the safety and tolerability of a gene therapy approach to the treatment of patients having a genetically confirmed diagnosis of choroideremia.

FIGURE 7.b

The Columbia University Irving Medical Center developed *RecruitMe*, a recruitment tool meant to connect those who want to participate in clinical trials or research studies to the researchers that are conducting them. **Lisa Hark, PhD, RD**



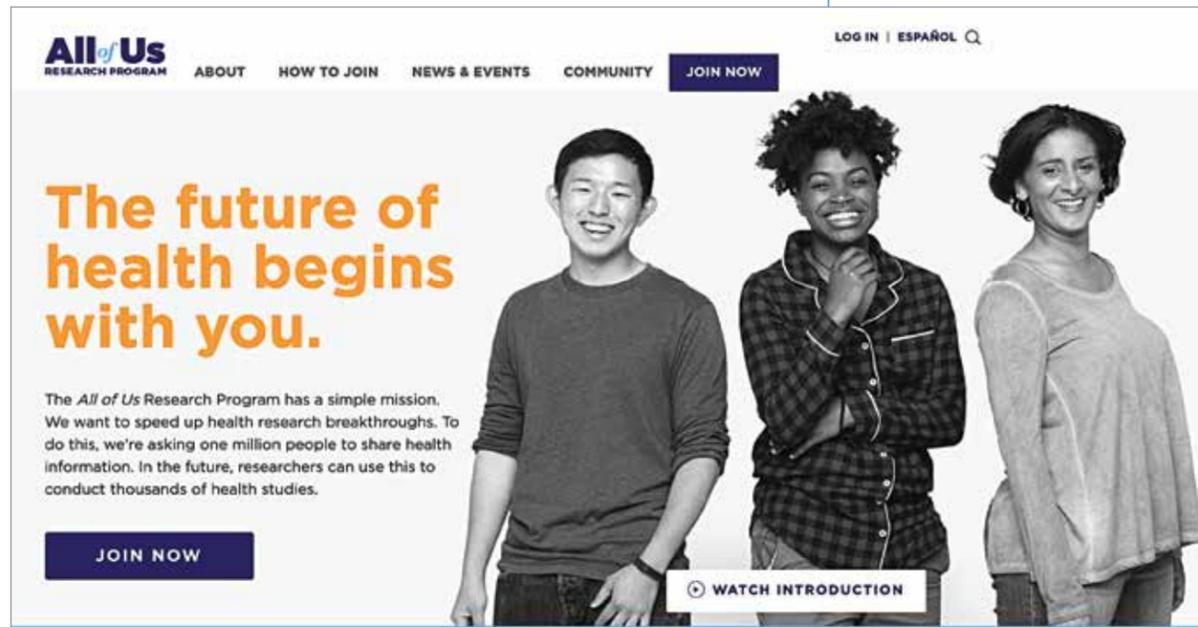
Natural History Studies

Many ocular conditions have a chronic and progressive nature. Therefore, the goal of treatment is to slow or halt the speed of progression, as is the case for diseases such as glaucoma, macular degeneration and retinal dystrophies. Natural history studies are research investigations in which patients affected by these chronic, progressive conditions are followed for relatively long periods of time to determine the course of the disease. For conditions with standard therapies, such as glaucoma, natural history studies determine the average rate of progression among patients while they are treated, as well as how much variability there is between patients with regard to their outcomes. For conditions that lack standard therapies, such as “orphan” diseases, these studies help better determine how rapidly they progress

and identify individuals at greatest risk of becoming visually impaired. In both cases, the goal of these studies is to generate pristine, reliable data for the design of clinical trials testing novel therapies that could improve their outcomes. Patients who participate in natural history studies may be offered the opportunity to participate in subsequent clinical trials that could potentially alter the course of diseases for which no treatment is currently available. For treatable diseases, they can help identify safer and more effective forms of therapy. The Clinical Trials Unit of the Department of Ophthalmology helps design and conduct a number of natural history studies that will serve as the basis for new therapies. These trials can make the difference in preventing blindness during a patient’s lifetime.

Overleaf: Structural model of the genome surgery nuclease Cas9 interacting with a gRNA.
 Gabriel Velez, MD, PhD;
 Vinit Mahajan, MD, PhD;
 Stephen Tsang, MD PhD

FIGURE 7.c



Clinical Trials Unit

The All of Us Research Program is a momentous effort to advance individualized prevention, treatment and care for people of all backgrounds. This national consortium is led by the Columbia University Irving Medical Center with the aim to enroll 1 million diverse people with differences in lifestyles, environments, and biological makeup, including genes. It is an example of the focus on Precision Medicine that embraces the entire Medical Center.

C. Gustavo De Moraes, MD, MPH, PhD

The Clinical Trials Unit (CTU) in the Department of Ophthalmology supervises all clinical research at the Edward S. Harkness Eye Institute. The CTU staff includes 12 full-time clinical research coordinators who manage the entire process of human research, including protocol development, institutional review board preparation and submission, participant recruitment, clinical trial enrollment, study procedures and database management. Principal investigators lead our research studies, and research coordinators aid in interfacing with sponsors and regulatory agencies. All research studies require Institutional Review Board (IRB) approval from Columbia's Human Research Protection Office, which requires adherence to rigorous ethical guidelines in order to protect all participants.

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 gene therapy technique for conditions including age-related macular degeneration (AMD), Stargardt disease, achromatopsia, glaucoma, retinitis pigmentosa and choroideremia. Long-term studies of retinal degenerations, corneal disease, and structure and function of the optic nerve often span many years and require the close coordination of study patients, coordinators, investigators and monitoring physicians.

Microbiome, Thyroid Disease & Thyroid Eye Disease

Columbia Ophthalmology works with physicians and researchers from across the entire Columbia University to accelerate discovery science and to promote health for all who seek care. An example of such is found in the research being conducted in diseases associated with the thyroid gland. The thyroid gland, located in the neck, produces a hormone called thyroxin that helps to regulate body metabolism. Graves' disease of the thyroid can be life-altering, often requiring radioactive iodine to reduce thyroxin production, surgery and the need for chronic medications. Its highly associated counterpart, thyroid eye disease, can cause the eyes to appear prominent and in some cases can be disfiguring and vision-threatening. Though we know that antibodies to the thyroid gland can also attack orbital tissues (the tissues

FIGURE 7.d



CT scan of the orbits showing enlargement of the extraocular muscles in the setting of thyroid eye disease. Lora Glass, MD

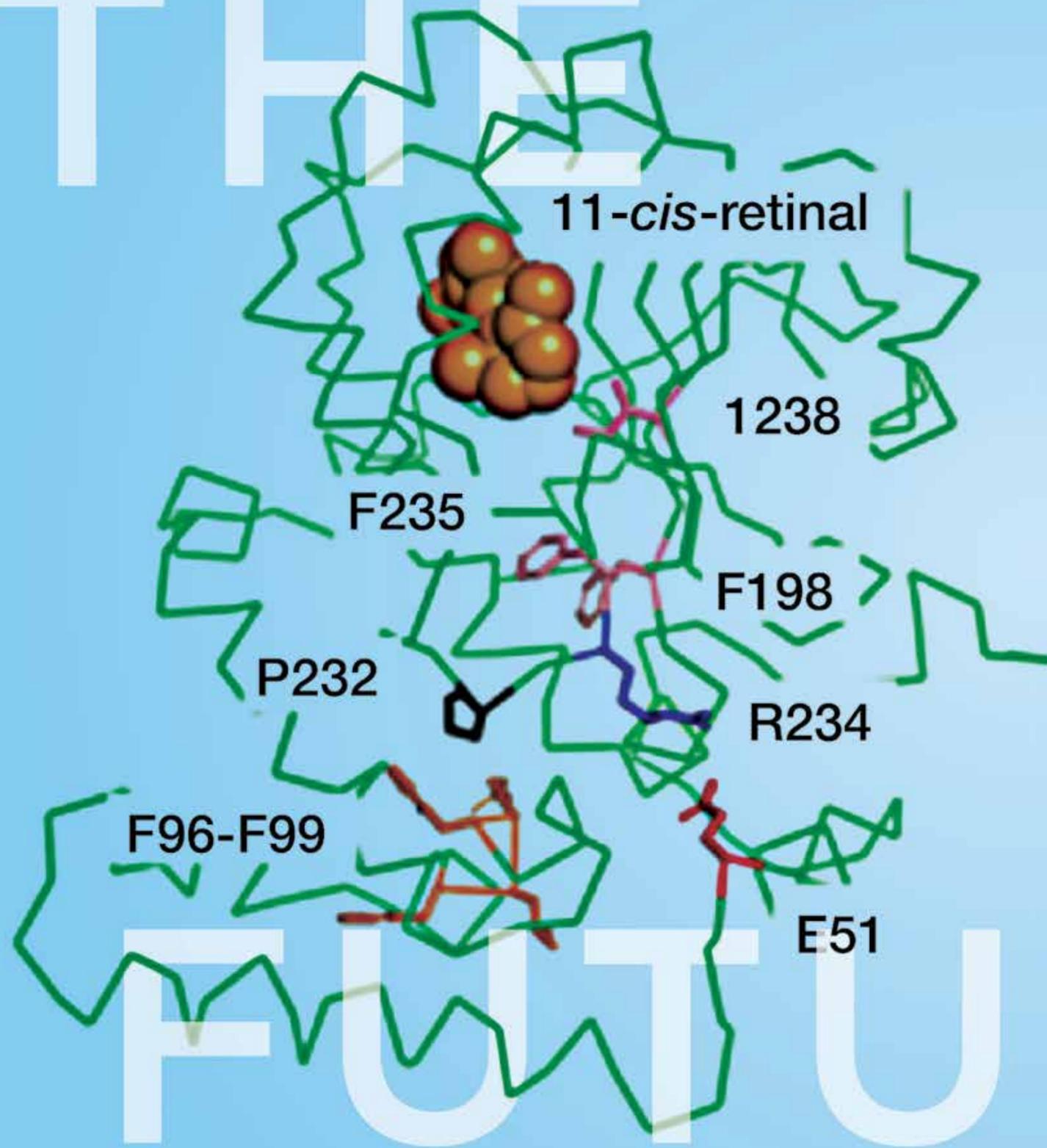
surrounding the eye), we do not yet understand why some patients with Graves' disease develop thyroid eye disease, while others do not.

Some studies suggest that the diversity and ratios of intestinal bacteria (the microbiome) have an impact on Graves' disease and other autoimmune conditions. Columbia Ophthalmology is working with colleagues in Endocrinology, General Surgery, Gastrointestinal Disorders, and Precision & Genomic Medicine to unravel this mystery. We are in the midst of a multi-institutional study of the microbiome diversity of patients with Graves' disease, patients with Graves' disease and thyroid eye disease, and matched counterparts without either condition, in an effort to better understand whether microbiome content—in the eye or gastrointestinal tract—may be responsible for elevated risks of thyroid eye disease presentation and severity. This is an example of a collaborative clinical trial that extends far beyond ophthalmology.

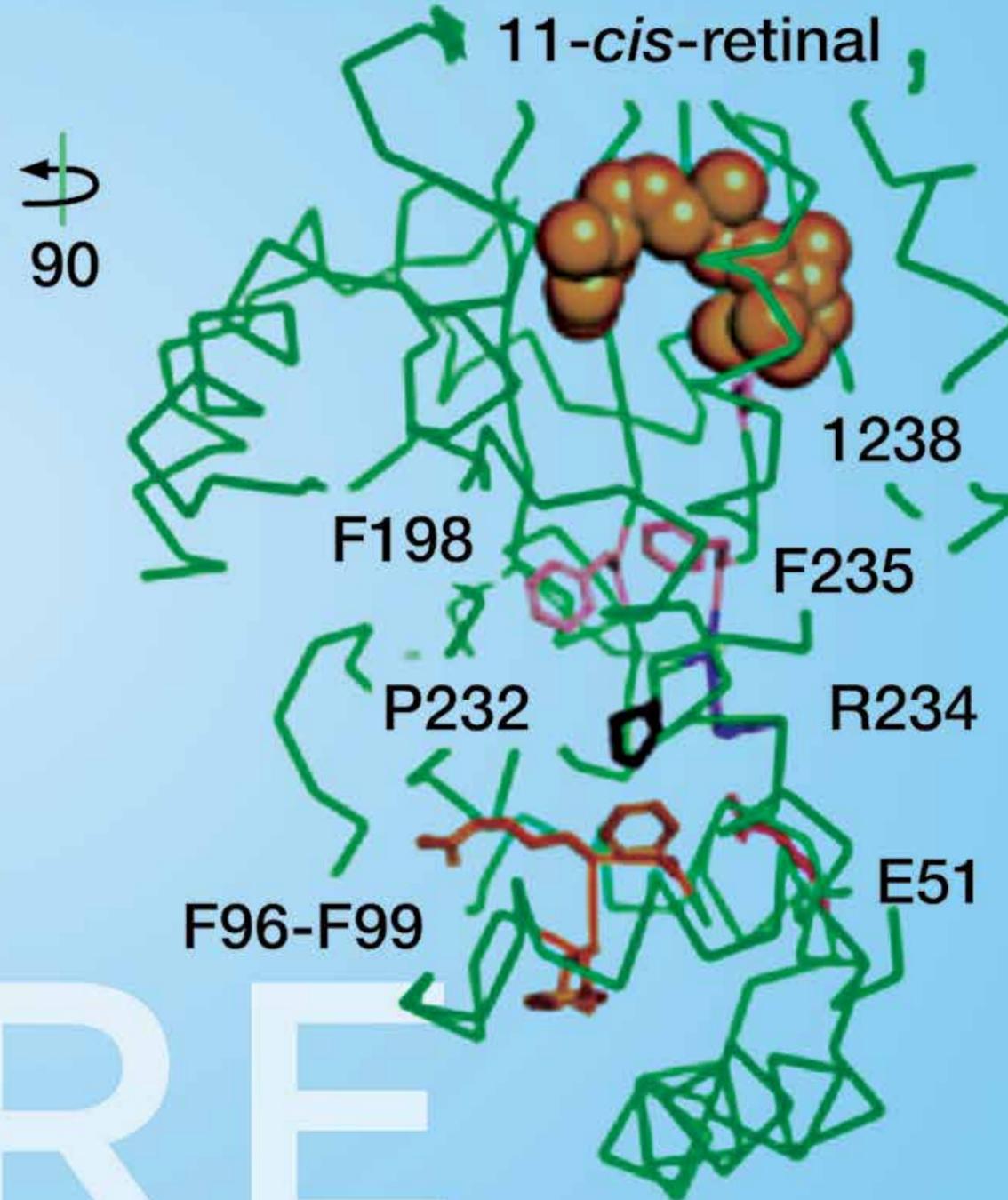


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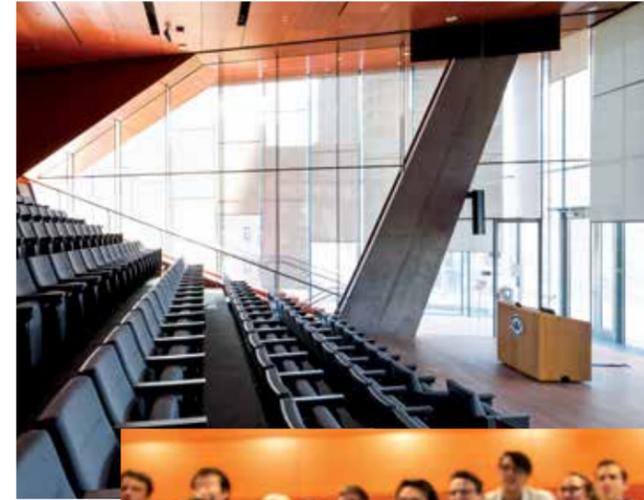
“The Applied Genetics and Precision Ophthalmology™ revolution will require a coordinated effort among scientists, clinicians, educators and institutes to push forward into a new era of individualized treatment and cures for blinding eye diseases and restoring vision to those who have lost it.” — Jeffrey Liebmann, MD



FUTURE



The Roy and Diana Vagelos Education Center at the Columbia University Irving Medical Center provides a state-of-the-art venue for educating the physicians and scientists of the future.



The Future Begins with Education

Genetics Residency and Fellowship

To place the field of Ophthalmic Applied Genetics on solid clinical ground for the future and to better serve our patients, we recognize that ophthalmology needs to be the next specialty to offer the option of formal training in the fundamentals of human genetics. With leaders in ophthalmology and genetics at the helm of this effort, Columbia Ophthalmology plans to be the first ophthalmology department to provide formal opportunities for dual training in ophthalmology and medical genetics. A combined residency or fellowship track will prepare our trainees to

become board certified in both ophthalmology and human genetics. This training pathway will be offered to future ophthalmologists who recognize the impact that medical and molecular genetics will have on the field. Our approach will prepare dual-trained physicians who can tackle future challenges in care, diagnostics and therapy in ophthalmic genetics.

Dual training in medical genetics has been successfully implemented in other fields of medicine in which genetics is fundamentally intertwined with the delivery of medical care, such as pediatrics and maternal-fetal medicine. A combined ophthalmology-medical genetics residency track, or a post-residency fellowship track

that allows for board-eligibility ophthalmology and medical genetics, provides an ideal way to train the future ophthalmic geneticists to deliver the highest-quality care to patients. This approach will allow our ophthalmic geneticists to effectively direct the multiple facets of an ophthalmic genetics team, whether it be communicating with molecular pathologists, genetic counselors, patients, the health care industry, foundations or governmental agencies.

Incorporating genetic education into resident and fellowship education

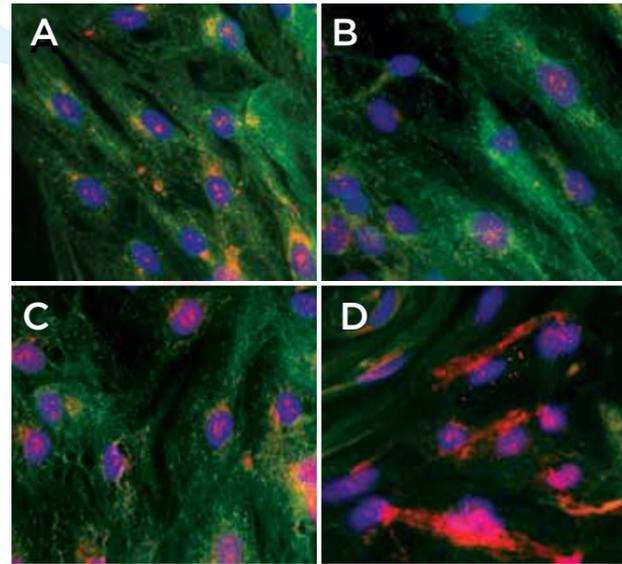
In addition to providing a formal path to dual training in ophthalmology and genetics, we also provide

ongoing educational opportunities in ophthalmic genetics for all subspecialties of ophthalmology, creating a higher standard for the education of future ophthalmologists and a model for other training programs. Within our residency program, we have given residents an opportunity to learn from leaders in the field at Columbia and elsewhere. Within the department, we have created multiple educational opportunities with emphasis on ophthalmic genetics. These conferences create an opportunity for ophthalmic geneticists at all levels to convene and discuss some of the most challenging cases in ophthalmic genetics. Moreover, our internationally recognized Basic

Science Course in Ophthalmology regularly invites some of the most recognized experts in inherited eye diseases to lecture to our residents, fellows and students from different parts of the world. These educational opportunities allow both novices and experts to learn more about ophthalmic genetics and to create leaders who will bring cutting-edge care to the clinic.

Overleaf: Crystal structure of cellular retinaldehyde-binding protein, a component of the visual cycle that binds the 11-cis-retinal (orange spheres) chromophore.
 Tingting Yang, PhD;
 Stephen Tsang, MD, PhD;
 Janet Sparrow, PhD

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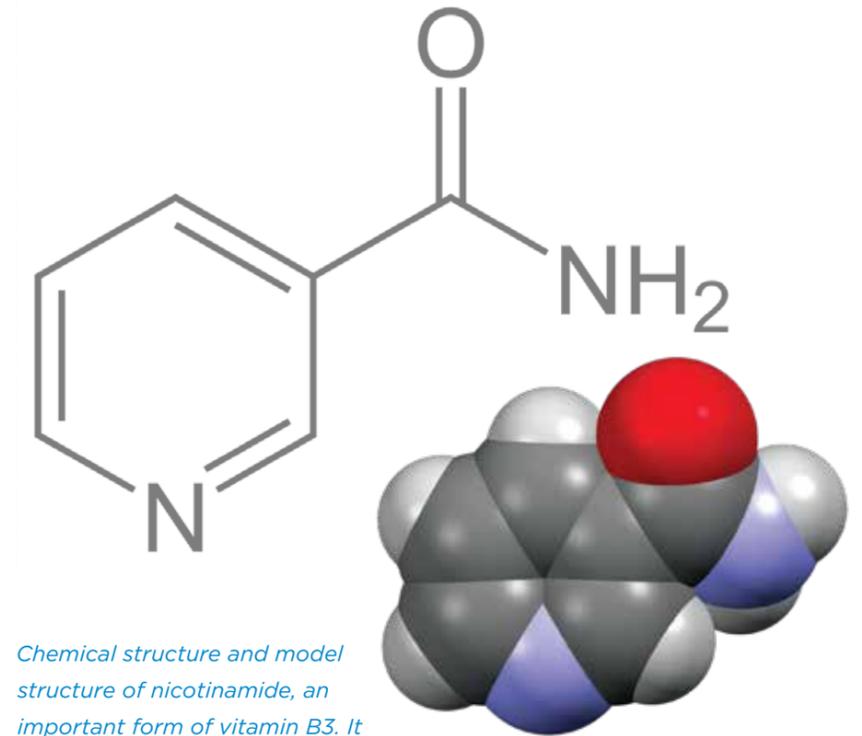


PHILANTHROPIC PARTNERSHIPS

Cells from patient with exfoliation glaucoma were exposed to the compound solvent (A) or test compounds (B-D). Compound B reduces the intensity of red staining, indicating that it facilitates substrate degradation and thus may be considered as a potential treatment. Compounds C and D increase the intensity, which indicates the undesired inhibitory activity. **Konstantin Petrukhin, PhD**

New Drug Development from Pharmacogenetics

Exfoliation glaucoma, accounting for 25% of all glaucoma worldwide, is a complex late-onset disease characterized by abnormal production and accumulation of fibrillary deposits called exfoliation material (XFM) in the anterior segment of the eye. Given the causative role of XFM in the pathogenesis of exfoliation glaucoma (XFG), it seems reasonable to suggest that inhibition of the formation of exfoliation aggregates represents a solid treatment strategy for XFG. A diminished capacity of cells in



Chemical structure and model structure of nicotinamide, an important form of vitamin B3. It has an amide (NH₂) component, or group of unique biochemical properties compared to the other forms of vitamin B3.

The Future Is Now: The Brown Initiative

The ability to create the programs and teams for the future depends on collaboration among research scientists, clinicians, patients, institutions and philanthropists. The Brown Initiative, made possible by a generous donation by Shirlee and Bernard Brown, longtime supporters of the Department of Ophthalmology and glaucoma research, seeks to enhance knowledge across a broad spectrum of glaucoma research and translate this newfound information into novel, patient-friendly treatments. To accomplish these goals, glaucoma researchers are focusing on three areas of intense interest: gene discovery, development of new medications, and devising ways of protecting the optic nerve from damage. This unique program serves as a model for accelerating and translating Precision Ophthalmology™

and Applied Genetics into tools that benefit patients.

Gene Discovery

A well-characterized phenotype facilitates genetic studies of any disease. Pigmentary glaucoma, a subtype of open-angle glaucoma, has a striking and very specific clinical presentation and primarily affects young adults in the prime of life. This study goal seeks to determine the genetic basis of this subset of glaucoma by identifying the genes that cause it. After our clinicians identify patients with this disease and blood samples are taken, our basic science genetics research team explores the genome of each patient to find the common gene defects among them to serve as target candidates for research to identify the proteins encoded by the genes and find ways to overcome them.

the eye for degradation of denatured and misfolded proteins seems to underpin the development of protein aggregates in XFG. As in many other age-related diseases, aggregate accumulation in XFG seems to be caused by aberrations in cellular degradation—specifically, in the mechanism of autophagy. We recently identified a drug-like lead molecule CU1079 as a potent lysosomal ion channel modulator that can improve degradation of misfolded and aggregated proteins in XFG, thus preventing the formation of exfoliation deposits. Our immediate objective is to perform characterization of CU1078 in order to develop data required for submission of the NIH grant application that will support optimization of this lead molecule and developing the XFG drug. Drug

studies are performed in a cell line established from a patient with exfoliation glaucoma. We also plan to conduct animal studies in mouse and rabbit animal models in order to establish in vivo activity of the test compound.

Nutritional Supplementation: Vitamin B3 Study

The earliest evidence of glaucoma damage occurs in mitochondria, which are present in every cell in our bodies. Mitochondria are critically important for the optic nerve cells because they are responsible for creating the energy that each of these cells uses. This study is focused on the clinical implications of promising basic research in vitamin B3 (nicotinamide) on glaucoma. It has been demonstrated in a mouse model that at the lowest dose tested, nicotinamide enhanced mitochondrial

health and prevented structural and functional loss of retinal ganglion cells, despite continued elevation of intraocular pressure. In the same mouse model, gene therapy targeting the retinal pathway that produces nicotinamide protected 70% of mice from glaucoma damage over 12 months—and the combination of gene therapy with nicotinamide supplementation produced the best protection of all. This identification of the cellular mechanisms underlying early glaucoma progression has opened a new avenue for exploration, and we are in the midst of human clinical trials that will assess whether neurodegeneration can be treated with vitamin B3 dietary supplementation, along with other compounds to promote mitochondrial health.

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THE FUTURE



Building an Ophthalmic Genetic Therapy Institute

Columbia Ophthalmology's Applied Genetics Initiative is one of only a handful of genetic eye disease programs in the world. We offer people with suspected genetic eye disorders access to a comprehensive range of services, including screening, diagnostics, genetic counseling and research study participation, all under one roof. Patients can be referred to the Applied Genetics Initiative either by an outside clinician or through internal referral by another Columbia physician. All patients undergo diagnostic testing and DNA analysis, along with genetic counseling.

If the analysis is negative—that is, there is no currently known gene associated with their condition—the

A VISION OF THE FUTURE

patient is offered the opportunity to participate in our gene discovery research program, with their demographic and clinical data stored in a database and their DNA samples maintained in Columbia Ophthalmology's BioBank. As more genes involved with ocular disease are identified, we will have a record of these patients and be able to screen their test results for the new genes.

For patients whose eye disease has been linked to a specific gene, his or her case will be presented to a review panel of experts that is responsible for developing a management plan based on the patient's genetic findings.

The Applied Genetics Initiative builds on an established system of referrals to Precision Ophthalmology™ studies ongoing in the Department, the University and around the world. Our past and ongoing gene discovery and intervention programs make Columbia Ophthalmology a center for innovation in this rapidly emerging and critically important field and an ideal home for a world-class clinical ophthalmic genetics program.



Images of the entrance to the Edward S. Harkness Eye Institute and the Roy and Diana Vagelos Education Center.



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The Russell Berrie Diabetic Retinopathy Research Unit

Basic Science Course in Ophthalmology

Foley Retina Research Fund

Bernard and Shirlee Brown Glaucoma Initiative

Anne Stean Corneal Research Fund

Flanzer Eye Center

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Jonas Children's Vision Care

Kirby Fellowship

The Louis V. Gerstner Jr. Clinical Research Center in Vision at Columbia University

Florence and Herbert Irving Translational Vision Research Laboratory

Gloria and Louis Flanzer Vision Care Center

Jean and Kent Sheng Glaucoma Fellowship

Foley Clinical Retina Fellowship

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\$10.4M

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28

Physicians in National & Regional Rankings

ABSTRACTS & PUBLICATIONS

322

In the Past Year

ONGOING CLINICAL TRIALS

40

PATIENT VISITS ANNUALLY

>100,000

SURGERIES ANNUALLY

>5,000

33%

Growth In Overall Departmental Budget Over 5 Years

272

Total Staff and Faculty

26

Part-Time Faculty

46

Full-Time Faculty

12

Ophthalmology Residents

10

Clinical Fellows

16

Postdoctoral Fellows

30%

Growth In Overall Grant Funding Over 3 Years

PATIENTS FROM 87 COUNTRIES



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Design: hgDesign NYC

Writing: Gina Shaw

Printing: The Standard Group

Editors: George A. Cioffi, MD
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Photography: Amelia Panico;
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Special thanks to
Ophthalmology Photography
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