

PRECISION OPHTHALMOLOGY™

COLUMBIA UNIVERSITY MEDICAL CENTER

DEPARTMENT
OF
OPHTHALMOLOGY



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PRECISION OPHTHALMOLOGY™

DEPARTMENT OF OPHTHALMOLOGY

COLUMBIA UNIVERSITY MEDICAL CENTER

NEWYORK-PRESBYTERIAN HOSPITAL

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THE DEPARTMENT OF OPHTHALMOLOGY
AT COLUMBIA UNIVERSITY 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 COLLABORATION BETWEEN OUR
OUTSTANDING, COMPASSIONATE PHYSICIANS
AND OUR TALENTED SCIENTISTS.

AT THE SAME TIME, WE TRAIN
OPHTHALMOLOGISTS AND SCIENTISTS TO BE
THE FUTURE LEADERS IN THE FIELD.
WE HAVE SUCCESSFULLY DEVELOPED NEW
DRUGS, DEVICES AND PROCEDURES TO
ENHANCE THE LIVES OF OUR PATIENTS. THAT
GROUNDBREAKING TRADITION CONTINUES
TODAY WITH **PRECISION OPHTHALMOLOGY™** AS
EVIDENCED IN THE FOLLOWING PAGES.



THE EDWARD S. HARKNESS EYE INSTITUTE TEAM

OUR VISION OF THE FUTURE

OVER THE PAST 150 YEARS, the Department of Ophthalmology at Columbia University Medical Center has

been at the forefront of most major advances in vision care. Today, we stand poised to transform the field yet again, as our specialty converges around a revolutionary concept called Precision Ophthalmology.™

Defined as customized genetic, diagnostic, and translational clinical care, Precision Ophthalmology™ uses each patient's own genetic profile to tailor a course of treatment specifically designed for him or her.

This approach aims to correct "nature's errors" and cure disorders that have impacted human beings for as long as we can remember. To create these individualized treatments, **we are merging previously disparate bodies of scientific knowledge** ranging from molecular and cellular biology to imaging, bio-informatics, and genomics in a team approach to medicine that combines research, the talents of our basic scientists and the clinical skills of our physicians.

Our integrative Precision Ophthalmology™

approach is already bearing fruit.

One of our world-renowned researchers is currently using translational genetics to study the way the eye is formed. Other investigators are collaborating to unlock the genetic basis of myopia and retinal degenerations, and to use these insights to develop novel therapies to prevent disease progression. Our glaucoma scientists are combining novel insights into the cellular causes of this serious disease to propose new diagnostic and therapeutic paradigms.

We have launched a major Clinical Trials Unit to speed progress of new therapies based on these and other discoveries. In addition, several of our laboratories have combined to genotype over 800 patients with retinitis pigmentosa and juvenile macular degeneration. Our researchers are now awaiting FDA approval for gene therapy approaches to restore these patients' sight and peace of mind. Such breakthroughs in vision science will empower our patients, both young and old, to live much more fulfilling lives.

Thanks to our place within Columbia University, one of the world's leading institutions for medical research, and our partnership with NewYork-Presbyterian Hospital, ranked sixth in the nation and the top hospital in New York, our Department of Ophthalmology is uniquely

positioned to realize the full potential of Precision Ophthalmology.™ When the White House announced a national initiative to advance Precision Medicine, Columbia embraced it wholeheartedly, securing major federal funding and placing itself at the vanguard of this revolution in healthcare.

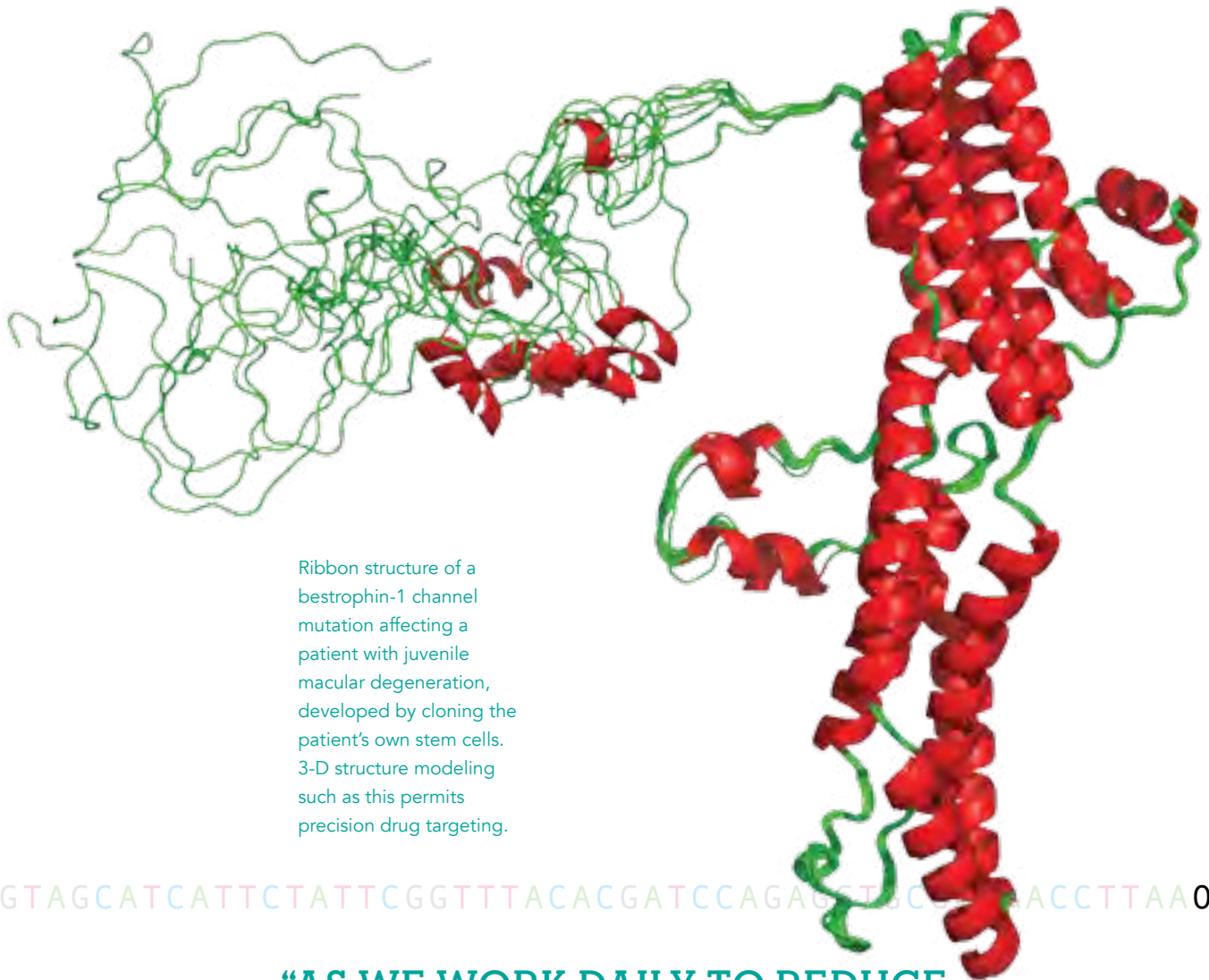
The Columbia Precision Medicine Initiative aligns scientific, medical and administrative leaders across the Columbia University campus, and our program is a cornerstone of this initiative. Within these pages, you will learn how we are unlocking the potential of Precision Ophthalmology.™ to assess disease risk among our patients, deploy a fine-tuned pharmacogenetics strategy for selecting among existing treatments, and develop the next generation of innovative therapies that will

protect and restore vision. Precision Ophthalmology.™ allows us to take a true patient-specific approach to vision care, diagnosing and treating eye disorders that affect large populations, but at a highly personalized, individual level. It is the ophthalmology of tomorrow, and we are excited to be bringing it to our patients today.



A handwritten signature in black ink, appearing to read 'Jack Cioffi'.

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



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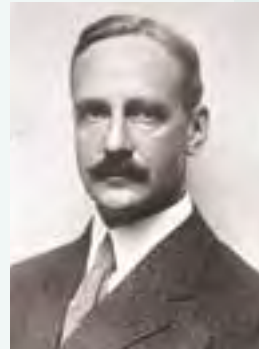
**“AS WE WORK DAILY TO REDUCE
THE BURDEN OF EYE DISEASE AND RESTORE VISION
FOR OUR PATIENTS, VISION SCIENTISTS PARTNER
WITH US TO USE PRECISION OPHTHALMOLOGY™
IN ADVANCING REVOLUTIONARY NEW THERAPIES
DESIGNED FOR EACH INDIVIDUAL.”**

— Stanley Chang, MD

DEPARTMENT MILESTONES



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

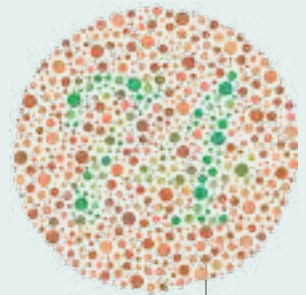


1903 Arnold H. Knapp, MD, son of Herman, appointed Professor of Ophthalmology at P&S and becomes the third clinic director.

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



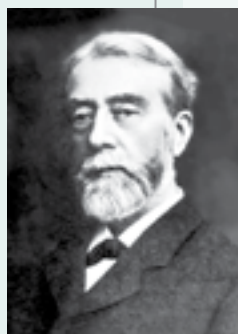
1869 Herman J. Knapp, MD, establishes the New York Ophthalmic and Aural Institute, which later becomes the Herman Knapp Memorial Hospital.



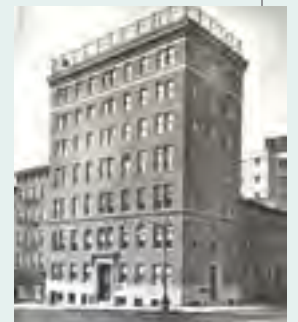
G C A T C A T T C A T T C T T A C A C G A T C C A G A G G T G C G T A A C C T T A A C C T C G C T A C G A A G C A



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.



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



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

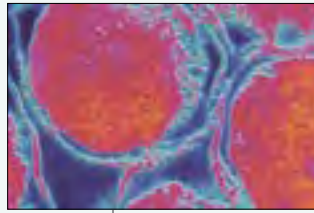


3rd Clinic Director
ARNOLD H. KNAPP, MD
1903-1928

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.

TCATTCTATTTCG TAGCAT ATTCTT CGGTT CACGATC AGGG GCGGTA CCAG9AT



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.



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



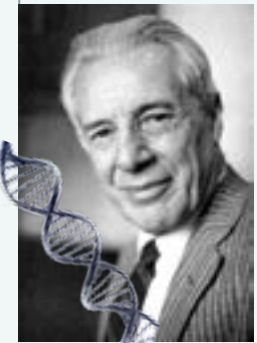
1933 Ramon Castroviejo, MD, performs the first corneal transplant on a human.



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

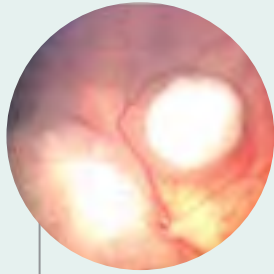


1936 The Muscle Clinic becomes the Eye Institute's first subspecialty clinic.



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

DEPARTMENT MILESTONES



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



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.



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

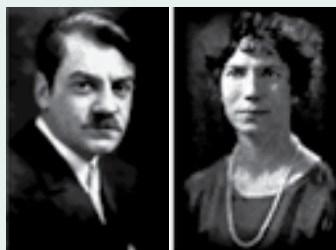


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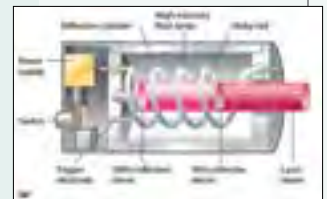


1948 The pupillography laboratory is established by Otto Lowenstein, MD, PhD, a pioneer in the quantitative measurement of pupil function.

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.



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



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

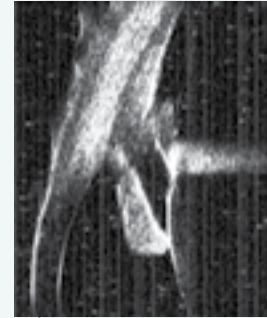
1962 First keratoprosthesis, developed by Hernando Cardona, MD, is presented to the 19th International Congress of Ophthalmology.



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



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.



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.



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



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

TCA TCTATTC GTA CAT ATTCTAT CGGT TACACGATCCA GGTGCGGTAACCAG 11A



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



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.



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.



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



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.



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

DEPARTMENT MILESTONES

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

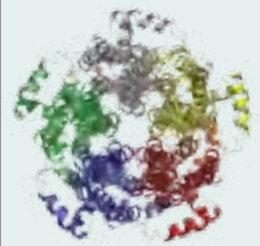


1983 Dr. Trokel publishes a major paper introducing the idea of using the laser to reshape or sculpt the cornea. Dr. Trokel and Dr. L'Esperance (pictured) patent the excimer laser for vision correction.

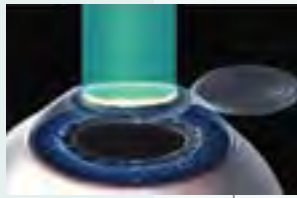
1994 Peter Gouras, MD, PhD, performs the first human retinal cell transplants.



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



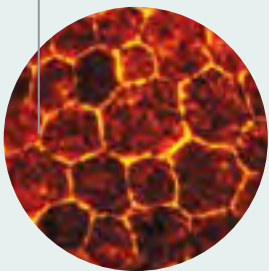
1998 Konstantin Petrukhin, PhD, discovers the gene responsible for Best's macular dystrophy.



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



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



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.



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.



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

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



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

2005 The Bernard and Shirlee Brown Glaucoma Research Lab opens.



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



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

2016 Clinical trial started for testing of an experimental compound developed by Dr. Ilyas Washington to treat Stargardt disease.



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, bringing with him several NIH-sponsored clinical trials.

TC TTCTA TCG TA CA CATTCTA TC GT TA ACGA C A AGGTGC GTAACC G13C



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



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



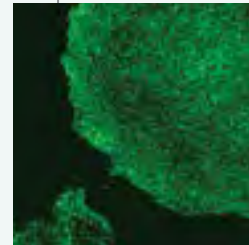
2014 Xin Zhang, PhD, is named the Jules and Doris Stein Research to Prevent Blindness Associate Professor



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.



2009 Janet Sparrow, PhD, discovered and structurally characterized vitamin A aldehyde-adducts responsible for some forms of retinal degeneration



2014 First use of human induced pluripotent stem cell-derived retinal pigment epithelial cells for gene therapy of retinitis pigmentosa in patient-specific cell lines is reported by Stephen Tsang, MD, PhD, and colleagues.



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

GENETICS

Precision Ophthalmology,[™] based on the concept of Precision Medicine, applies comprehensive, interactive components of patient care, integrating state-of-the-art clinical characterization, and an unprecedented depth of genetic analyses to achieve personalized treatment of eye diseases. Next-generation sequencing technology has sparked a revolution in genetic studies, allowing us to acquire detailed genetic data on entire genomes in hundreds of thousands of individuals. Using this data, we have been able not only to determine disease-causing mutations in single genes, but also to identify all genetic variation in an individual that is associated with all observed phenotypes—from individual variation, such as height and weight, to simple and complex diseases.



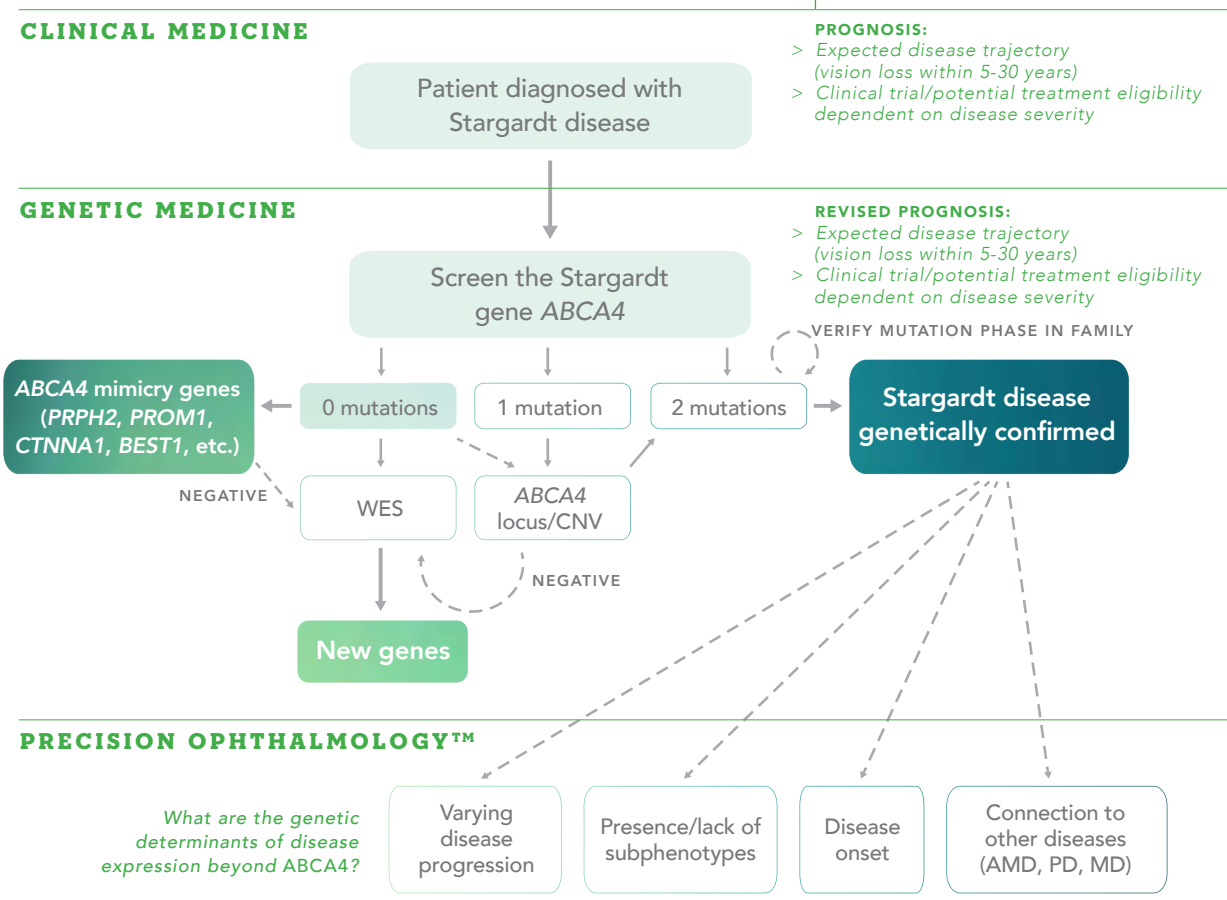
The revolution in genetic studies has given us the ability to make molecular diagnoses for hundreds of inherited eye diseases, leading to diagnostic refinement and individualized therapy. Technologies have also emerged that allow us to study individual genetic variants in disease models and, ultimately, to correct specific genetic errors in individual patients. At Columbia Ophthalmology, we are applying state-of-the-art genetic methods to diagnose and treat specific eye diseases.

TTC16ATTTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCATT

Through sequencing genomes and exomes (genomes' protein-coding regions) in thousands of patients affected with eye diseases, we have defined specific genetic variations causing single-gene diseases, such as retinitis pigmentosa and macular dystrophy, and complex, multifactorial diseases such as age-related macular degeneration and myopia. These variants have been introduced to mouse and cell-based models, which facilitate functional studies and serve as platforms to identify specific, precisely defined, genetics-based therapeutic approaches. Our goal is to use this information to design treatment modalities based on small molecules, stem cells, gene therapy, and gene correction therapy, alone or in combination, to treat human disease. These newly acquired capabilities form the cornerstone for the individualized precision medicine of the future.

Overleaf: Traditionally represented in the colors green, red, blue and black, the four nucleotides that compose DNA are adenine, thymine, cytosine and guanine (ATCG). DNA sequencing determines the exact order of these nucleotides within a DNA molecule—the fundamental step in all genetic science. From there, gene sequence can be connected with gene function.

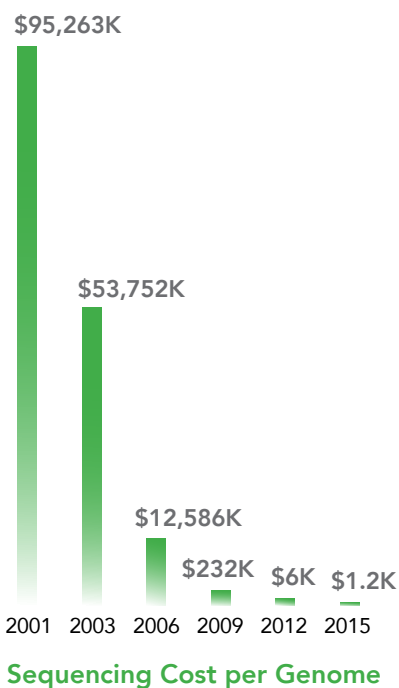
FIGURE 1



CTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGTTGCGGTAACCTTAA17CTC

Rando Allikmets, PhD

William and Donna Acquavella Professor of Ophthalmic Science (in Ophthalmology, and Pathology and Cell Biology); Malcolm Aldrich Research Director



The cost of sequencing

an individual genome has dropped dramatically in the last 15 years, largely due to improvements in technology. Source: NIH's National Human Genome Research Institute

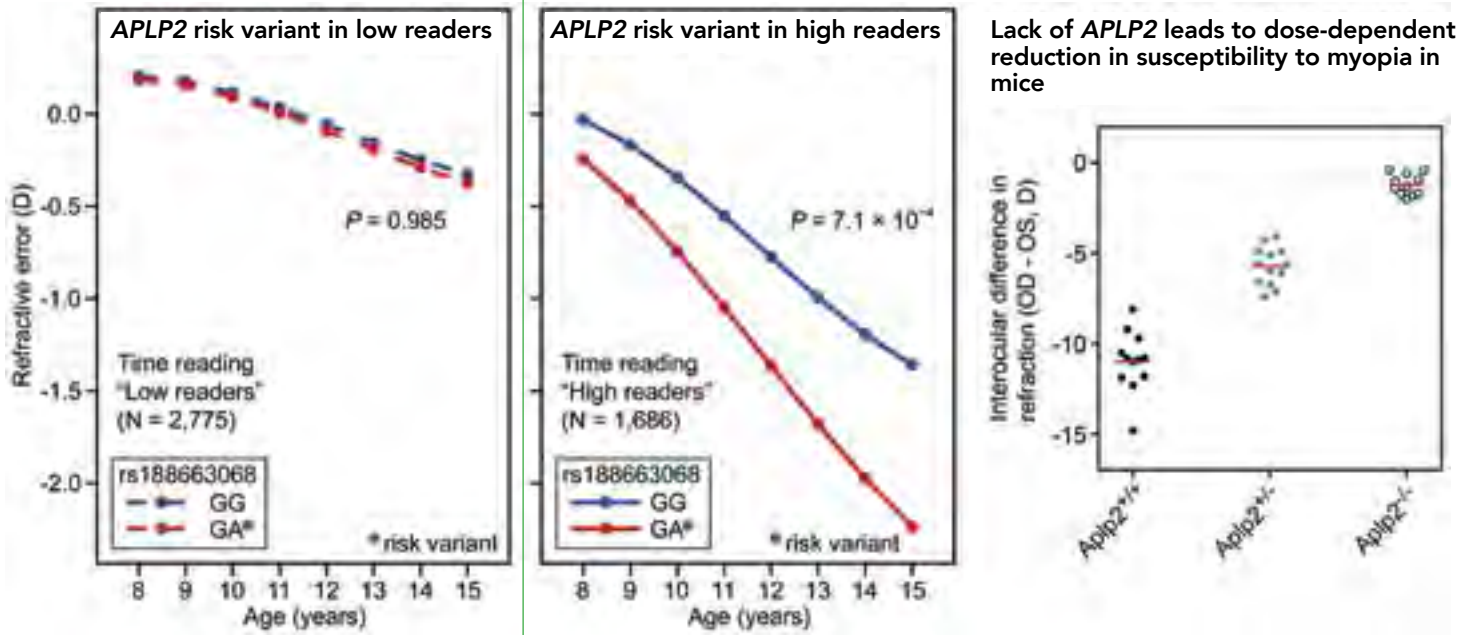
Figure 1: Application of Precision Ophthalmology™ to Stargardt Disease

Clinical Medicine Stargardt disease is suggested by clinical ophthalmic examination.

Genetic Medicine In approximately 70% of clinically defined cases, two mutations are identified in the ABCA4 gene, genetically confirming Stargardt disease. Of the remaining cases, 20% have one of the two mutations, and 10% of cases initially diagnosed as Stargardt disease are, in fact, a different retinal disease. Many of these cases are found to have mutations in other genes.

Precision Ophthalmology™ In addition to confirming Stargardt disease clinically and genetically, variation in other genes is determined to cause a specific clinical presentation of the disease.

FIGURE 2



TTC18ATTTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCATTT

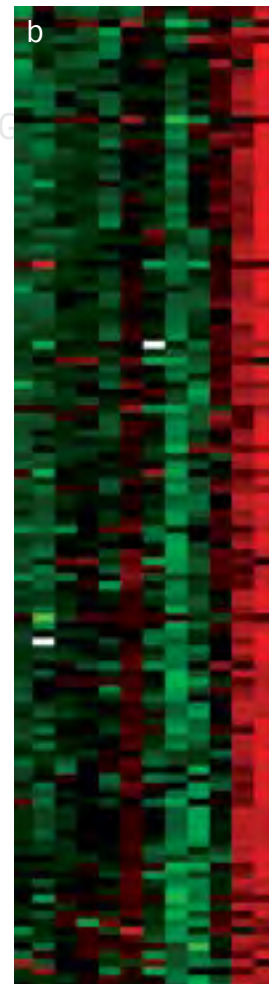
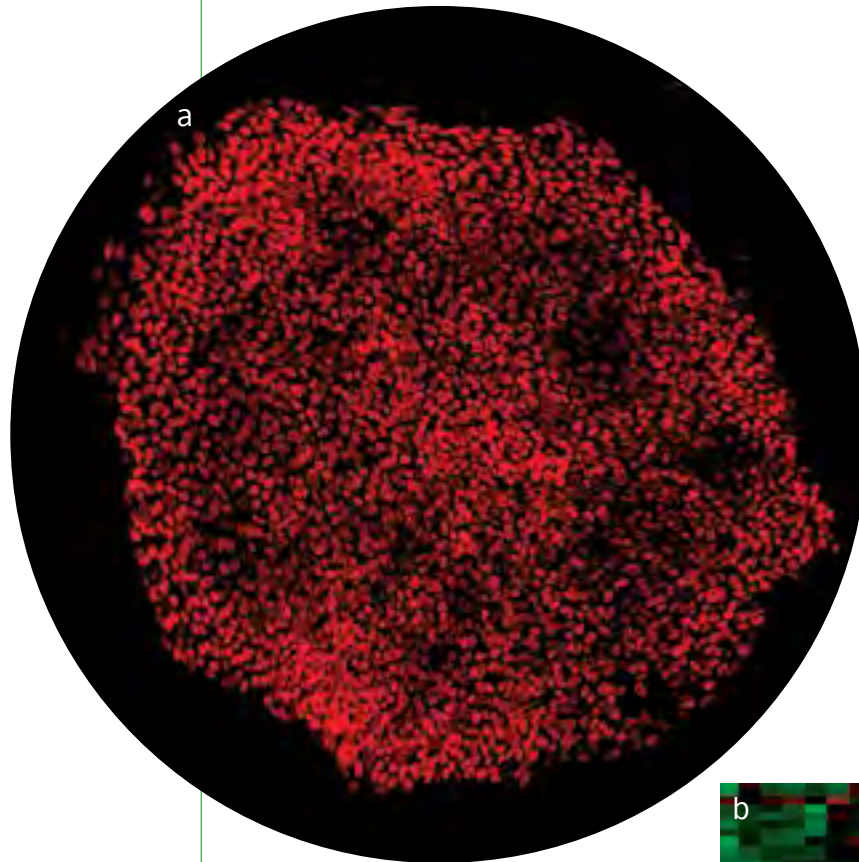
Andrei Tkatchenko, MD, PhD

Associate Professor of Ophthalmic Science (in Ophthalmology, and Pathology and Cell Biology)

Dr. Tkatchenko's research focuses on **identification and characterization of genes and genetic networks underlying refractive error development.** Using advanced system genetics approaches to uncover the causes of myopia, his laboratory recently discovered the first gene demonstrated to cause myopia in children. Genetic analysis revealed that children who carry a specific variant of *APLP2* are five times more likely to develop myopia if they read more than one hour a day, providing evidence of interaction between *APLP2* and visual environment. Functional analysis of *Aplp2* in the mouse model of myopia, in which *Aplp2* was

genetically removed from the genome, demonstrated that lack of *Aplp2* expression leads to a dose-dependent reduction in susceptibility to myopia. Dr. Tkatchenko's data suggest that reducing the level of *APLP2* expression in the retina can significantly reduce susceptibility to myopia, providing hope that myopia can be treated.

FIGURE 3



Stephen Tsang, MD, PhD

Laszlo T. Bito Associate Professor of Ophthalmology and Associate Professor of Pathology and Cell Biology

(a) The stem cell line above was derived from a patient evaluated at the Edward S. Harkness Eye Institute's Louis V. Gerstner Jr. Clinical Research Center in Vision.

(b) Precision Metabolome of patients' retinal cells

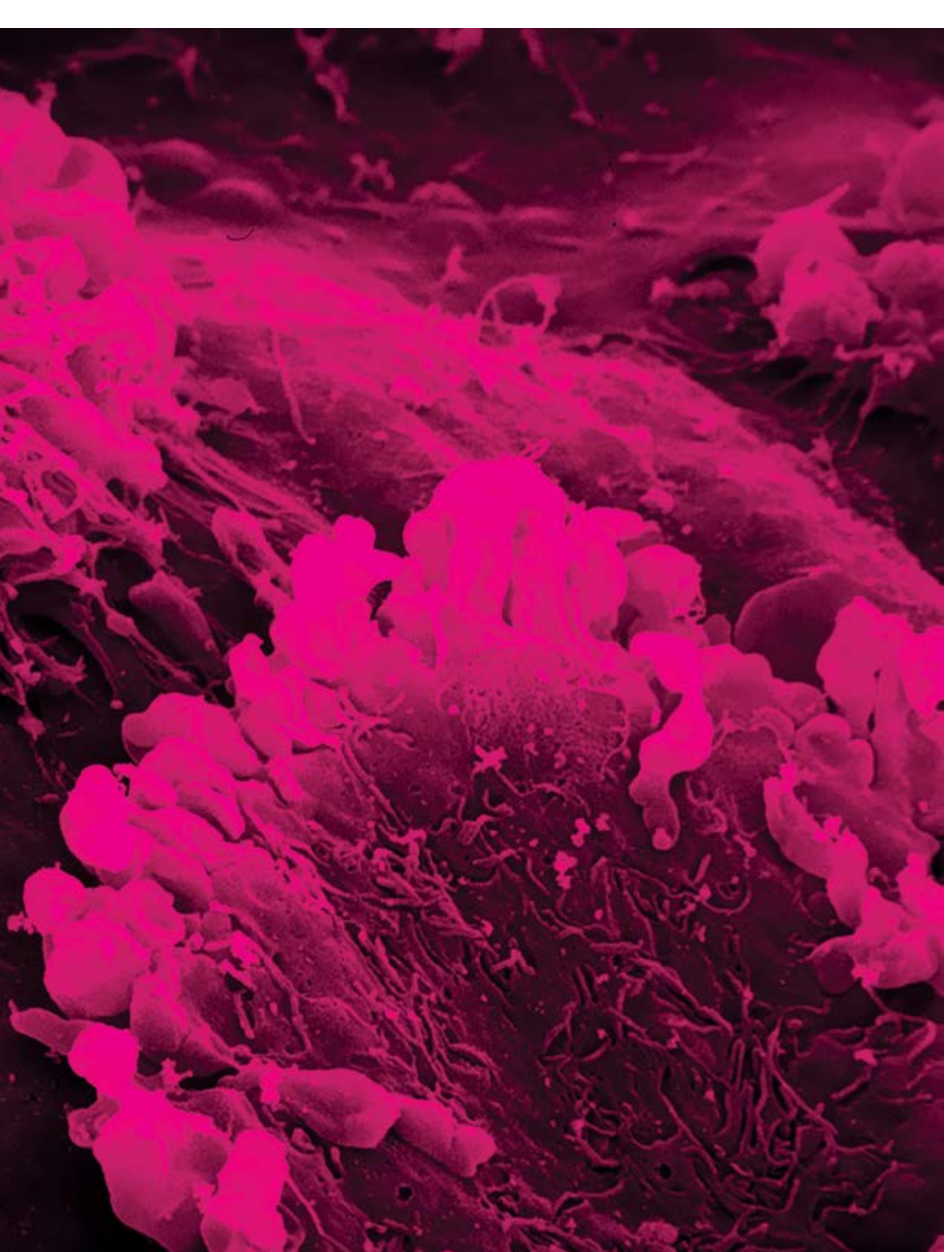
The heat map, at right, shows upregulation of the metabolites in the glycolysis pathway associated with treatment efficacy compared to control.

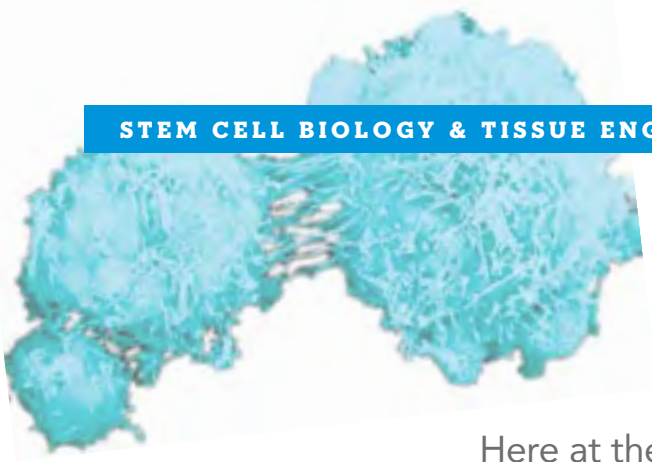
CTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGCTTTAA19CTC

A detailed microscopic image of a neural network, likely a retinal or optic nerve cross-section. The image shows a dense array of neurons with their cell bodies and intricate dendritic and axonal branching. The neurons are stained with fluorescent markers, with some cell bodies appearing in bright red and others in green, set against a dark background. The overall structure is highly organized and complex.

STEM CELL BIOLOGY & TISSUE ENGINEERING

Degenerative eye disorders resulting from heredity, genetic defects or the aging process represent the next frontier for prevention of vision disability. Retinal disorders, such as retinitis pigmentosa or Stargardt disease, age-related macular degeneration, and glaucomatous optic neuropathy, are the primary causes of irreversible vision loss, worldwide. Current treatments can slow disease progression but cannot completely arrest the loss of vision; neither can they restore sight to those who have lost it.





Here at the [Edward S. Harkness Eye Institute](#), the birthplace of retinal cell transplantation, the once-unreachable dream of sight restoration is now within our grasp, thanks to cutting-edge tissue engineering techniques and patient-specific stem cell transplantation technology. The quest to reconstruct disrupted macular anatomy has recently reached a stage of evolution with a more comprehensive approach called “maculoplasty.” Recognizing that grafted retinal cells do not survive or function unless the damaged subretinal milieu is repaired, we are employing tissue engineering techniques to reconstruct a healthy extracellular environment beneath the damaged retina.

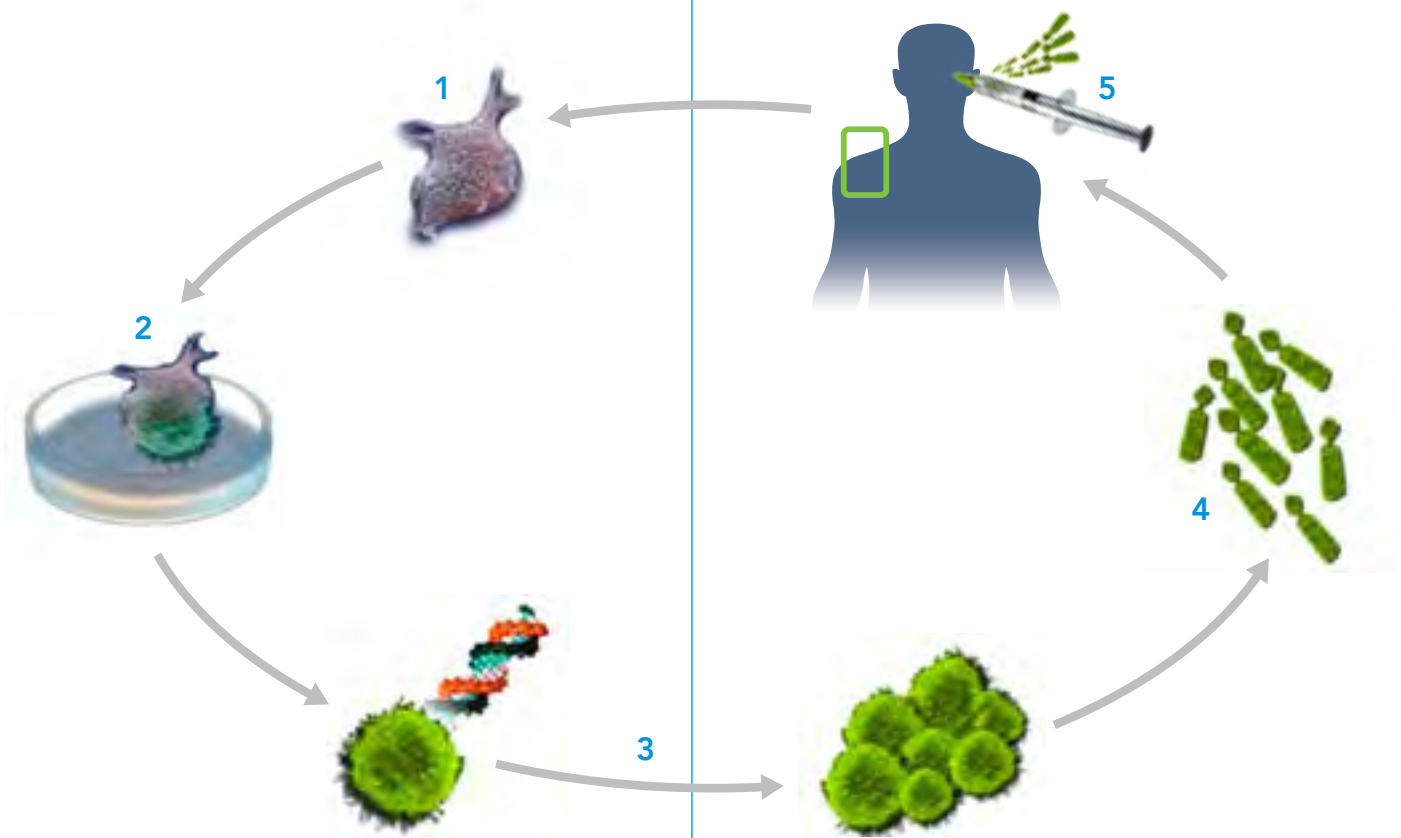
Tongalp Tezel, MD

Chang Family Professor
of Ophthalmology

Overleaf: Retinal pigment epithelial cells seeded onto human Bruch's membrane. Resurfacing of the host Bruch's membrane with these transplanted cells will achieve the ultimate goal of restoring sight in patients with macular degeneration. Image from the lab of Dr. Tongalp Tezel.

Our scientists generate autologous stem cells from each patient's own cells and precisely repair unique, individual, cellular and molecular defects with genome surgery, also known as gene-editing techniques. These bioengineered cells can then be reprogrammed to generate unlimited numbers of healthy retinal cells to replace damaged or missing cells, and seeded into the improved subretinal environment where they can flourish. Implantation of new cells is optimized with new microsurgical tools developed by our clinician-scientists working in tandem with our basic science teams. We are also applying these same techniques to nascent studies of trabecular meshwork and optic nerve tissue studies for the treatment of glaucoma.

FIGURE 1



Stephen Tsang, MD, PhD

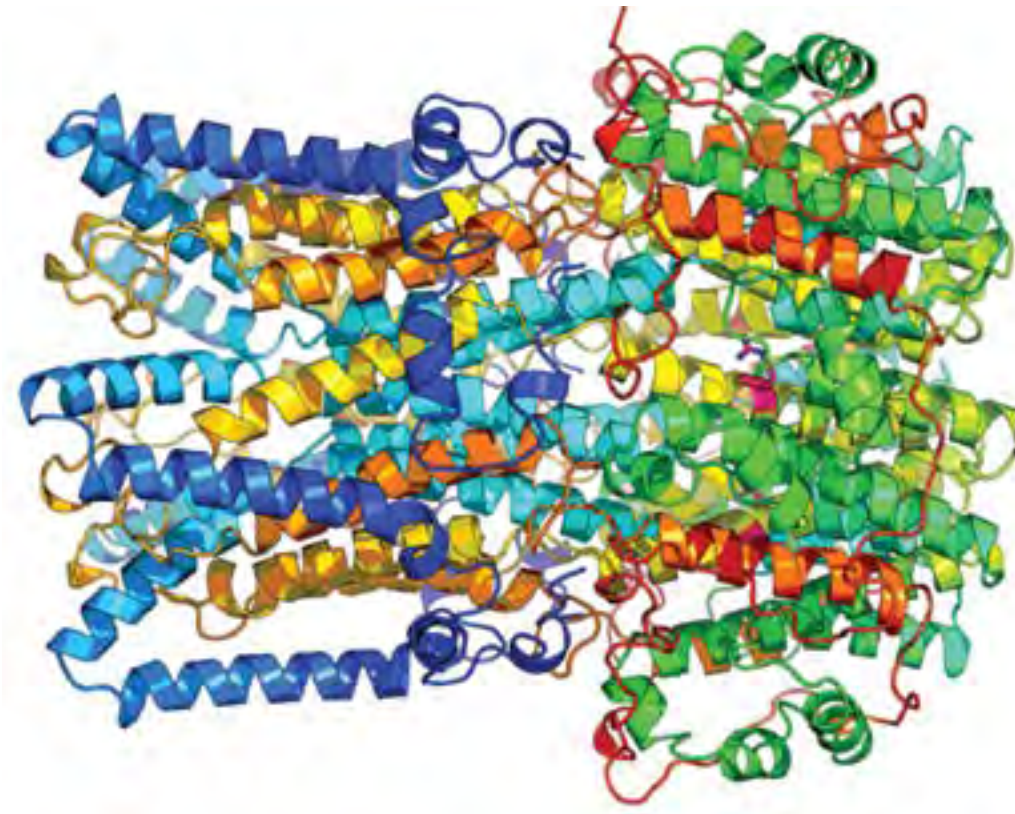
Laszlo T. Bito Associate Professor of Ophthalmology and Associate Professor of Pathology and Cell Biology

"A technique with almost limitless potential is the use of induced pluripotent stem (iPS) cells, derived from the patients themselves, as therapy."

— Dr. Francis Collins, Director of the National Institutes of Health (NIH), Bethesda, MD. For vision disorders that can be traced to genetic mutations, such as Stargardt disease, retinitis pigmentosa and Leber's congenital amaurosis, it may be possible to correct the genetic mutation (1) in patient-derived iPS cells in the laboratory (2), then repair and differentiate those cells (3) into retinal cells (4) and transplant them back into the same patient (5). Once perfected, this approach will offer the added advantage of utilizing a patient's own cells, avoiding problems with the body's rejection of foreign tissue.

** Image adapted from Stem cells as a therapeutic tool for the blind: biology and future prospects Mandeep S. Singh, Robert E. MacLaren. Proc. R. Soc. B 2011. Published August 3, 2011*

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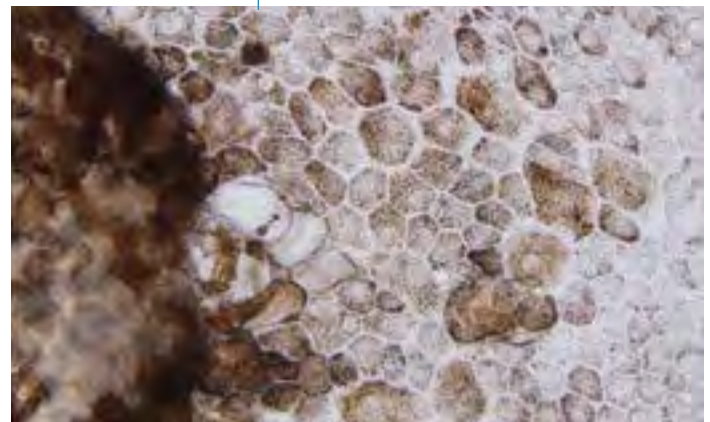
Modeling of patient *BEST1* mutations on human bestrophin-1 protein structure

Mutations in the bestrophin-1 (*BEST1*) gene, first cloned by [Dr. Konstantin Petrukhin](#), underlie Best vitelliform macular dystrophy, a dominantly inherited, juvenile-onset form of macular degeneration. While the physiological role of bestrophin-1 is still not completely understood, its three-dimensional structure has been recently determined.

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Patient's retinal cells (20x)



Patient's retinal cells (40x)

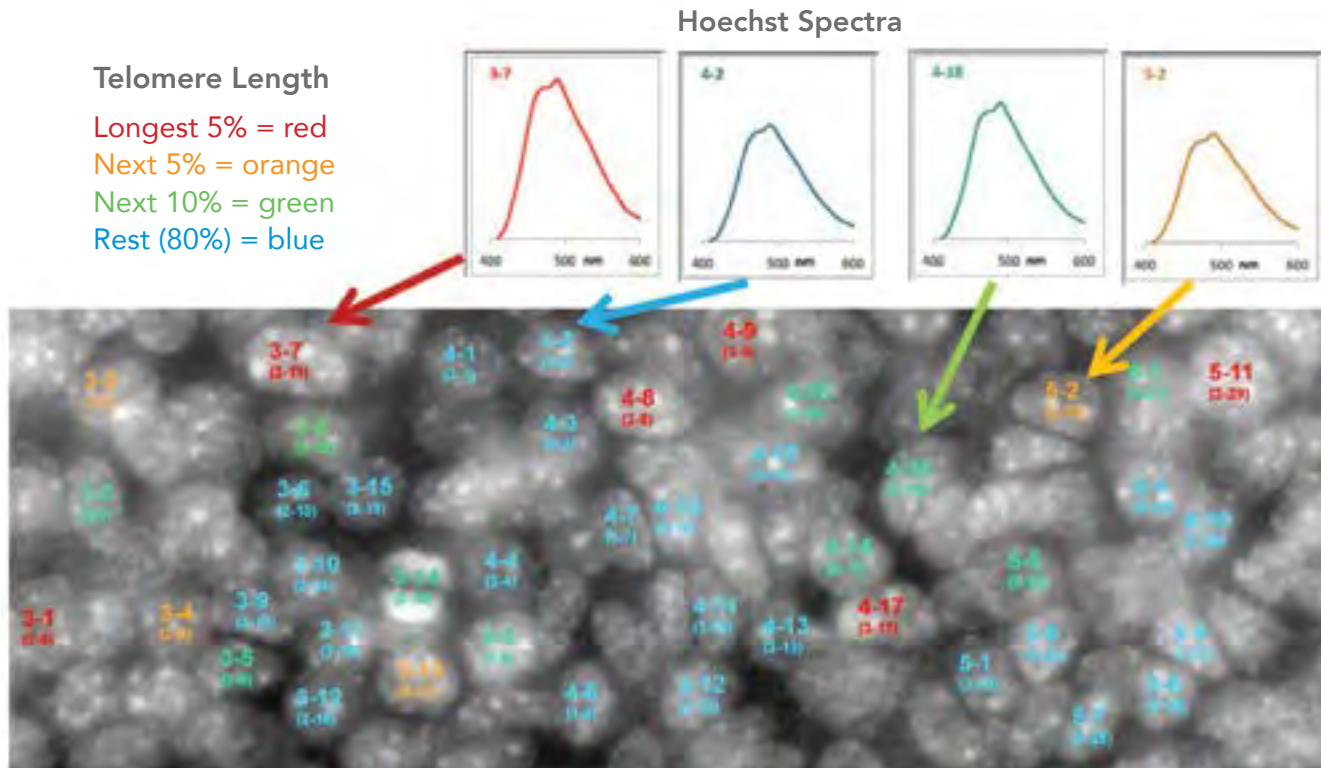
[Stephen Tsang, MD, PhD](#)

Laszlo T. Bito Associate Professor of Ophthalmology and Associate Professor of Pathology and Cell Biology

Stem cell-derived retinal cells with *BEST1* mutation.

Retinal cells were derived from induced pluripotent stem cells (page 19, Fig 3) generated from juvenile macular degeneration patients due to *BEST1*.

FIGURE 4

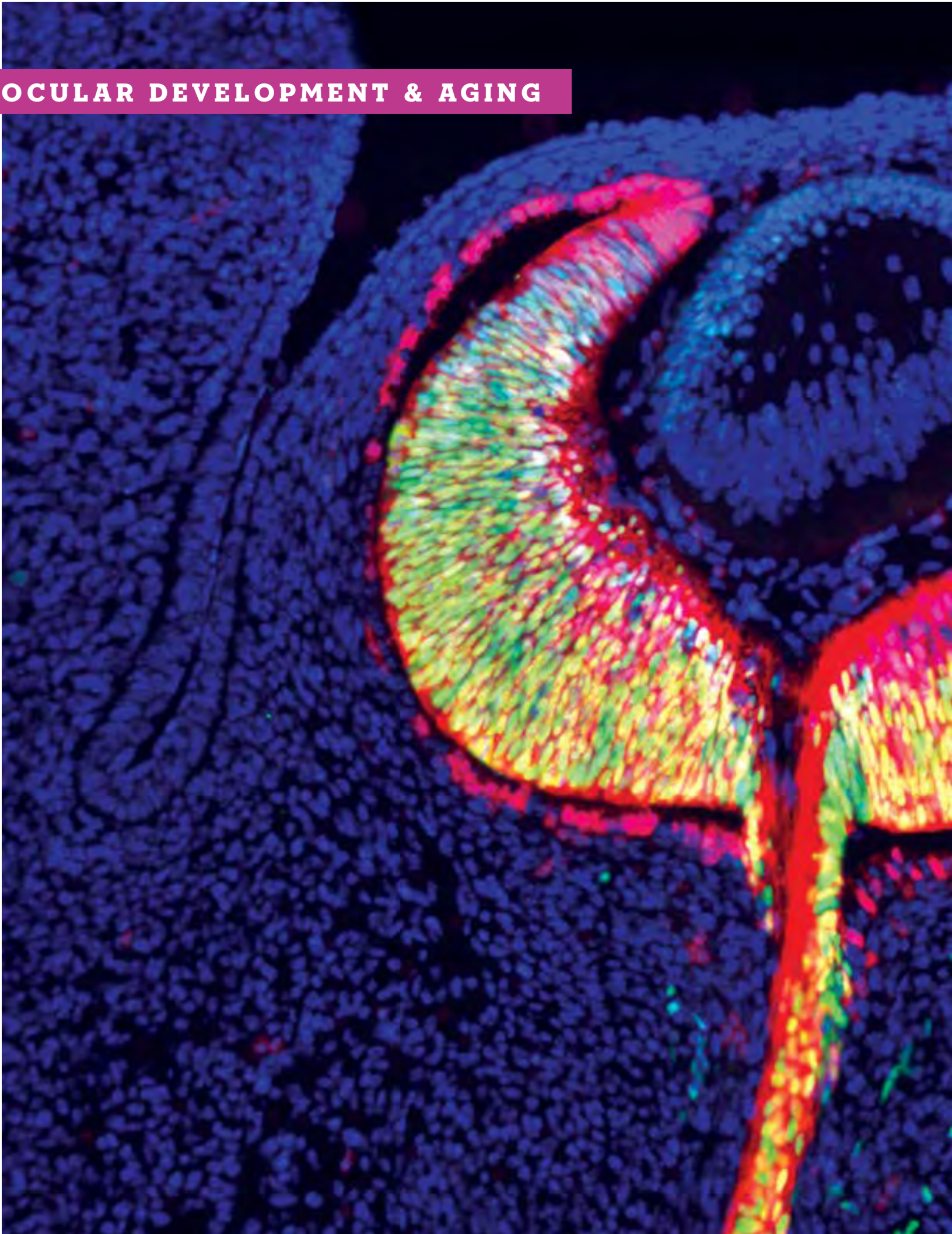


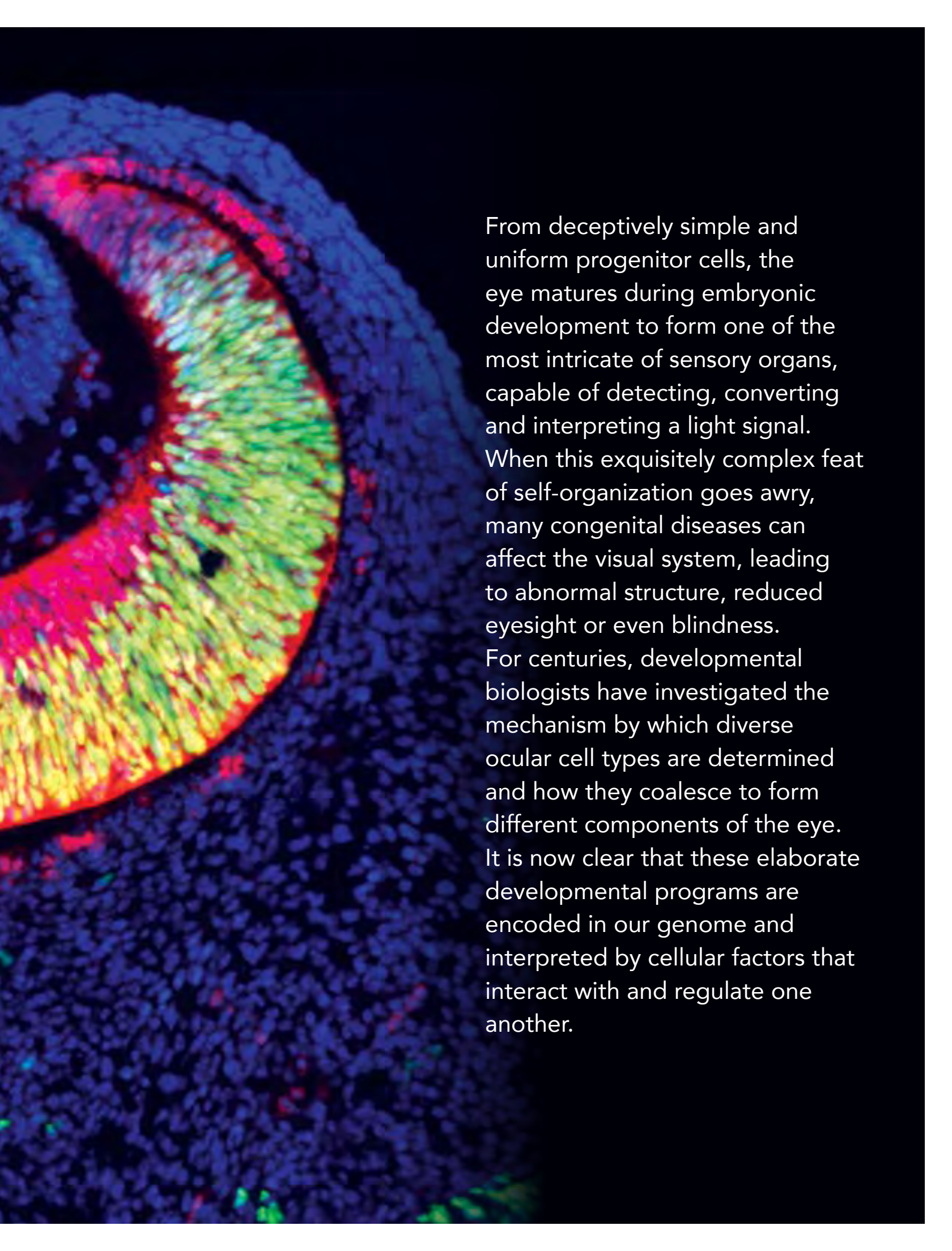
Takayuki Nagasaki, PhD
Assistant Professor of Ophthalmic Science
(in Ophthalmology) at CUMC

Stem cells in the cornea have tremendous potential as the source materials for repairing damaged tissues because they are readily accessible. Dr. Nagasaki's lab is using animal models of corneal stem cell biology to identify these cells so that they can be isolated and coerced in the laboratory to function specifically to the therapeutic target of choice—including, but not limited to, the cornea. The figure shows one of our many ideas for stem cell identification.

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OCULAR DEVELOPMENT & AGING





From deceptively simple and uniform progenitor cells, the eye matures during embryonic development to form one of the most intricate of sensory organs, capable of detecting, converting and interpreting a light signal. When this exquisitely complex feat of self-organization goes awry, many congenital diseases can affect the visual system, leading to abnormal structure, reduced eyesight or even blindness. For centuries, developmental biologists have investigated the mechanism by which diverse ocular cell types are determined and how they coalesce to form different components of the eye. It is now clear that these elaborate developmental programs are encoded in our genome and interpreted by cellular factors that interact with and regulate one another.

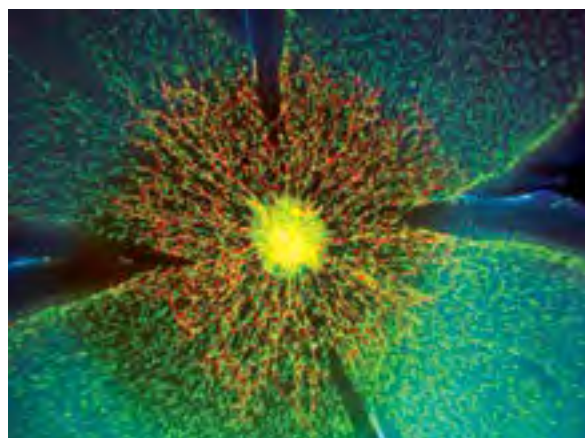
At the Harkness Eye Institute, our researchers are studying the cell communication pathways that orchestrate ocular development, neuronal connections that transmit visual signals, structural integrity of the eye necessary for optical clarity, and cellular aging that impairs the visual system. For instance, an important hallmark of the aging retina is the accumulation of visual cycle products that form in photoreceptor cells (rods and cones) and are deposited in retinal pigment epithelial (RPE) cells as a consequence of the phagocytic load borne by these cells.

TTC28ATTTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCAT

Overleaf: This section of the developing mouse eye at embryonic day 13, from the lab of Dr. Xin Zhang, shows the overlapping expression of neural retinal marker Sox2 (green) in the neural retina and optic stalk and that of fluorescent protein tdTomato (red) recapitulating Rax gene expression in the optic cup.

Right: Whole mount staining of a postnatal day 3 retina showing astrocytes (GFAP in green), blood vessel (IB4 in red) and photoreceptors (Rhodopsin in blue).

Our researchers are examining the burdens on RPE and photoreceptor cells imposed by these light-sensitive compounds and have gained insight into the resulting cumulative damage that contributes to retinal disease mechanisms over a person's lifetime. Taken together, these efforts to elucidate both ocular development and the effects of aging lay the foundations for the understanding and treatment of ocular diseases.



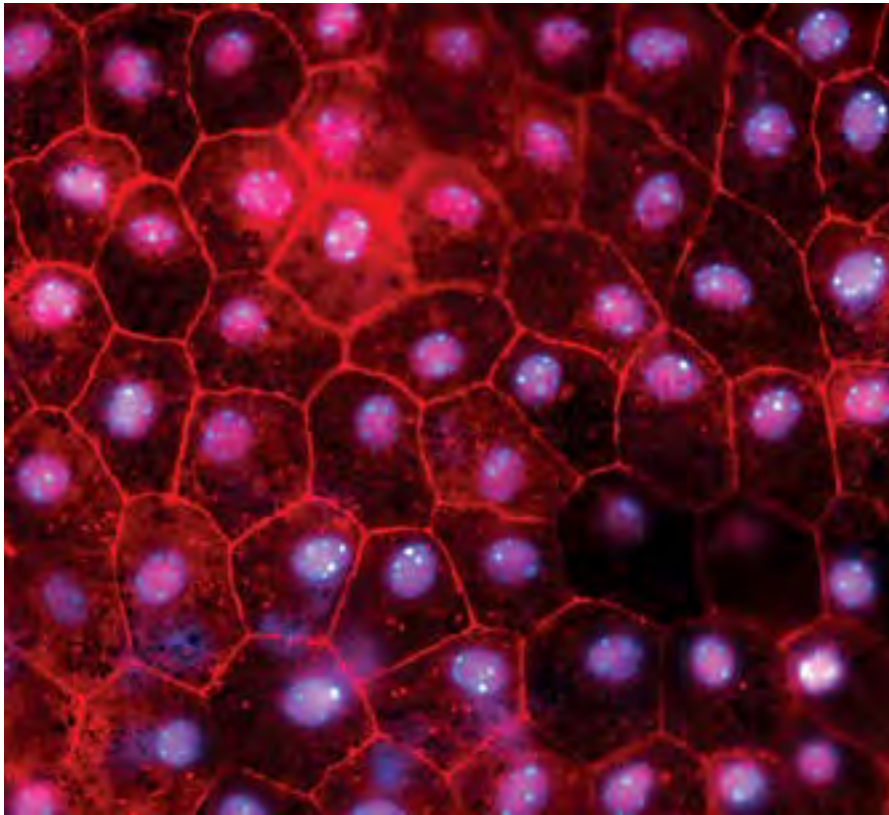


FIGURE 1

Janet Sparrow, PhD

Anthony Donn Professor of Ophthalmic Science (in Ophthalmology); Professor of Pathology and Cell Biology

CTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGGTGCGGTAACTTAA29CTC

Vitamin A aldehyde-derived adducts that accumulate with age in retinal pigment epithelial (RPE) cells are a major focus of Dr. Sparrow's research. This family of fluorescent compounds, unique to RPE, exhibits bisretinoid structures. Her laboratory is working toward understanding the structures and properties of the bisretinoid compounds, factors determining the rate at which these compounds form, and the adverse effects of these compounds on the light-absorbing photoreceptor cells and RPE. This research expands our understanding of several retinal disorders, including the pathogenesis of macular

degeneration, both inherited and age-related forms. The lab is also exploring therapies aimed at reducing bisretinoid accumulation and therapeutic strategies that target downstream effects of bisretinoid. The figure above depicts a whole mount of RPE stained to detect the tight junction protein ZO-1.

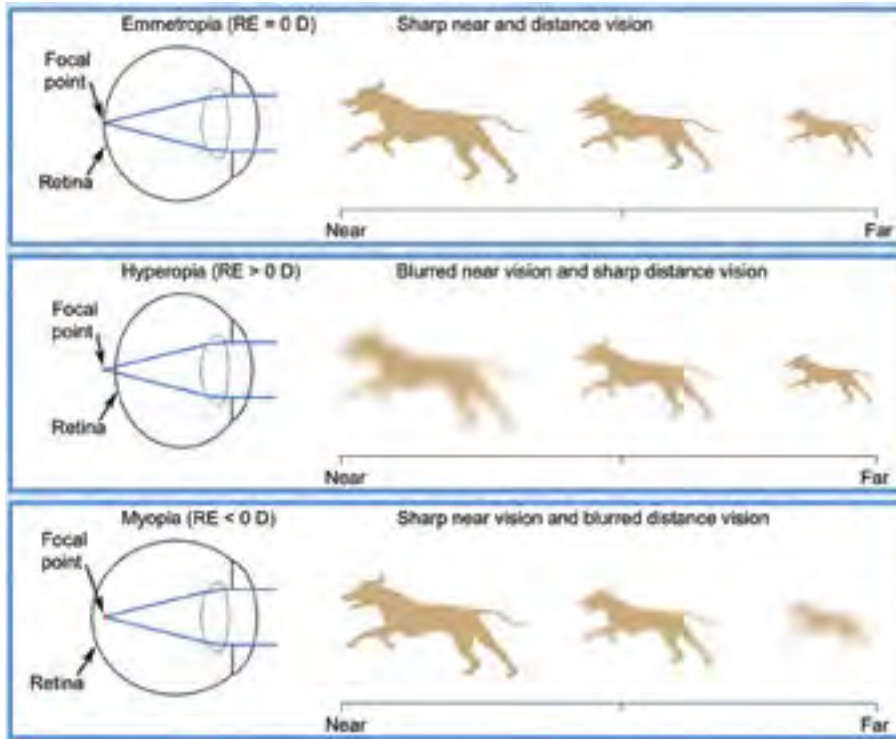


FIGURE 2

Refractive Error
in the U.S. (2014-2015)

32%

10%

58%

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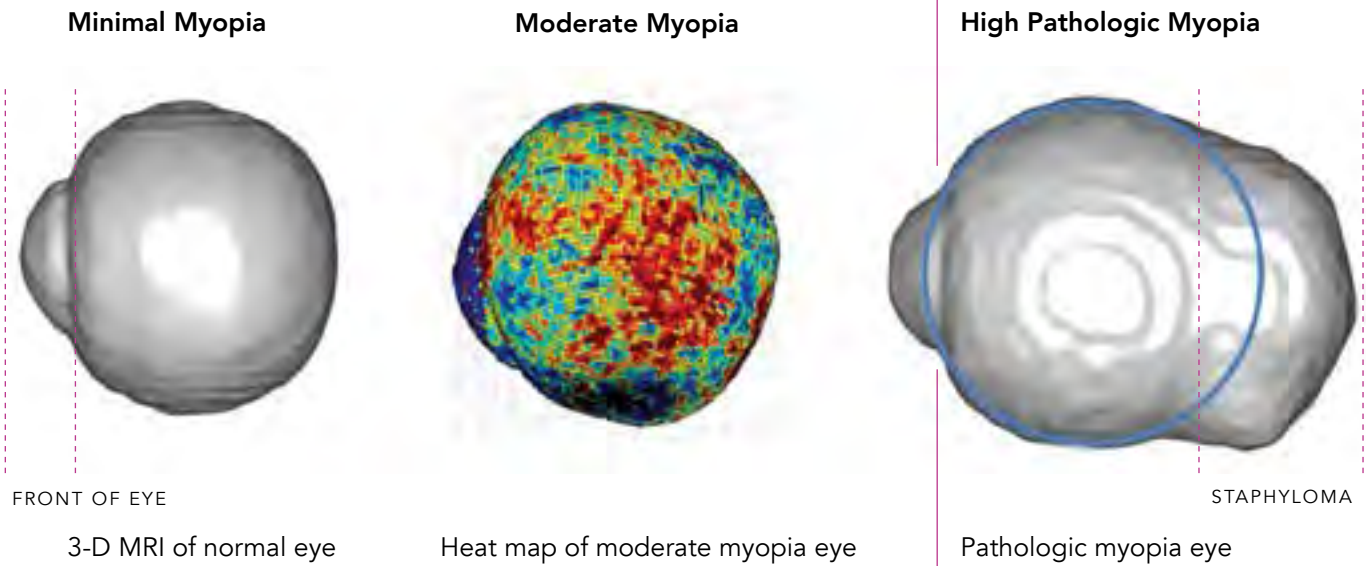
Andrei Tkatchenko, MD, PhD

Associate Professor of Ophthalmic Science
(in Ophthalmology, and Pathology and Cell
Biology)

**Myopia is the most common
ocular disorder worldwide.**

The prevalence of myopia in the U.S. has increased from 25% to 58% in the last 40 years, and it borders on an epidemic in urban Asian communities, where it is as high as 80%-90%. It is estimated that 4.8 billion people—half of the world's population—will be affected by myopia by 2050. Treatment options for myopia are limited to optical correction, which does not prevent progression of myopia or complications associated with the disease. The Tkatchenko Myopia Genetics Laboratory studies how genetic and environmental factors interact to guide refractive eye development, and searches for genetic factors responsible for the development of myopia.

FIGURE 3

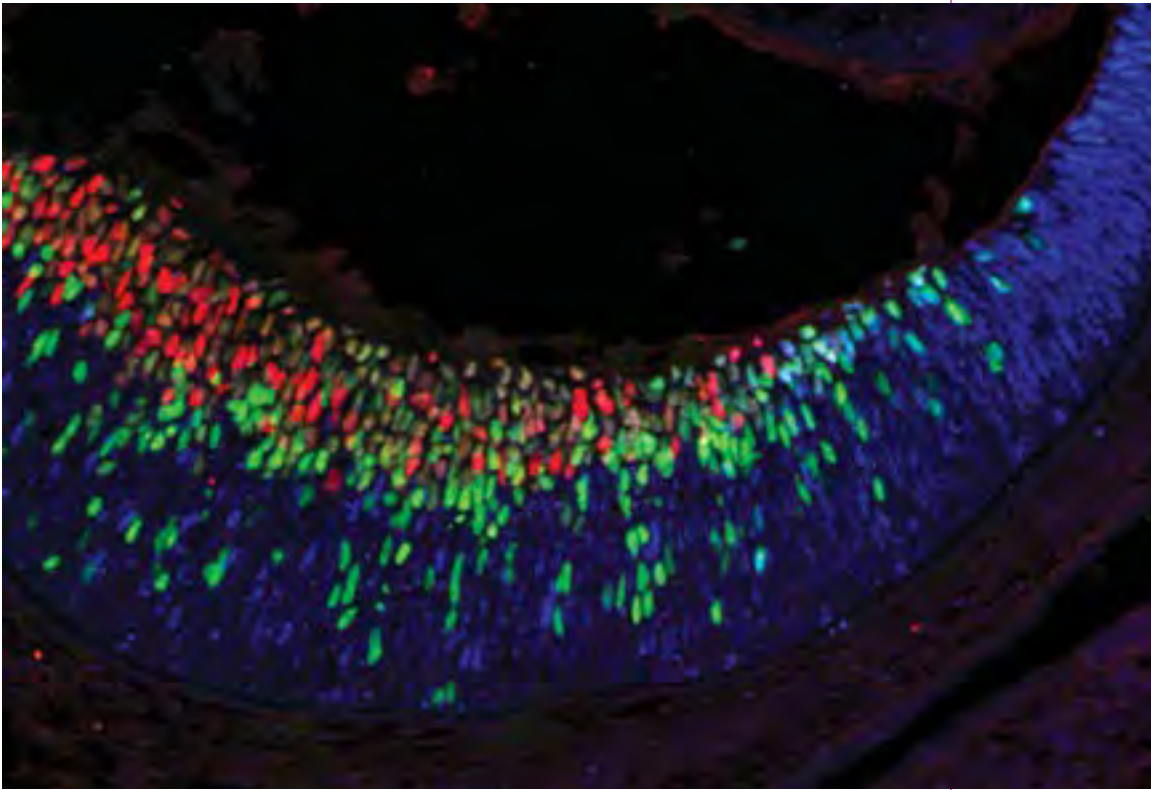


Quan Hoang, MD, PhD
Assistant Professor of
Ophthalmology at CUMC

While minimal levels of nearsightedness are a minor inconvenience requiring spectacle correction, pathologic myopia—extreme nearsightedness—can lead to irreversible vision loss and is a leading cause of blindness worldwide. This condition occurs when there has been progressive eye elongation and subsequent eye wall (sclera) thinning, allowing for localized outpouchings called staphyloma. In the above **3-D magnetic resonance imaging (MRI)**, staphyloma appears between the red lines in the right panel, compared to the more spherical-shaped eye in the left panel. As the structural integrity of the collagen component in the eye wall deteriorates, myopia progresses, leading to irreversible vision loss. Work in the Hoang

High Myopia Laboratory seeks to (1) use multimodal imaging to identify localized regions of eye wall weakness (middle panel, red areas) in a given patient, and (2) concurrently develop cross-linking agents that can be used to strengthen targeted sclera regions in a given patient to prevent myopia progression and avoid pathologic myopia (right panel).

CTATTTCCGGTAGCATCATTCTATTCCGGTTTACACGATCCAGAGGGTGC GGTAACCTTAA31CTC



Carol Mason, PhD

Professor of Neuroscience,
Professor of Pathology and Cell
Biology, Professor of Ophthalmic
Science (in Ophthalmology)

Stem cell therapy is one approach to repairing the damaged or diseased retina. To direct stem cells to become retinal ganglion cells (RGCs), the only retinal cells that project to the brain, we must understand the genes expressed in young RGCs when they normally grow, so they can successfully regenerate and reconnect in the mature brain. This **view of the ventral aspect of the embryonic retina in the albino**, a congenital perturbation, shows the range of developing RGC expression: All immature RGCs express the transcription factor Brn3 (green). RGCs that cross the optic chiasm and project contralaterally express Brn3a (red), and RGCs that project

ipsilaterally express Zic2 (blue). Compared with the pigmented retina, fewer RGCs in the albino express Zic2. The ipsilateral projection is thus smaller, and stereo vision is perturbed. Micrograph from the laboratory of Dr. Carol Mason.

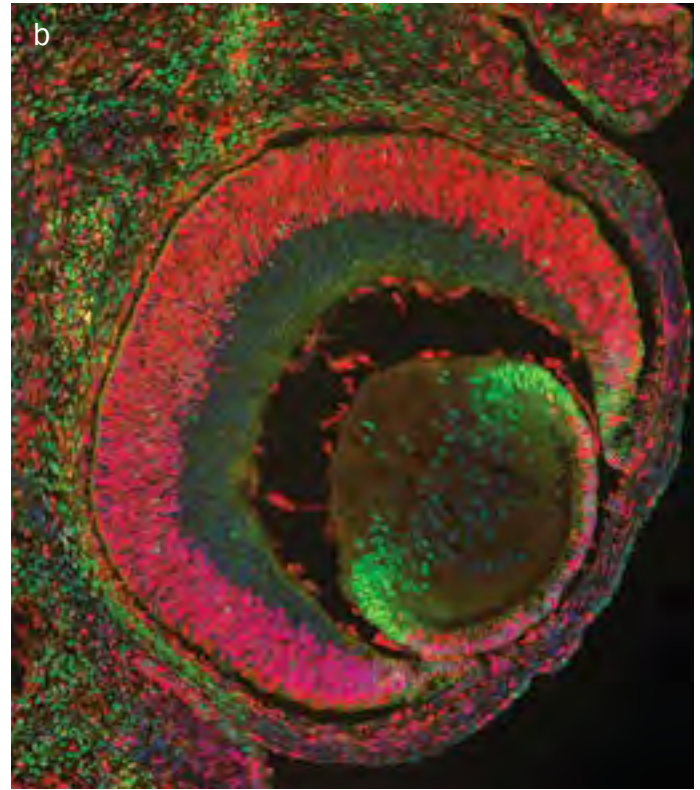
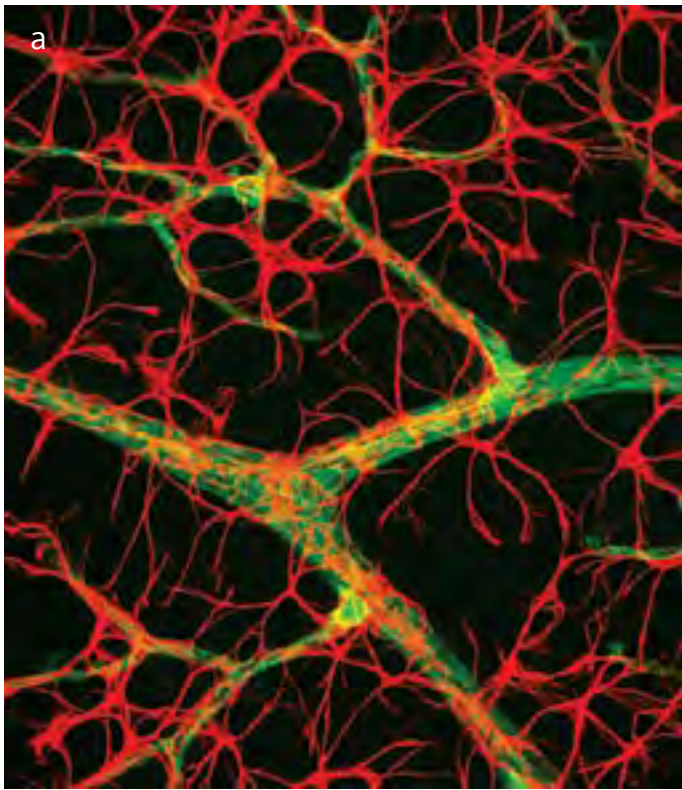


FIGURE 5

Xin Zhang, PhD

Jules and Doris Stein Research to Prevent Blindness Associate Professor; Associate Professor of Ophthalmic Science (in Ophthalmology, and Pathology and Cell Biology)

(a) Astrocytes play key roles in development and function of the retinal vasculature. In **this confocal microscopy image of a postnatal day 21 retina**, astrocytic scaffolds (GFAP in red) wrap the vasculature network (IB4 in green), forming a part of the blood-retinal barrier necessary for preventing vessel leakage.

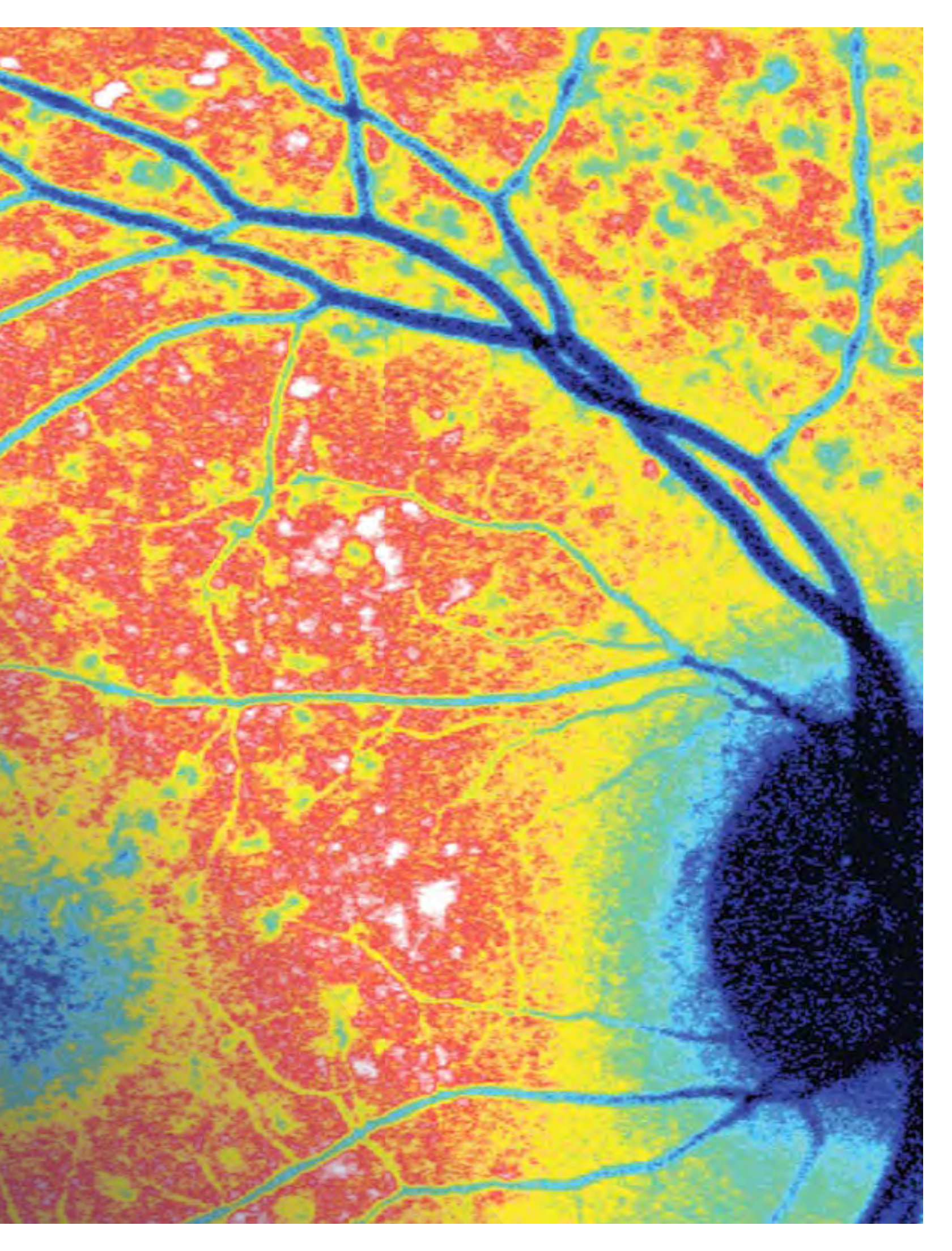
(b) A mouse lens at embryonic day 14: Ki-67 (red) marks proliferating cells, and p57 (green) denotes cells exiting the cell cycle. The developing lens is composed of two distinct cell types: anterior proliferating lens epithelial cells, and posterior differentiated and elongated fiber cells. Dynamic interaction between factors that promote and inhibit cell proliferation is responsible for the proper growth and differentiation of the eye. Micrographs from the laboratory of Dr. Xin Zhang.

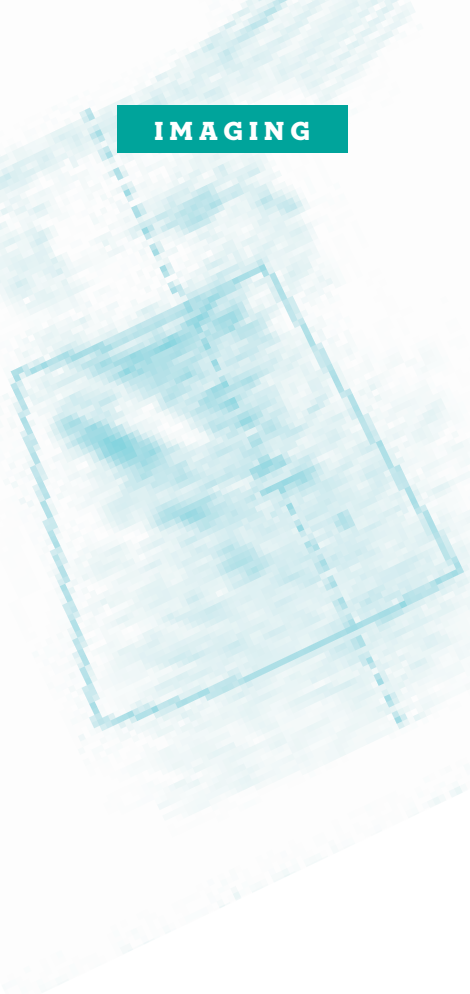
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IMAGING

Imaging systems are able to examine the interior of the eye in exquisite detail because of the unique access afforded by the transparency of anterior segment structures. Optical imaging methods are therefore widely used both in research and in the clinic for diagnosing and tracking disease. Through a multifaceted “molecules to fundus” approach, we have been able to develop a standardized method for quantifying fundus autofluorescence (qAF) intensities in both humans and mice. We use qAF as a biomarker to guide clinical diagnosis and genetic testing. In addition, fundus autofluorescence, together with spectral domain optical coherence tomography (SD-OCT), allows us to relate retinal phenotypes to genetic anomalies.





Recent advances in computer technology and in the sensitivity of SD-OCT, swept-source OCT, en-face OCT imaging and adaptive optics are being leveraged to detect early retinal and glaucomatous damage. We can also use these imaging modalities to monitor disease progression by quantifying the loss of retinal ganglion cells and by detecting ever-earlier retinal nerve fiber layer deficits. This work has revolutionized our understanding of optic nerve structure and function.

TTC36ATTTCGGTTTACACGATCCAGAGTGCGGTAACTTAACCTCAGCTACGAGAGCATCAT

Ultrasound can image tissue regions where light cannot penetrate. Cutting-edge, ultrafast (20,000 images/second) ultrasound systems being developed here allow depiction and measurement of blood flow in the orbit, choroid, and anterior segment, and in tumors. Novel ultrasound biomicroscopy systems, which provide high-resolution images of the cornea and sclera and their biomechanical properties, are being used to study diseases as diverse as keratoconus, preeclampsia and pathologic myopia.

Overleaf: Mapping of fundus autofluorescence distribution. Fluorescence intensities are coded in color from blue (low) to red (high). From the lab of Dr. Janet Sparrow.

Ophthalmic artery ultrasounds and OCT angiography: Representative color flow Doppler tracings from (a) severe preeclampsia subject and (b) normotensive postpartum subject. The peak ratio (PR) represents a ratio between the second and first peaks in each cardiac cycle and is demonstrably larger in preeclampsia subjects. (c) En-face OCT-angiography image of the choroid in a severe preeclampsia subject. The choroid is known to be responsive to angiogenic factors, which are dysregulated in preeclampsia.

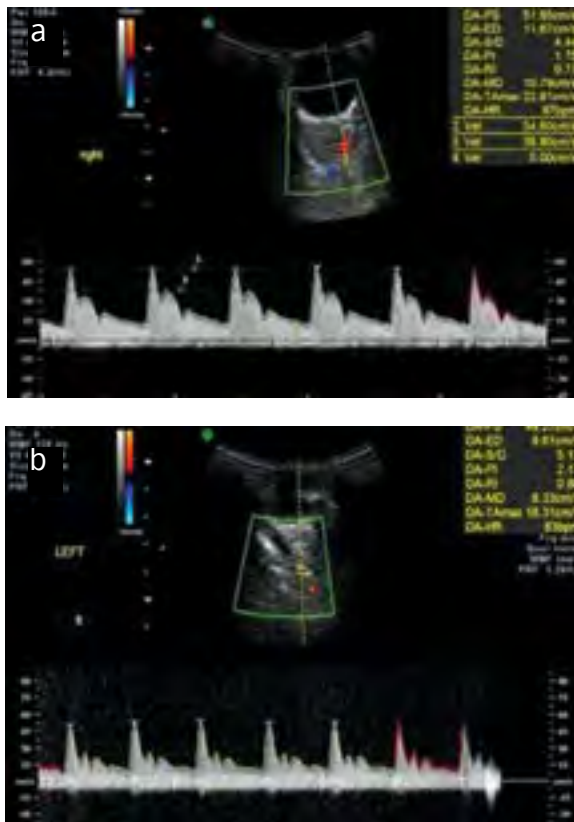
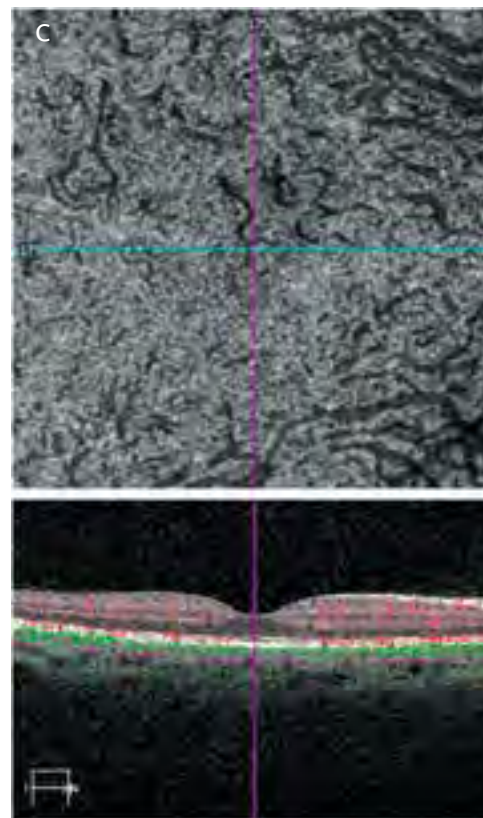


FIGURE 1



CTATTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGTGCGGTAACCTTAA37CTC

Srilaxmi Bearely, MD, MHS
Assistant Professor of
Ophthalmology

Blood vessels in the placenta and those in the choroid of the eye, supplying the retina, have remarkably similar characteristics and roles. Both are vascular organs that provide blood and nutrients to vital tissues, and both produce angiogenic factors. But only the eye has vasculature that is readily visible for noninvasive imaging, making it a target for evaluating pregnancy-related vascular disorders, like preeclampsia, which is a leading cause of maternal morbidities and adverse perinatal outcomes. The eye's accessibility to optical and high-resolution ultrasound imaging provides anatomic and blood-flow information of greater detail than indirect evaluation of placental blood flow, as with Doppler flow studies.

Our multidisciplinary team, including Ronald Wapner, MD, and Cande V. Ananth, PhD in the Department of Maternal Fetal Medicine at Columbia University, and Ronald Silverman, PhD, at the Harkness Eye Institute, is working to develop a novel retinal imaging and molecular biomarker panel to probe fundamental questions about vascular health and disease during pregnancy. We believe that such an imaging panel, involving tools such as ophthalmic ultrasound and OCT-angiography, could improve clinical practices by providing an early presymptomatic marker of preeclampsia.

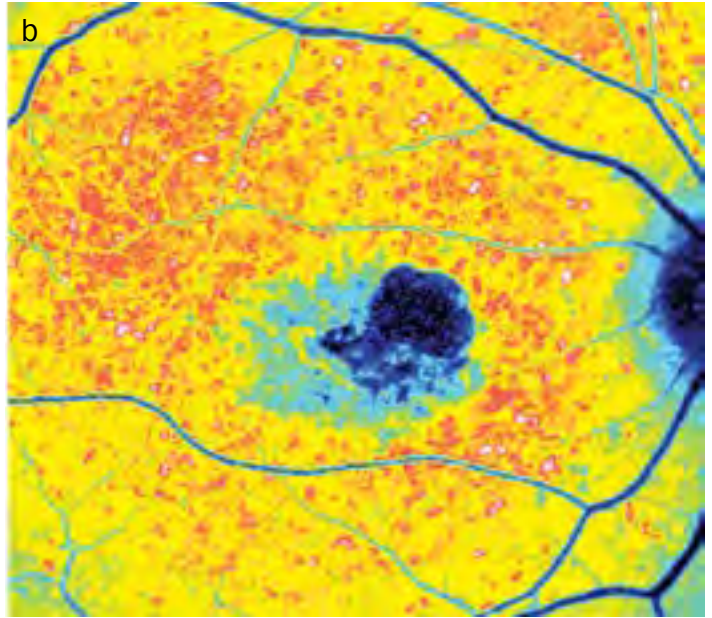
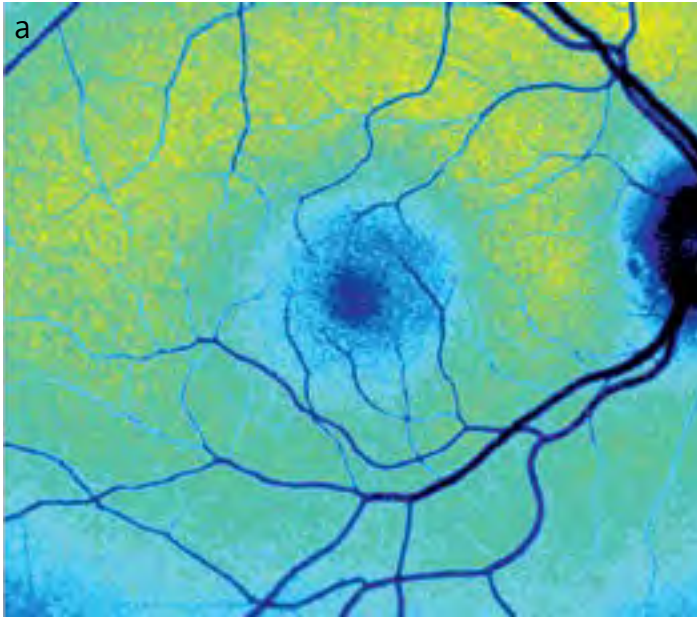


FIGURE 2

TTC38ATTTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCATT

Janet Sparrow, PhD

Anthony Donn Professor of Ophthalmic Science (in Ophthalmology);
Professor of Pathology and Cell Biology

The retina emits an intrinsic autofluorescence that can be excited by short-wavelength visible light and imaged as fundus autofluorescence. Since disease-related processes can alter the distributions and intensities of the autofluorescence signals, in vivo imaging of fundus autofluorescence provides a window within which to view the natural course of some retinal diseases, as shown in the above **color maps of fundus autofluorescence intensities. Image (b) depicts recessive Stargardt disease.**

Our understanding of the properties of these fluorescent molecules are applied to the clinical interpretations of fundus autofluorescence patterns.

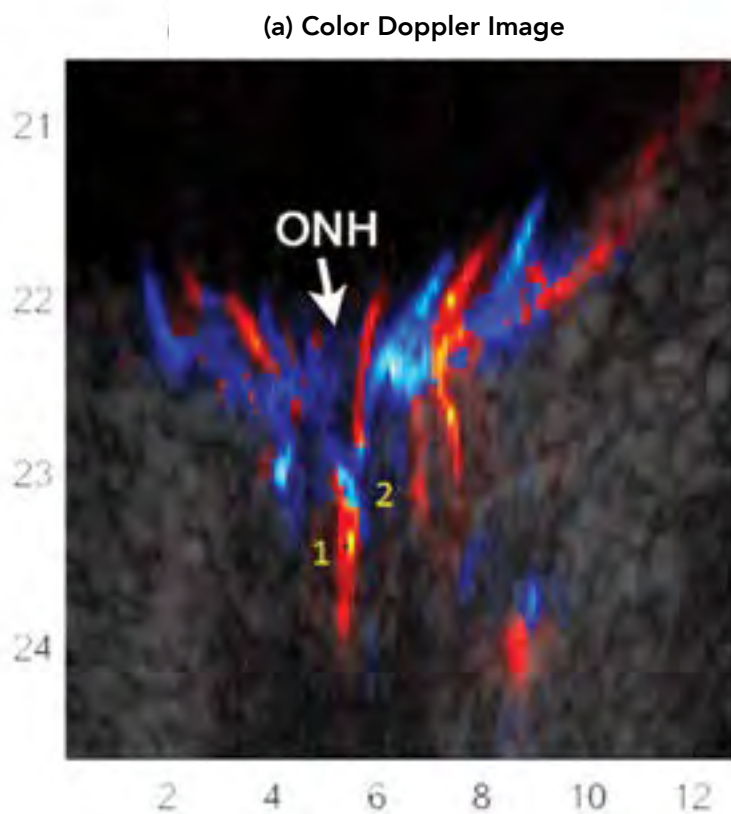
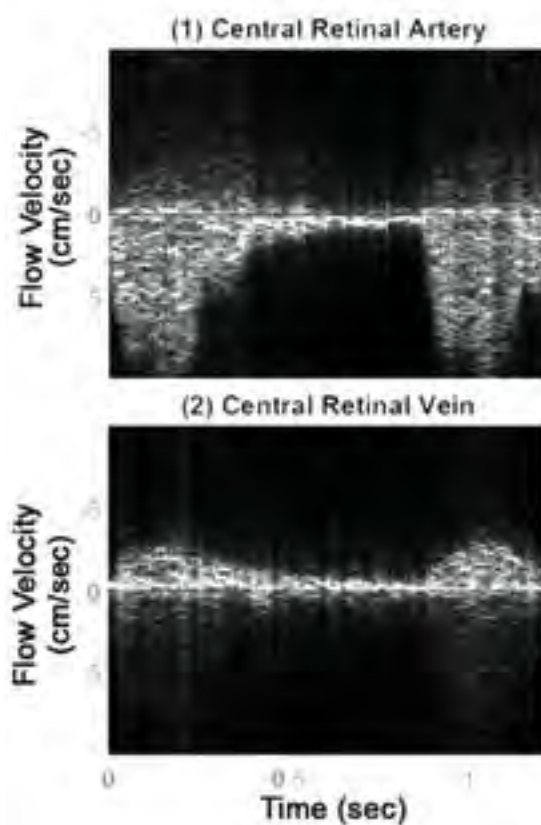


FIGURE 3

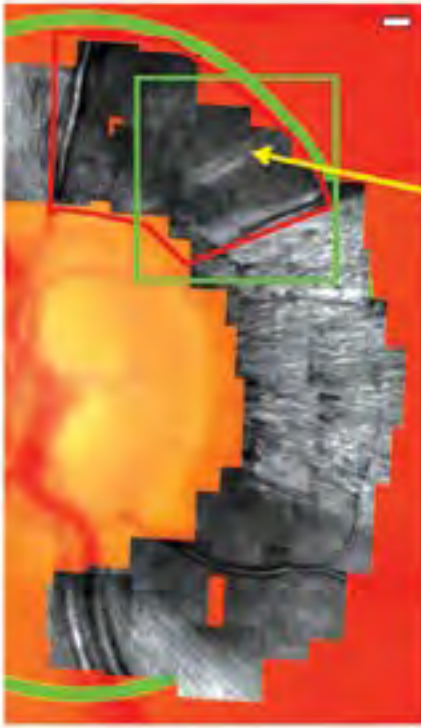


Ronald Silverman, PhD
 Professor of Ophthalmic Science
 (in Ophthalmology)

The above left image of blood flow in the region of the optic nerve in a normal human eye was obtained using **ultrafast compound coherent plane-wave ultrasound imaging**, a technique being adapted for imaging the eye in the Silverman Lab. Here, 20,000 images per second were acquired at five angles using an 18-MHz array probe. Red coloration depicts arterial flow, and blue depicts venous flow. The spectrogram on the right displays flow velocities in the central retinal artery and vein over a 1.3-second period. The ability to image flow in this new way will be invaluable for study of glaucoma, macular degeneration, tumors and vascular malformations.

CTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGTGCGGTAACCTTAA39CTC

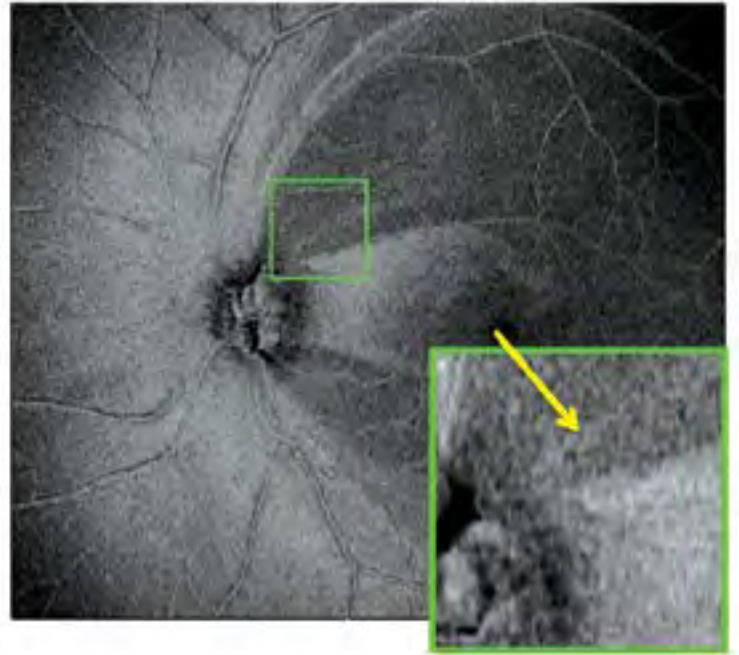
a. AO-SLO images



b. OCT scan



c. En-face OCT slab image

**Donald Hood, PhD**

James F. Bender Professor of Psychology;
Professor of Ophthalmic Science (in
Ophthalmology)

OCT scans of the optic disc

are routinely used to detect glaucomatous damage. To better understand the damage seen on these scans, Adaptive Optics (AO)-SLO images (a) were compared to circumpapillary OCT scans (b). The yellow arrow in (a) indicates a region of preserved retinal nerve fiber layer (RNFL) bundles within a region largely devoid of RNFL bundles. The yellow arrow in (b) shows a small hyperreflective region that suggests that local RNFL details are present in OCT scans, a finding confirmed with the OCT en-face slab image in (c). While the AO-SLO images in (a) took over an hour to obtain, the image in (c) required only two seconds, suggesting that en-face OCT imaging may be useful and efficient for following progression of glaucoma in the clinic.

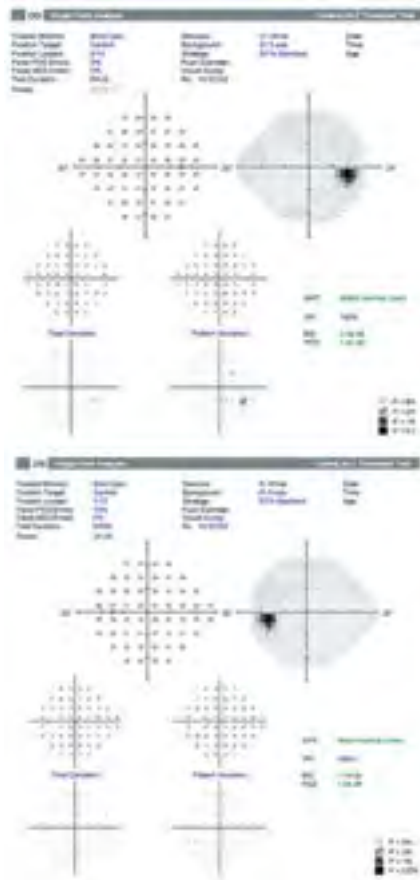
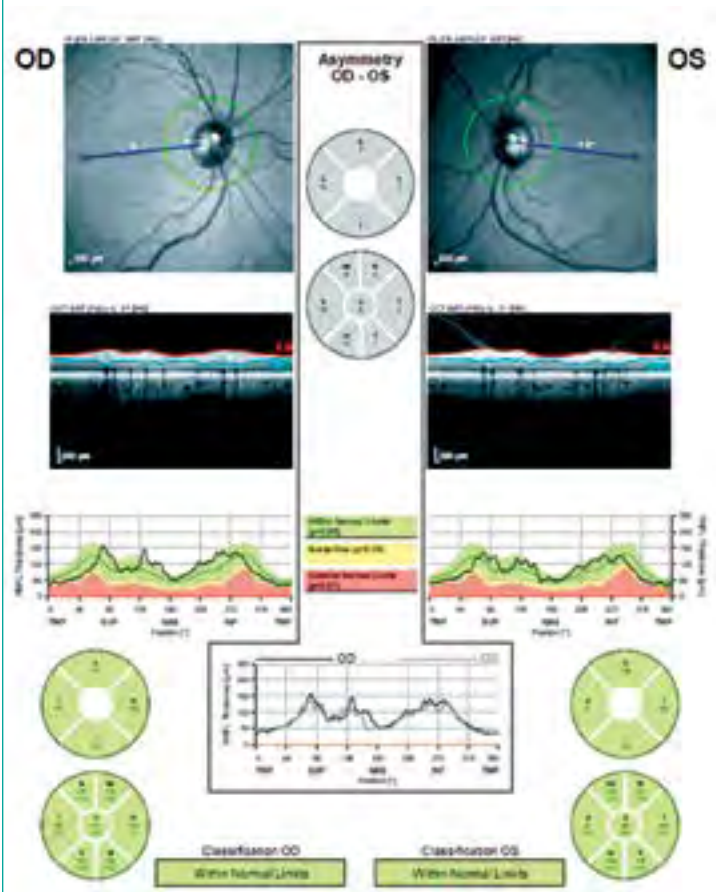


FIGURE 5



C. Gustavo De Moraes, MD, MPH

Associate Professor of Ophthalmic Science (in Ophthalmology), Director of Clinical Trials Unit

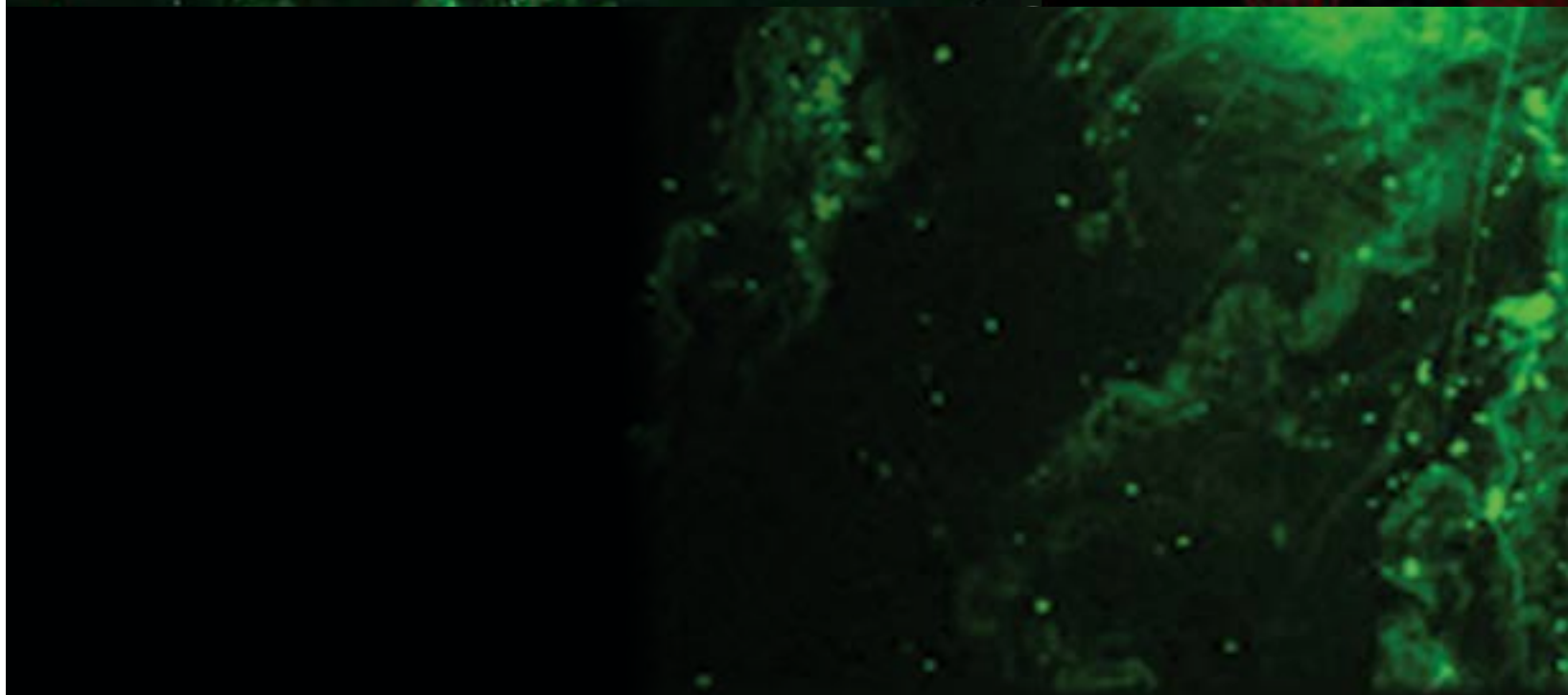
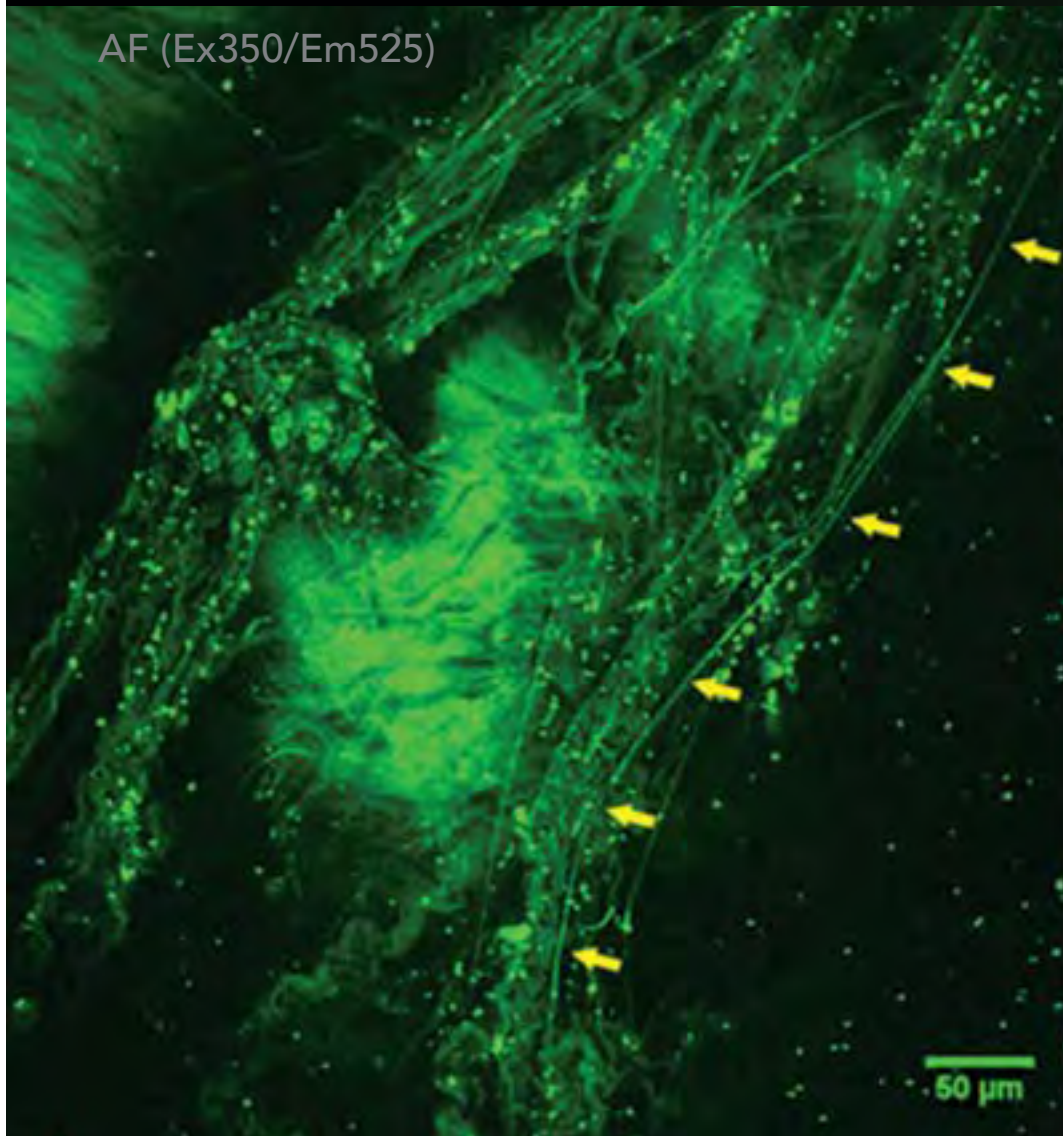
Jeffrey Liebmann, MD

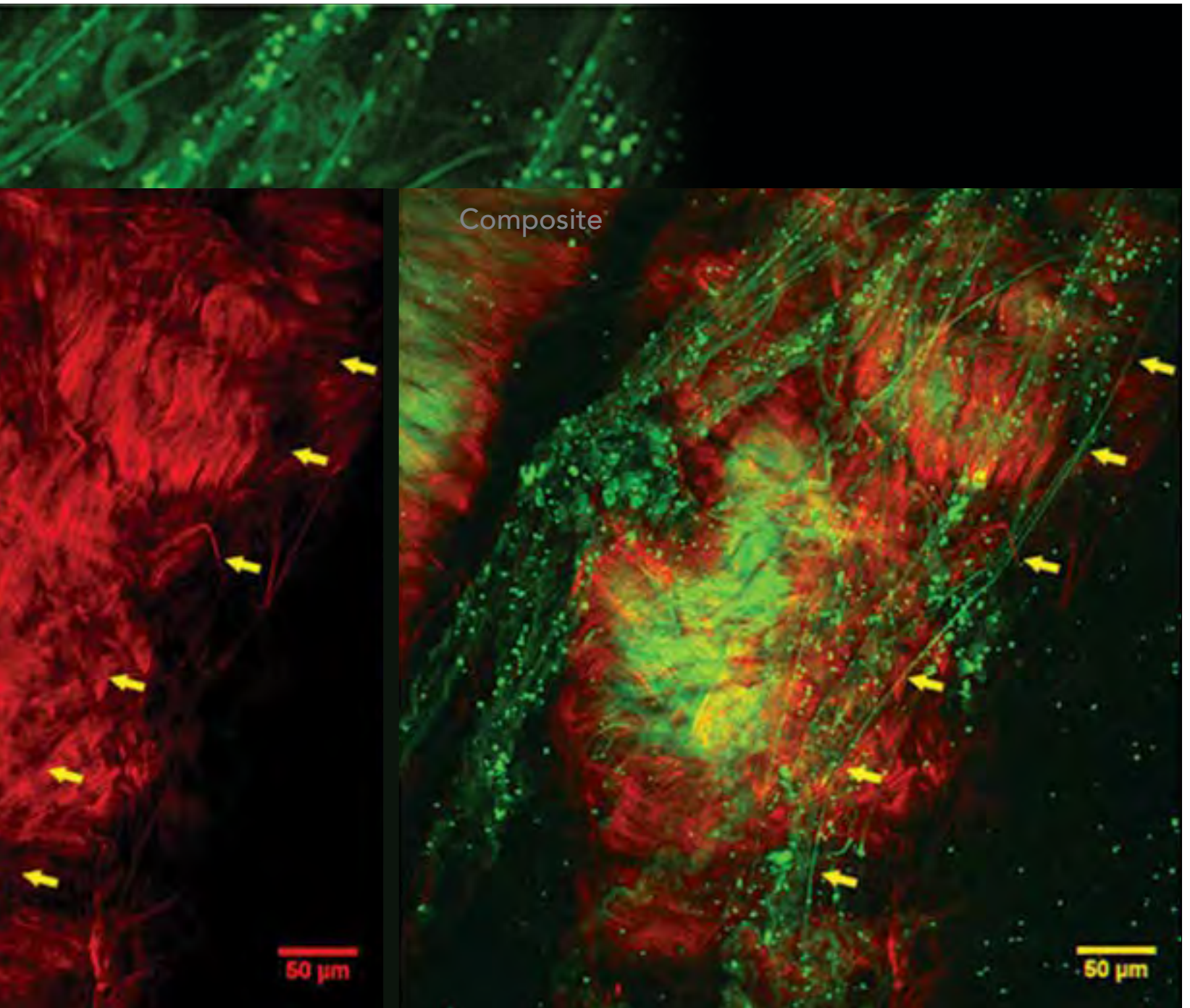
Shirlee and Bernard Brown Professor of Ophthalmology and Vice-Chair, Department of Ophthalmology

In the Edward S. Harkness Reading Center (ESHRC), experts review images and reports from a wide range of technologies used to diagnose and manage eye conditions. The Glaucoma Reading Center, part of ESHRC, helps clinicians **interpret the results of visual fields, OCT (macula and peripapillary), and disc photographs**. It also provides the masked review often required for endpoint and/or safety determination in NIH- or industry-sponsored clinical trials. The figure above depicts a combination of visual fields (left) and peripapillary OCT (right) of a patient referred to our center as a glaucoma suspect. Normal results in both eyes suggests low disease risk.

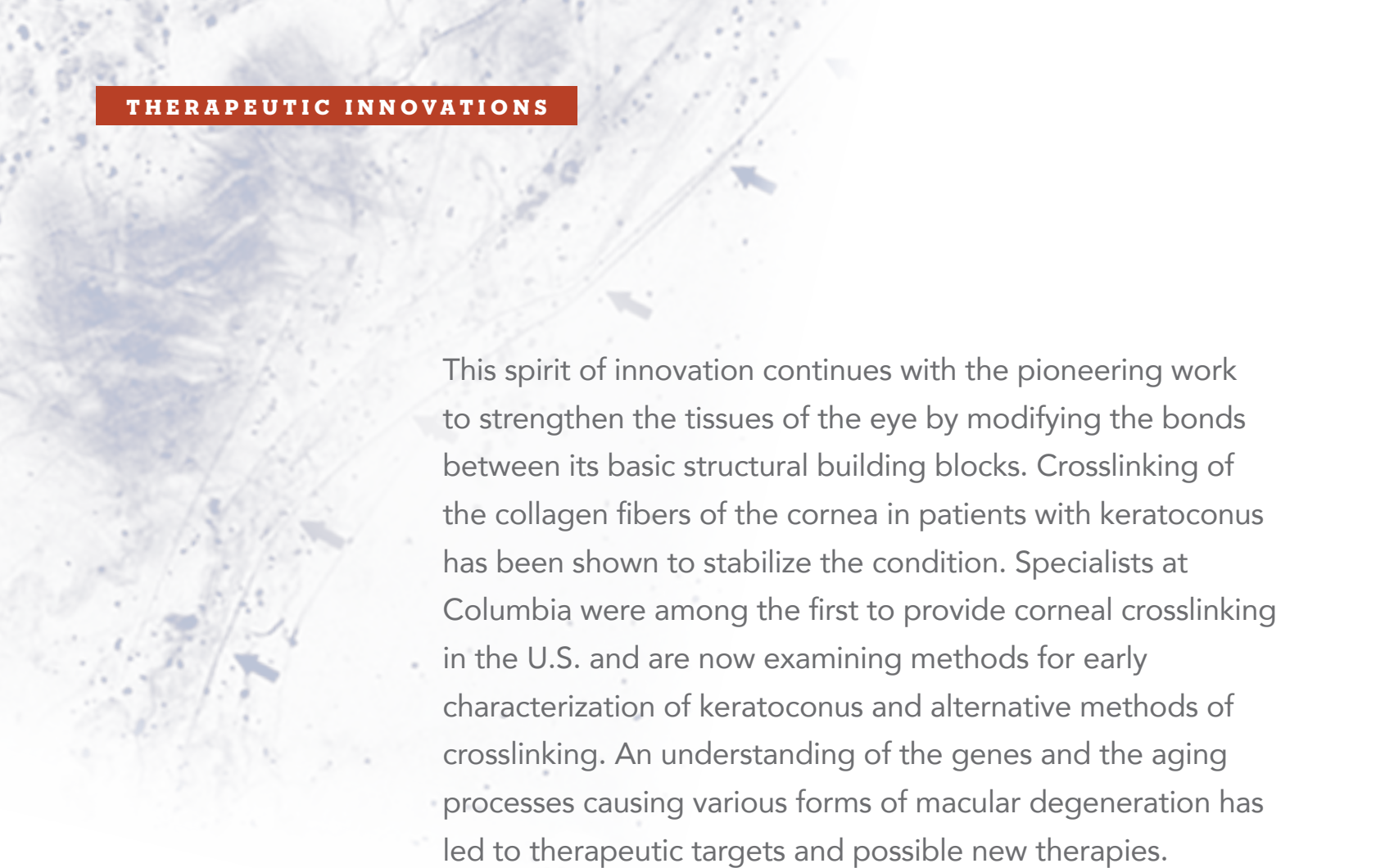
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THERAPEUTIC INNOVATIONS





As basic science research helps us to understand the fundamental and underlying cellular mechanisms in health and disease, we strive to improve human health by applying this knowledge to develop novel therapeutics. Working together, our scientists and clinicians have pushed the frontiers of therapeutic eye innovations, from the first corneal transplant and the first use of laser therapy in humans to the development of latanoprost, the specular microscope, viscoelastics for eye surgery, perfluorocarbon liquids and panoramic viewing for vitreoretinal surgery, and excimer laser for keratorefractive surgery.

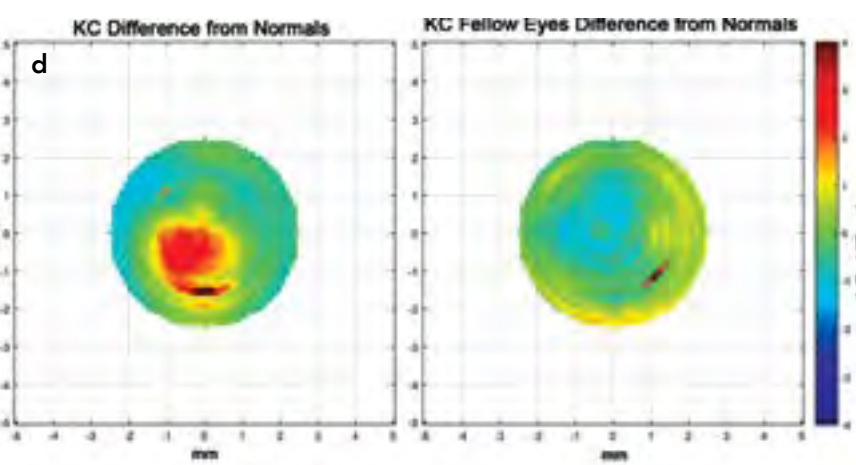
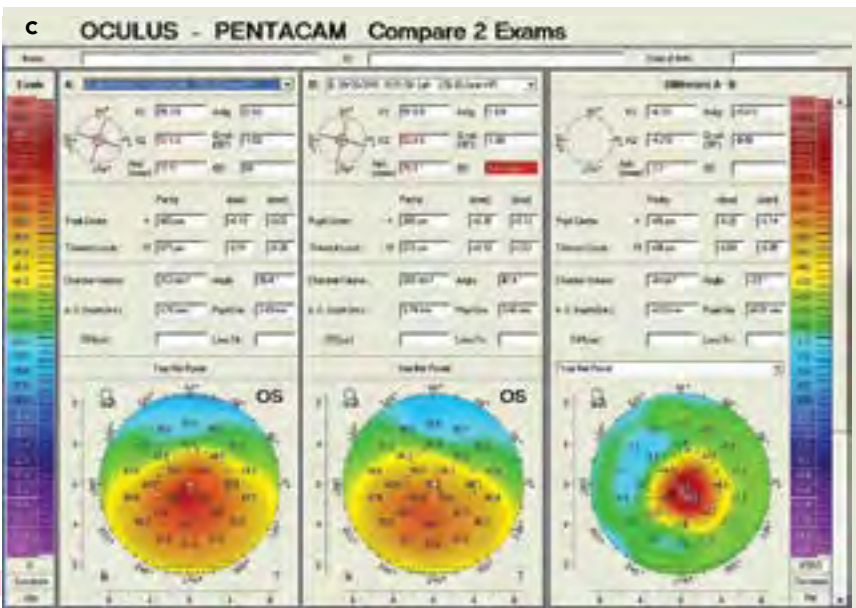
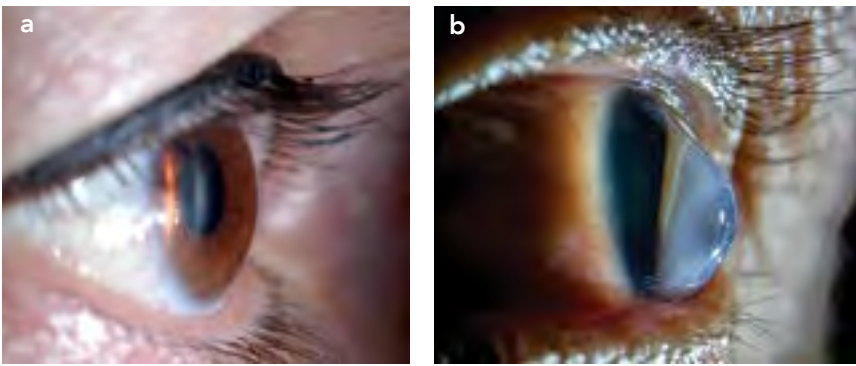


This spirit of innovation continues with the pioneering work to strengthen the tissues of the eye by modifying the bonds between its basic structural building blocks. Crosslinking of the collagen fibers of the cornea in patients with keratoconus has been shown to stabilize the condition. Specialists at Columbia were among the first to provide corneal crosslinking in the U.S. and are now examining methods for early characterization of keratoconus and alternative methods of crosslinking. An understanding of the genes and the aging processes causing various forms of macular degeneration has led to therapeutic targets and possible new therapies.

TTC44ATTTCGGTTTACACGATCCAGAGTGC GGTAACCTTAACCTCAGCTACGAGAGCATCAT

Overleaf: Connective tissue proteins (shown here in rabbit sclera), such as fibrillar collagens and elastic fibers, provide mechanical strength and elastic recoil to tissues such as the cornea and sclera. Therapeutic tissue cross-linking (TXL) aims to strengthen failing tissues, rather than replacing them with transplantation. Using a two-photon excitation confocal microscopy system, the lab of Dr. David Paik is studying the interplay between these structural proteins and quantifying TXL's strengthening effect. Second harmonic generated (SHG) images in red are produced by collagen fibers, while green autofluorescence images are emitted by elastic fibers (yellow arrows). The composite image shows the interplay between these two important proteins.

Currently two of these pharmacological therapies, for dry macular degeneration and Stargardt disease (a juvenile form of macular degeneration), have moved from the laboratories at Columbia to clinical trials across the country. A vigorous effort in regenerative medicine through the use of gene modifying and stem cell therapy is on the verge of clinical application. It is the desire to prevent visual disability that pushes our scientists and clinicians to work to advance new therapies and accelerate their development.



Leejee Suh, MD
 Miranda Wong Tang Associate Professor of
 Ophthalmology at CUMC

David Paik, MD
 Assistant Professor of Ophthalmic Science
 (in Ophthalmology)

FIGURE 1

(a) Normal cornea, (b) cornea with keratoconus. Keratoconus, the most common primary ectasia of the cornea, is characterized by localized corneal thinning with subsequent astigmatism, myopia, and scarring, leading to vision loss. Keratoconus affects a young population, with many requiring corneal transplantation. Our institution was a leader in the first national trials showing that corneal collagen crosslinking can effectively halt the progression of keratoconus and other types of ectasia, thereby avoiding the need for transplantation.

(c) Pentacam corneal mapping of patient that shows keratometry before (left) and after (center) corneal collagen crosslinking. The difference map (right) shows a flattening effect on the central cornea after this procedure.

(d) A new method for early diagnosis of keratoconus, developed by the Silverman Lab, involves in vivo assessment of the stiffness of the corneal structure known as Bowman's layer. The image at left demonstrates increased acoustic impedance, a proxy for stiffness, in the area of maximum corneal deformation in advanced keratoconus. By contrast, at right, stiffness is decreased centrally compared to normal corneas in otherwise asymptomatic fellow eyes of subjects with unilateral keratoconus.

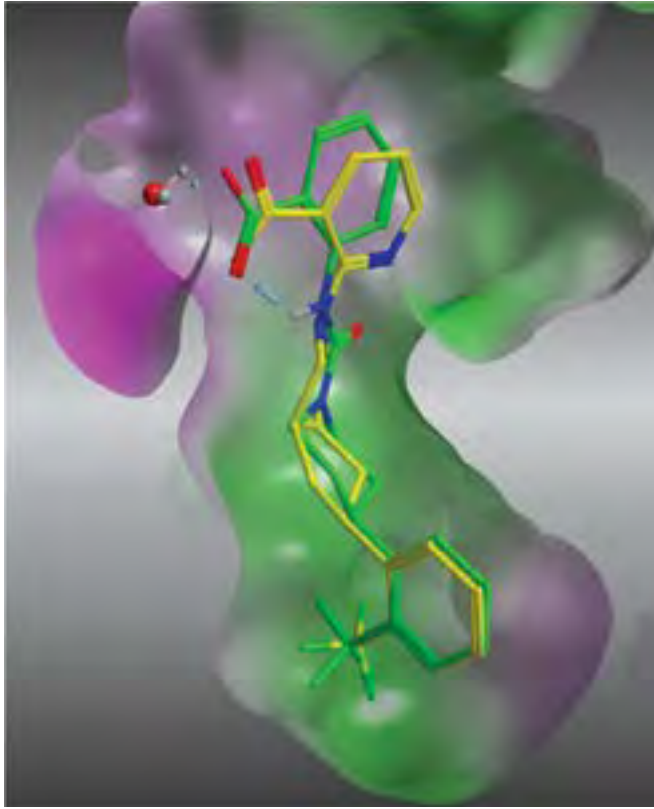
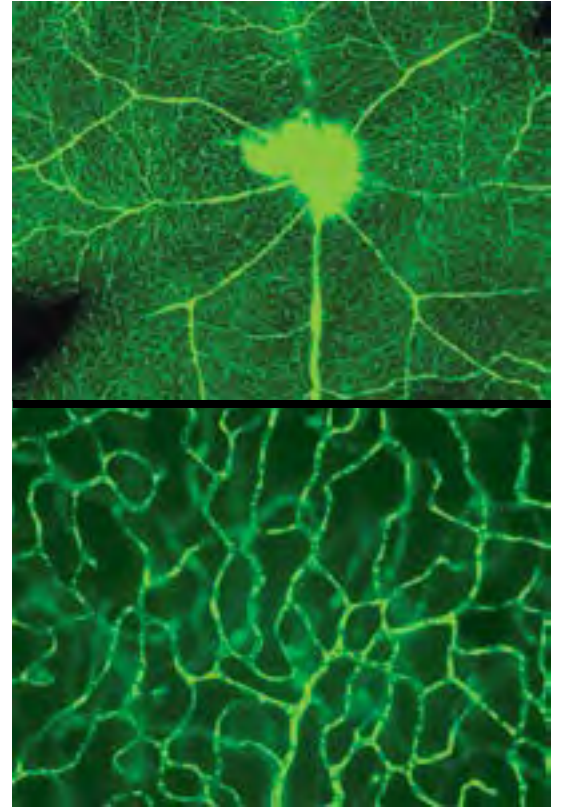


FIGURE 2,3



TTC46ATTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCATT

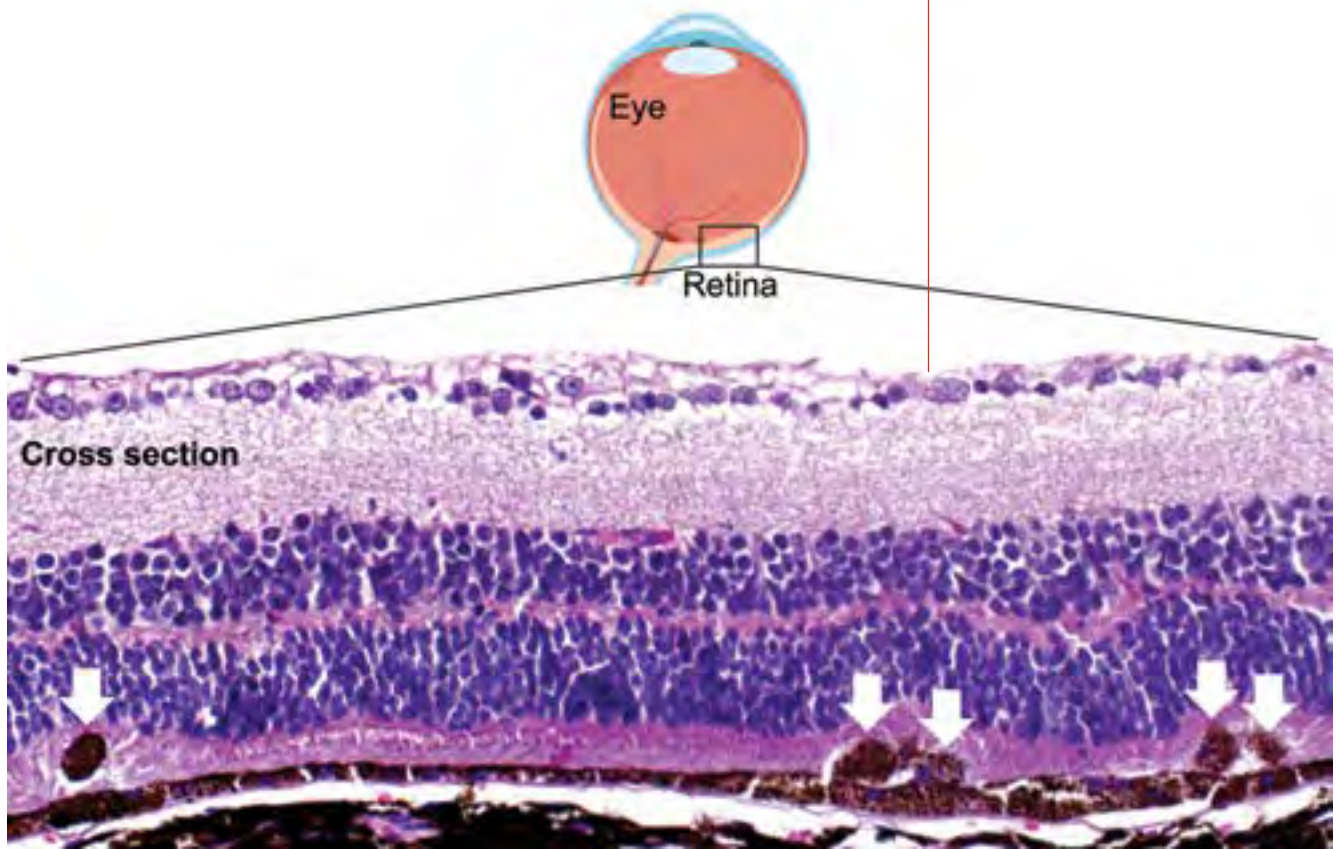
Konstantin Petrukhin, PhD

Associate Professor of
Ophthalmic Science (in
Ophthalmology) at CUMC

We employ **computational strategies for rational design of pharmacological treatments for atrophic age-related macular degeneration and Stargardt disease**. A computerized molecular docking approach, shown above, models the interaction of synthetic retinol antagonists with retinol-binding protein 4 at the atomic level. This allows us to select drug candidates with optimal binding potency against the drug target. Optimized analogs reduce accumulation of cytotoxic vitamin A derivatives in the eye, which is predicted to inhibit the progression of atrophic changes in the retina. Current diabetes treatments have limited efficacy in addressing the

risk of developing microvascular complication of diabetes such as diabetic retinopathy, the most frequent cause of new cases of blindness among working-age adults. Despite intensive glycemic control, 80% of Type 2 diabetes patients will progress to retinopathy within 15 years of disease onset. In addition, diabetic retinopathy develops in most individuals with Type 1 diabetes. We are investigating the potentially beneficial effects of synthetic retinol-binding protein 4 ligands on normalizing vascular function in animals with diabetic retinopathy. **The above images illustrate the protective effect of a pharmacological treatment on vascular integrity in the retina of a diabetic animal.**

FIGURE 4



Ilyas Washington, PhD

Assistant Professor of Ophthalmic Science (in Ophthalmology)

In retinal diseases such as **Stargardt disease, retinitis pigmentosa, and age-related macular degeneration (AMD)**, the retina undergoes several anatomical changes. We attempt to identify the causes of these changes, on a molecular level, to gain a stronger scientific understanding of retinal disease. For example, **the above image shows a cross section of a mouse retina.** Like the human retina, the mouse retina is composed of several types of neuronal cells, layered on top of one another. White arrows point to abnormal structures that appear in the retina of these mice as they age. Similar structures appear in the retina of people with AMD, Stargardt disease, and retinitis pigmentosa.

We developed therapeutic approaches to prevent these pathological changes in animals, and thus may also have the potential to halt loss of vision in humans. We have partnered with the pharmaceutical industry, and are now evaluating these therapeutic approaches in patients.

CTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGTTGCGGTAACCTTAA47CTC

The background of the entire page is a dense grid of small, multi-colored spots (red, green, yellow, blue) on a black background, resembling a DNA microarray or a gel electrophoresis result. A solid blue horizontal bar is positioned at the top left, containing the text 'BIO-INFORMATICS' in white, uppercase letters.

BIO-INFORMATICS

Personalized medicine

The background of the entire page is a black field filled with a dense, random pattern of small, glowing dots in various colors including red, green, yellow, and cyan. The dots vary in size and brightness, creating a bokeh-like effect.

offers the potential to tailor healthcare

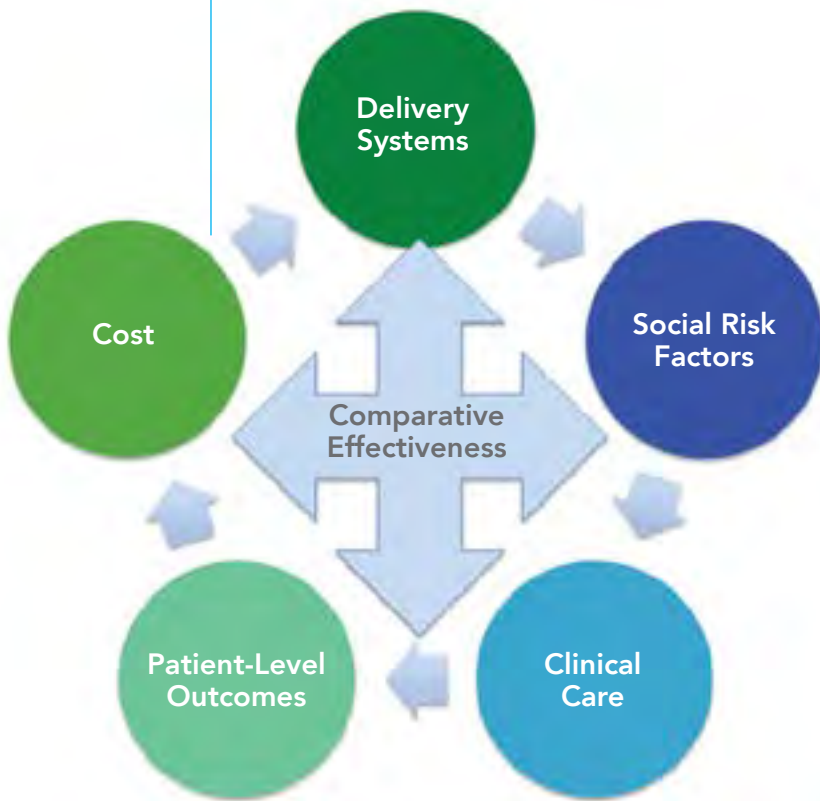
to the needs of an individual patient, improving health and leveraging healthcare resources more efficiently. The premise and promise of personalized medicine is that it will lead to powerful new diagnostics and therapeutics for treatment and prevention, based on each person's unique genetics, behavior and environment. A "Big Data" approach, utilizing multiple data points from various sources, permits the development of these individualized, patient-specific treatment plans. By combining Big Data resources and evidence-based practice, we are developing an ophthalmologic model that integrates determinants of ocular health at multiple levels, ranging from genetic to clinical to population-level diagnostic and intervention strategies. Ongoing research includes detection of new disease diagnostic biomarkers, remote patient monitoring, and identification of new environmental, behavioral and policy interventions that impact eye disease.

The process of taking large data sets and turning them into epidemiologic and clinical research is complex and requires innovative statistical and modeling techniques. By integrating Big Data from diverse sources, including electronic medical records, surveys, healthcare claims, and pharmaceutical claims, we can determine real-world comparative effectiveness and clinical effects closer to the delivery of care. Our ongoing work at Columbia University uses a pioneering data set of approximately 100,000 patients obtained from merging claims and survey data.

Overleaf: The gene array for the *ABCA4* gene, cloned by Rando Allikmets, PhD. The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. It is expressed exclusively in retina photoreceptor cells. Mutations in this gene are found in patients diagnosed with Stargardt disease, retinitis pigmentosa, cone-rod dystrophy, early-onset severe retinal dystrophy, fundus flavimaculatus, and age-related macular degeneration.

Next-generation sequencing has also made rapid acquisition of whole genome and exome sequences of individual patients a reality. This has revolutionized the genetic analyses of eye diseases, but it has also exponentially increased the amount of genetic data that must be obtained, stored and analyzed. One exome of a single patient contains 5-10 billion base pairs of data; one genome contains 100X more. At Columbia Ophthalmology, we are approaching 2,000 exomes being sequenced and analyzed, a volume that cannot be handled by individual laboratories. In a prime example of truly integrated genetics research under the Columbia Precision Medicine Initiative, our data are acquired and analyzed in collaboration with the Institute for Genomic Medicine (IGM), where our resources are complemented with IGM's sequencing, data storage and analysis tools.

FIGURE 1

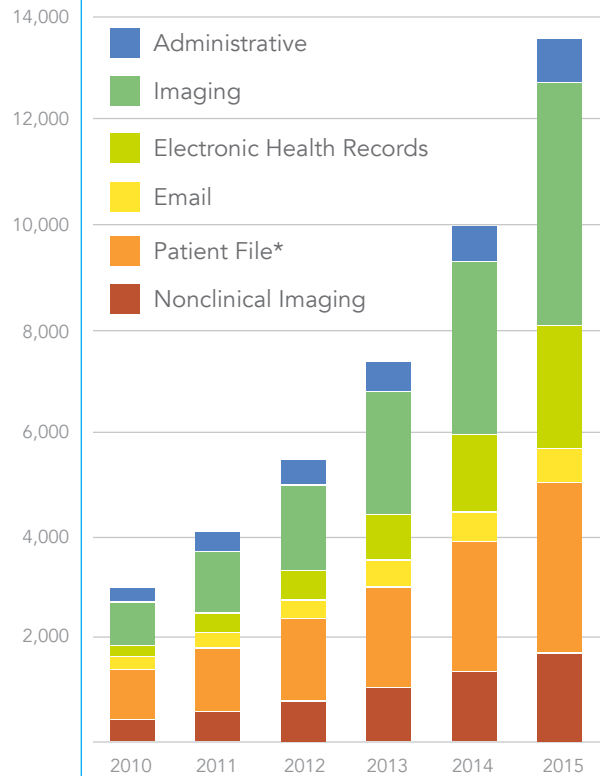


Dana Blumberg, MD, MPH

Assistant Professor of Ophthalmology at CUMC

The Institute of Medicine defines comparative effectiveness research (CER) as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care.” CER sits at the intersection of clinical research, health services research, economics, and epidemiology. Its aim: to better inform clinical decision-making at all levels. Big Data allows CER researchers to compare interventions across settings of care, patient populations, and payers to generate personalized results.

FIGURE 2



Sources of Healthcare Big Data in North America in Petabytes

The explosive increase in smart devices and emergence of fast, reliable and more affordable gene sequencing has enabled the development of patient-specific, health-related data resources. In recent years, medical data has grown at unprecedented speed, with projections to reach 25,000 petabytes by 2020, a 50-fold increase from 2012. For reference, all the data in all North American libraries make up less than two petabytes.

* Patient File refers to files and paperwork in a patient chart that are not part of the electronic health record.

CTATTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGTGCGGTAACCTTAA51CTC

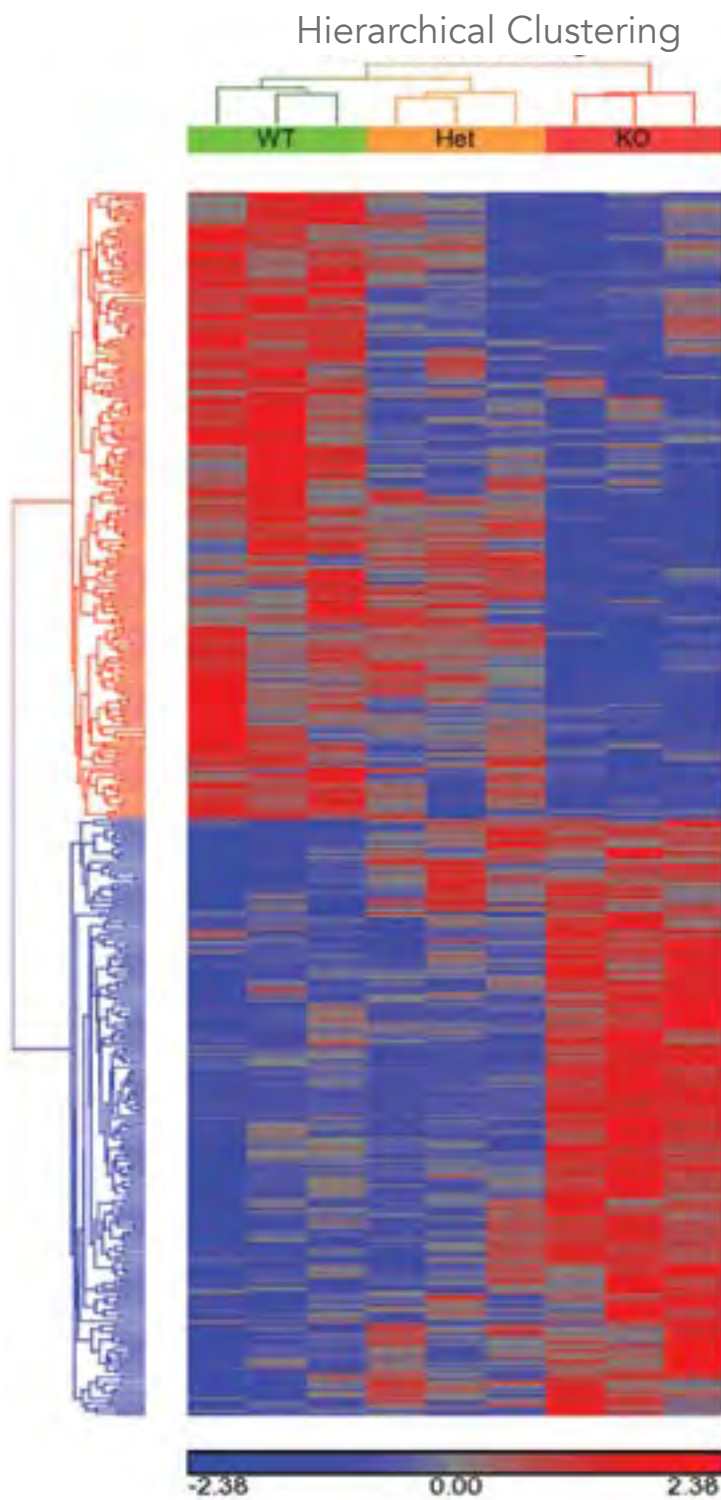


FIGURE 3

Andrei Tkatchenko, MD, PhD

Associate Professor of Ophthalmic Science
(in Ophthalmology, and Pathology and Cell
Biology)

Hierarchical cluster analysis of the retinal RNA-seq data from a knockout mouse, in which the myopia-causing gene was deleted from the genome. This image also shows gene clusters that distinguish knockout mice from the wild-type and heterozygous animals.

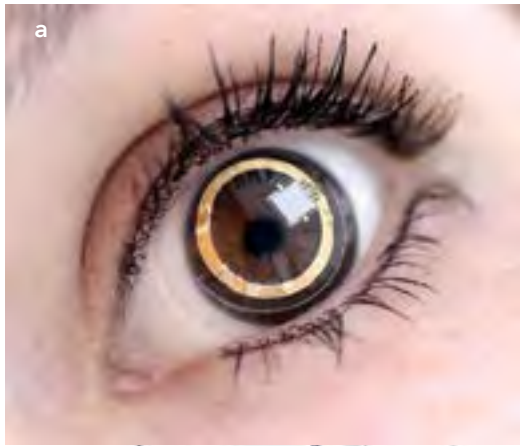
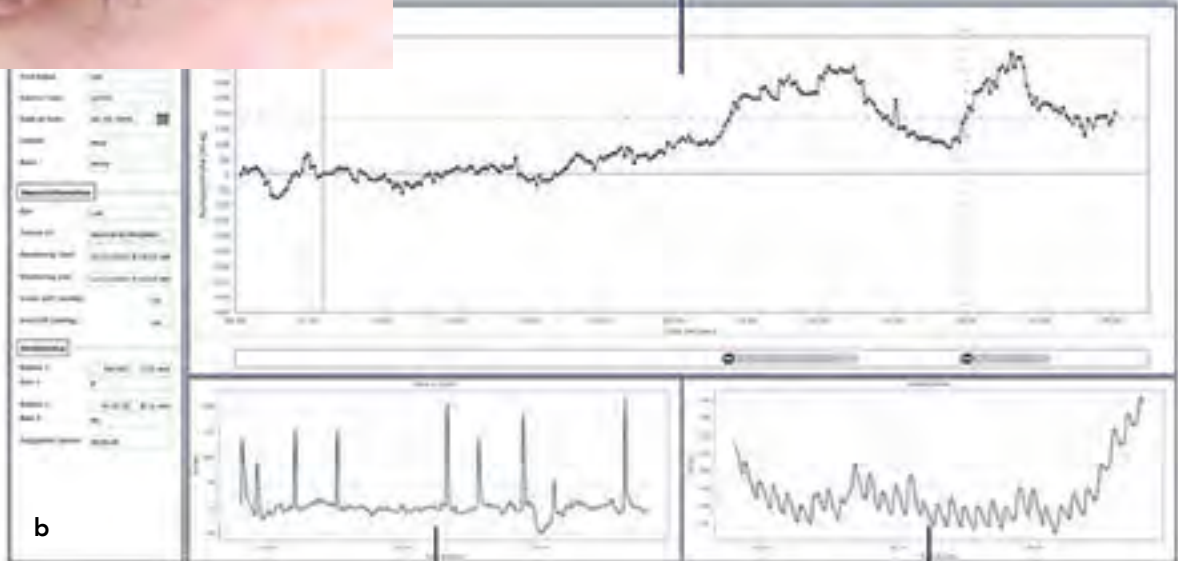


FIGURE 4

24-hour profile of ocular dimensional changes



Example of a detailed view of eye blinks during 30 seconds.

Example of a detailed view of ocular pulsation during 30 seconds.

C. Gustavo De Moraes, MD, MPH

Associate Professor of Ophthalmic Science
(in Ophthalmology), Director of Clinical Trials Unit

(a) This breakthrough contact lens sensor (Triggerfish, Sensimed) estimates intraocular pressure based on changes in the curvature of the cornea and volume of the eye. Our studies show that these measurements can help clinicians assess the risk of future visual field progression in glaucoma patients.

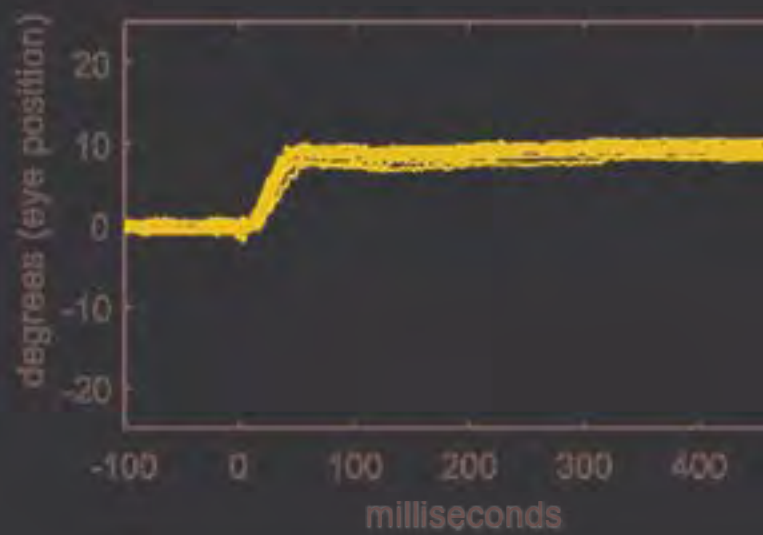
(b) Output of the contact lens sensor shows a patient's 24-hour intraocular pressure patterns. Individual patients can have their treatment tailored according to their specific features and needs.

TRANSLATIONAL MEDICINE & CLINICAL TRIALS

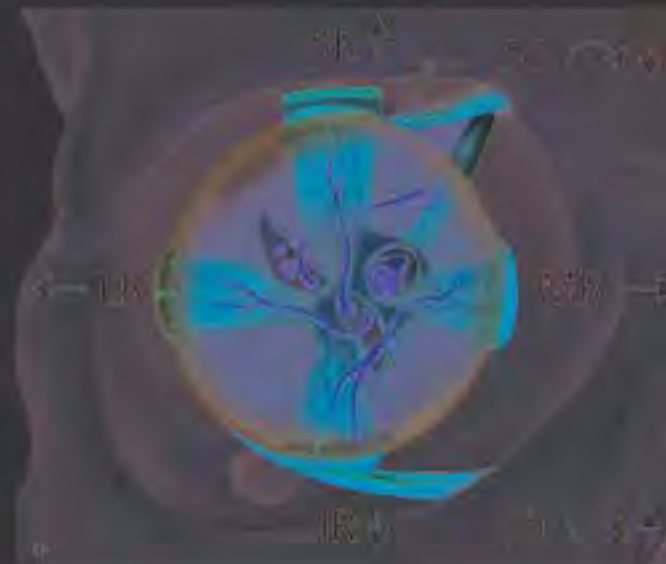
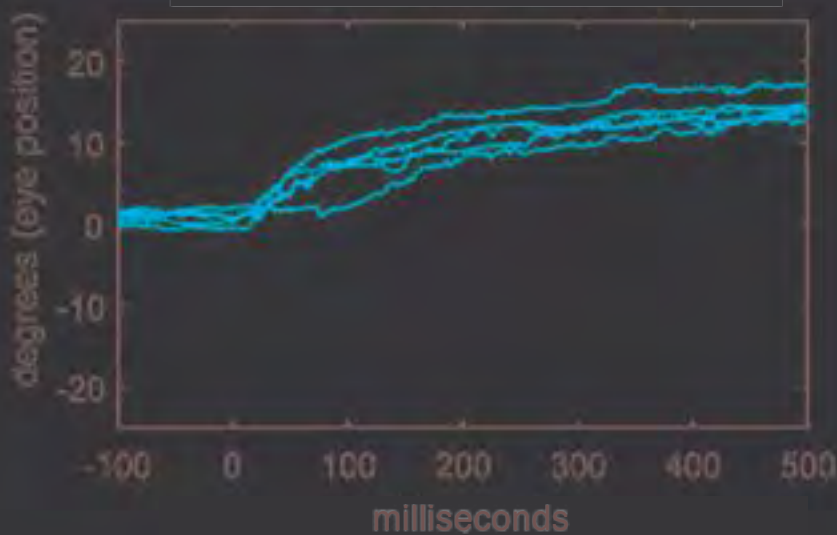
Saccade Speed Summary



10-degree Saccade Downwards



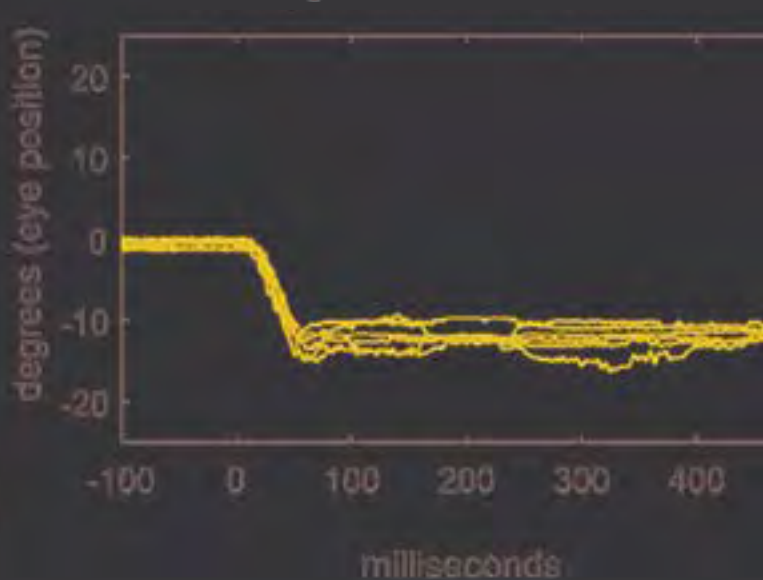
10-degree Saccade to Right



Main Sequence: Horizontal Saccades



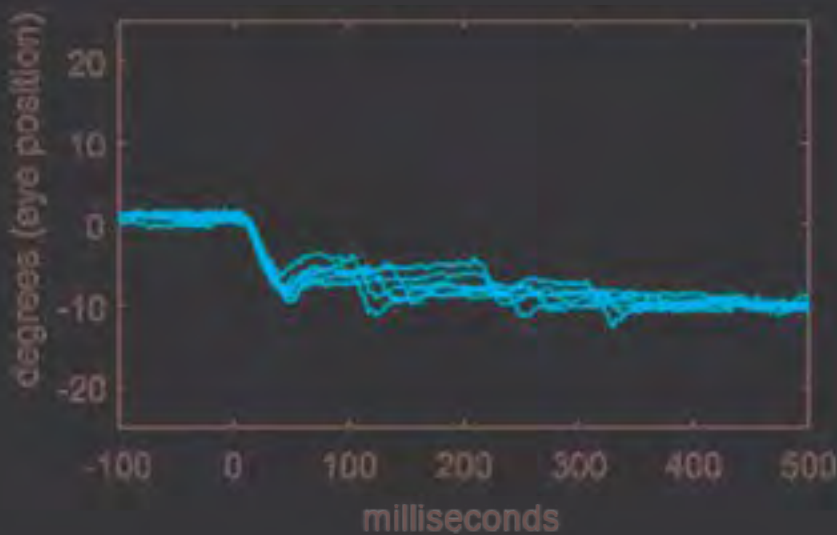
10-degree Saccade Downwards



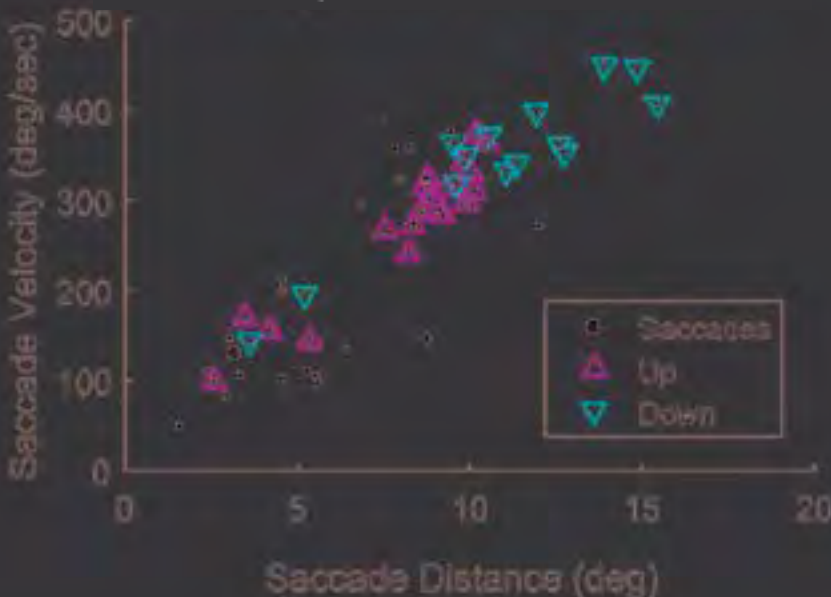
Eye Movement Velocity

Saccade Right : 128 deg/sec (CI = 101-155)
Saccade Left : 347 deg/sec (CI = 313-380)
Saccade Up : 312 deg/sec (CI = 290-336)
Saccade Down : 393 deg/sec (CI = 342-443)

10-degree Saccade to Left



Main Sequence: Vertical Saccades



Translational Research has two key components: the process of applying discoveries generated through laboratory research and preclinical studies to the development of human trials and studies, and research aimed at enhancing the adoption of best practices in the community. Underpinning both of these is research on cost-effectiveness of prevention and treatment strategies. Translational research is therefore a unidirectional continuum, moving research findings from the researcher's bench to the patient's bedside and the community.

The Clinical Trials Unit (CTU) of the Edward S. Harkness Eye Institute was created in March 2014 to bridge breakthrough basic science research into clinical care while safeguarding patients' safety during all phases of clinical studies. The CTU fosters the implementation of clinical studies from the initial idea, through regulatory affairs, data storage, management and analysis, and publication, to application in daily practice. These studies range from enhanced diagnosis and management of glaucoma, regeneration of the optic nerve and retinal tissues, new treatment options for age-related macular degeneration, Stargardt disease, keratoconus, and the development of new drugs or delivery systems to the eye. The CTU also oversees collaborations with other Columbia departments, as well as multicenter clinical studies.

Overleaf: With images like this from the high-resolution, high-frame-rate eye tracker (shown on next page), eye movements including saccadic gain, intrusions, smooth pursuit and nystagmus can be quantified. This helps to pinpoint potential neurological etiologies including vascular, inflammatory, autoimmune, neurodegenerative, congenital, genetic, toxic, infectious, neoplastic and elevated intracranial pressure. From the lab of Dr. Linus Sun.

We are investigating how the brain uses a proprioceptive sense of eye position to encode for positions of objects in visual space. By improving our understanding of visual stability and object tracking, we hope to treat conditions including nystagmus, double vision, optic ataxia, oculomotor apraxia, and visuospatial dysgnosia. Using proteomics and bio-informatics analysis tools, followed by pharmacologic or transgenic testing in animal models, we will pursue novel molecular biomarkers for early identification of glaucoma, as well as neuroprotective and immunomodulatory strategies for treatment. We are also deploying advanced imaging and novel perimetric strategies to assess ocular structure and function, including a new central visual field index that optimizes detection of changes in macular function, and statistical models to detect and predict progression using standard field testing strategies.

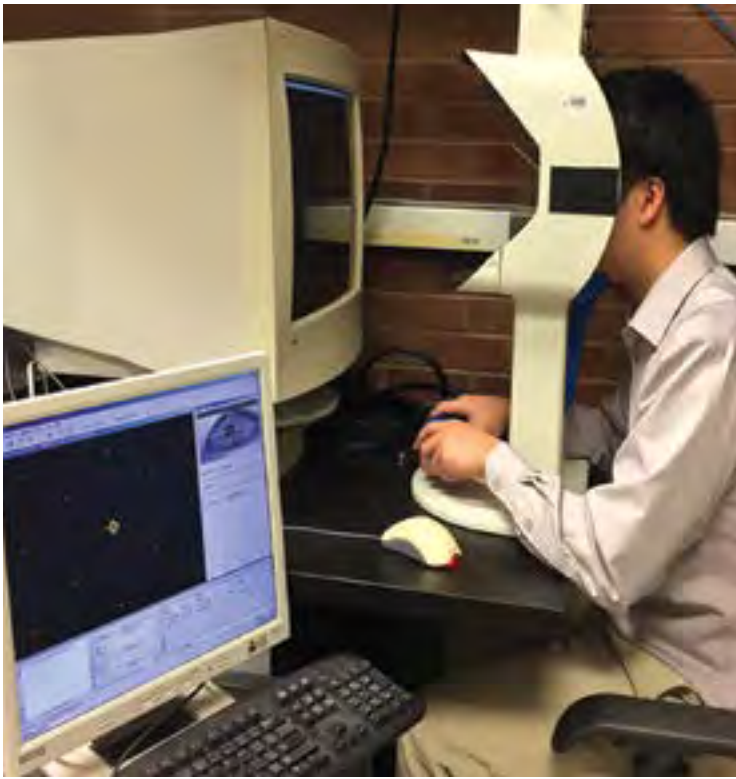


FIGURE 1

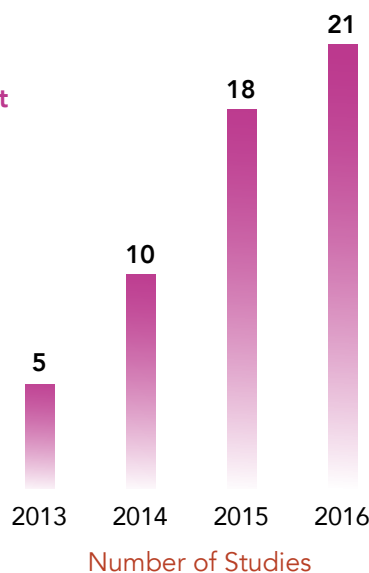
Abnormal eye movements can signal a number of possible underlying neurological conditions, including disorders of the neuromuscular junction, extraocular muscles, cranial nerves, vestibular apparatus, cavernous sinus, brain stem, cortex, and cerebellum. Historically, however, eye movements have been characterized descriptively, and subtle eye movement abnormalities have often remained unidentified after the physical exam.

Linus Sun, MD, PhD

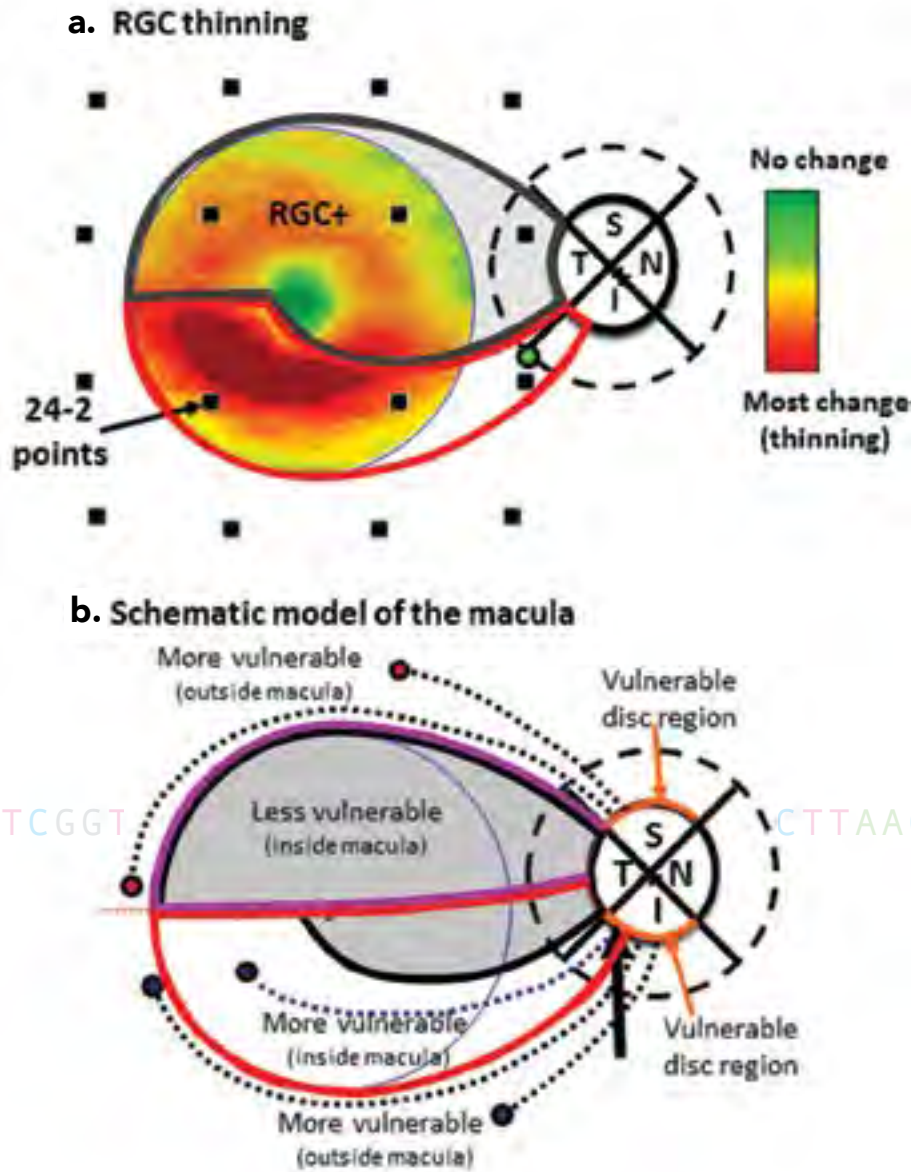
Instructor in Neurology
(in Ophthalmology)

Growth of Clinical Trials Unit

The Edward S. Harkness Clinical Trials Unit had a fourfold increase in the number of studies since 2013, and includes industry-sponsored studies and studies funded by the National Institutes of Health / National Eye Institute (NIH / NEI).



Dr. Sun, board certified in neurology and director of the clinical eye movement laboratory, uses a high-resolution, high-frame-rate eye tracker to precisely quantify eye movements and facilitate a more accurate diagnosis. When a patient requires a neuro-ophthalmic consultation for symptoms such as loss of vision, doubling of vision, illusions, hallucinations, optic nerve disease, abnormal eye movements, or nystagmus, time domain and main sequence eye movement offer a simple and effective way to review the oculomotor exam. These measurements may also become part of the standard of care for a patient's visit to the general ophthalmologist or neurologist.

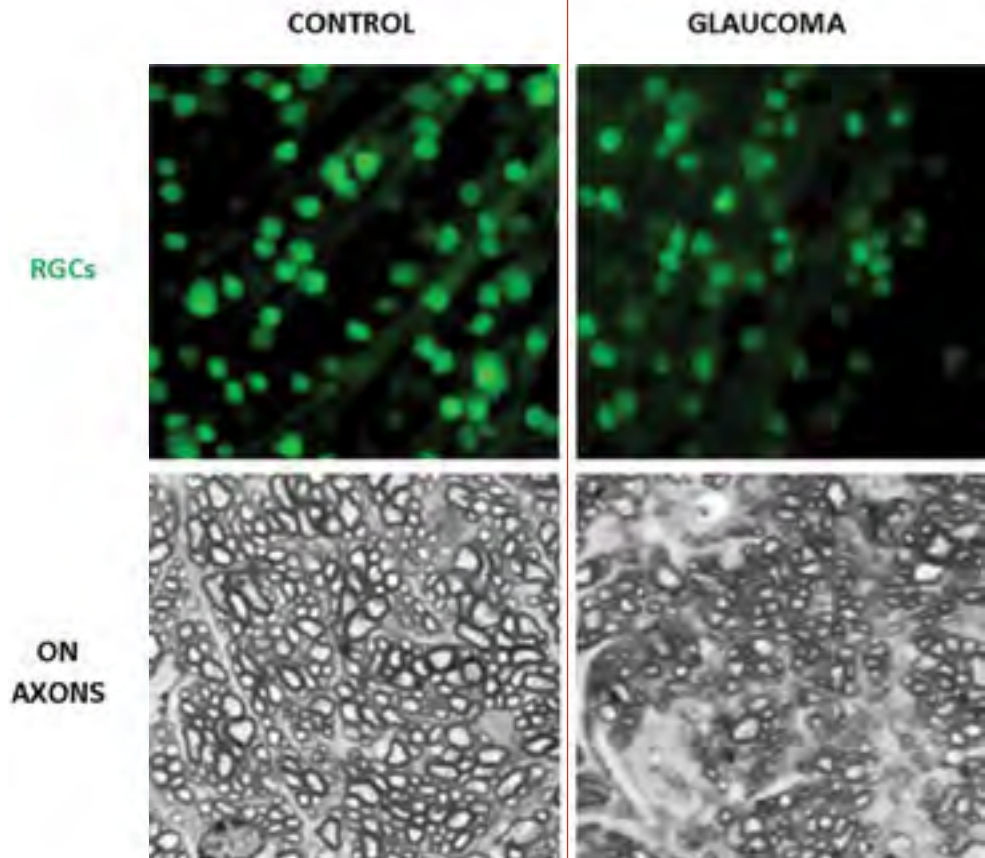


Donald Hood, PhD

James F. Bender Professor of Psychology; Professor of Ophthalmic Science (in Ophthalmology)

Recent OCT and behavioral (i.e., perimetric) evidence indicate that **the essential region of the retina for reading and recognizing faces, the macula, is damaged in early glaucoma.** This damage, shown in the dark red region in (a) has been largely overlooked because the test points (black squares) of the perimetric test typically used to screen for glaucoma fall largely outside the damaged region. As illustrated by the schematic model in (b), the retinal ganglion cells (RGC) from the macular region within the red borders send their axons to the inferior quadrant (black arrow) within one of the two more vulnerable regions of the disc (orange arcs).

FIGURE 3



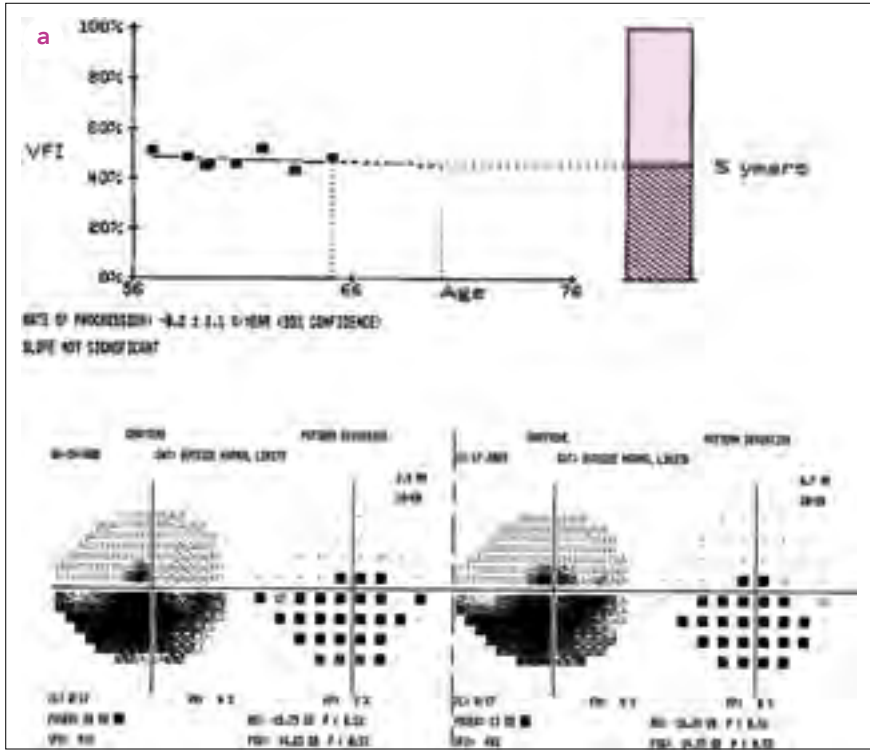
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Gülgün Tezel, MD

Professor of Ophthalmic Science
(in Ophthalmology)

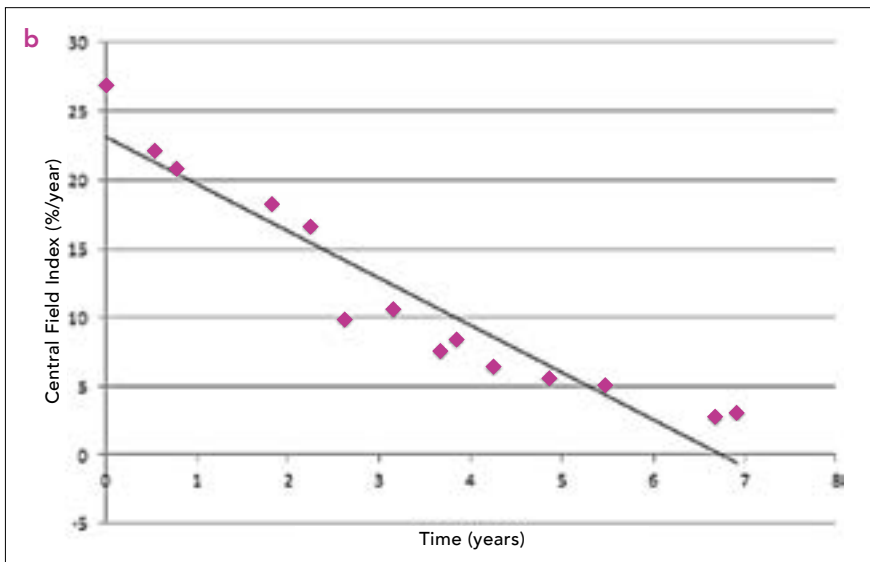
Our high-throughput and cell type-specific proteomics data sets, obtained from retinal ganglion cells and glia, provide a framework to generate hypotheses that can be translated into better understanding and treatment of neurodegeneration in glaucoma. Using animal models, we functionally assess these molecules and pathways as potential treatment targets for neuroprotection and immunomodulation. Here, we analyze the effects of specific pharmacological treatments or cell type-targeted transgenic deletions on glaucomatous injury to retinal ganglion cells (top panels, control and glaucoma,

respectively) and optic nerve axons (bottom panels, control and glaucoma, respectively) in animal models of induced glaucoma.



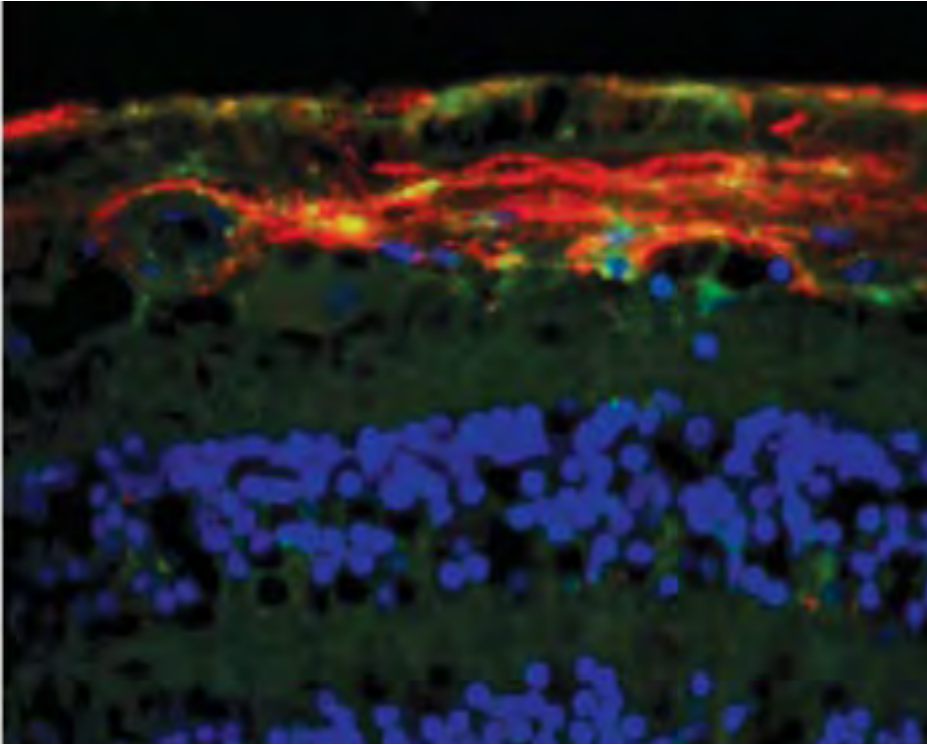
C. Gustavo De Moraes, MD, MPH
 Associate Professor of Ophthalmic Science (in Ophthalmology),
 Director of Clinical Trials Unit

TTC60ATTTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCATT



Progression of this patient's glaucoma would have been missed, and aggressive treatment delayed, using only the conventional method of assessment depicted in image (a). In this commercially available report depicting the visual field index (VFI) rate of change and the event-based analysis of a glaucoma patient (GPA, Carl Zeiss, Meditec, Inc.), the flat slope (-0.2%/year) did not reach statistical significance. The novel central visual field index plotted in (b), however, reveals a significant deterioration with a slope of -3.4%/year ($P < 0.001$).

FIGURE 5



Gülgün Tezel, MD

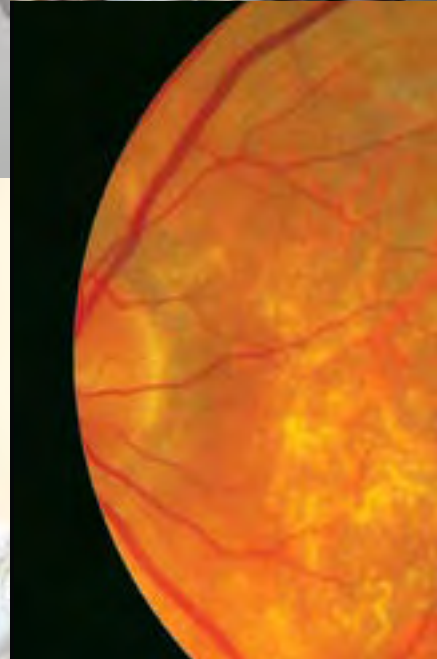
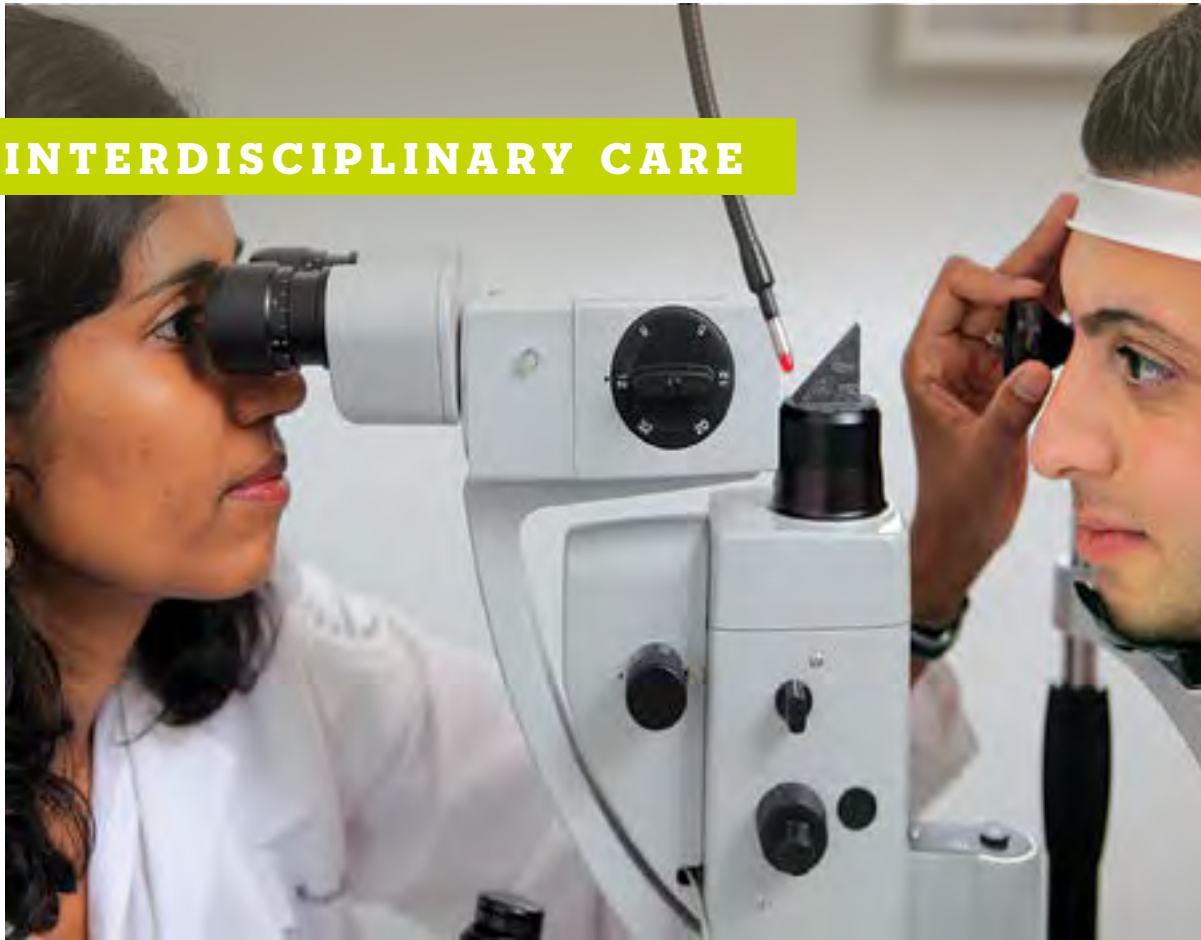
Professor of Ophthalmic Science
(in Ophthalmology)

CTATTTTCGGTAGCATCATTCTATTTCGGTTTACACGATCCAGAGGTTGCGGTAACCTTAA61CTC

The complexity of glaucoma requires a treatment strategy that, to be the most effective, targets multiple sites of injury and multiple pathogenic pathways. Our recent findings suggest that oxidative stress and neuroinflammation, which reflect common processes impacting neuron survival and glia-driven secondary processes at different injury sites from retina to brain, are promising treatment targets. Among the inflammatory molecules we are testing to provide immunomodulation and neuroprotection in glaucoma is glial NF-κB, a redox-sensitive

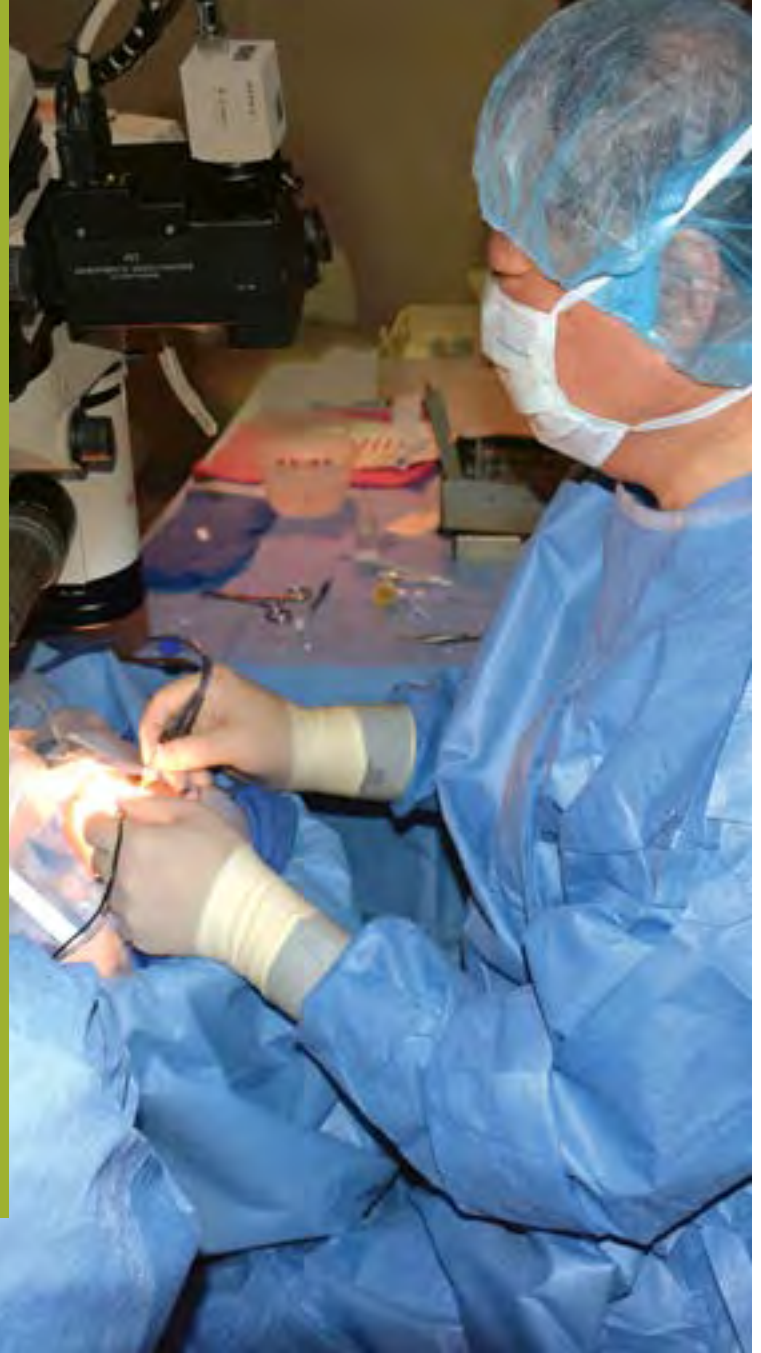
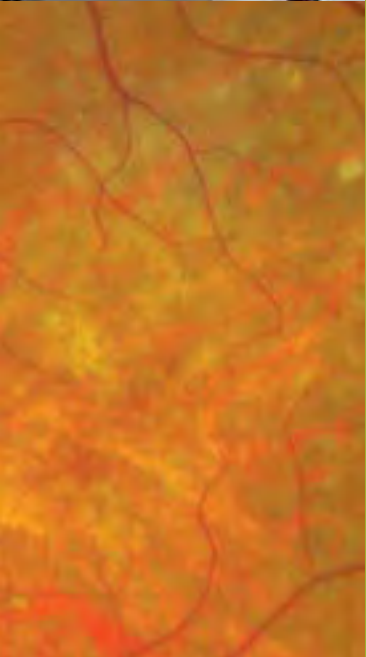
transcription factor activating the inflammatory mediators. Shown here is prominent localization of increased phospho-p65 (a subunit of NF-κB) immunolabeling (green) in GFAP-positive astroglia (red) in the ocular hypertensive retina. Blue corresponds to nuclear DAPI labeling.

INTERDISCIPLINARY CARE





As our knowledge of diseases affecting the eye continues to expand, and physicians become ever more subspecialized, preservation of vision depends on a multifaceted approach that merges the application of basic scientific and clinical research with new technology and outstanding clinical care. Integrating these components is key to our core philosophy. We deliver care for the most complex ophthalmic problems, often involving the combined clinical and surgical efforts of multiple subspecialists. At the same time, our scientists continue to expand our understanding of disease and develop innovative ways to apply genetic and epigenetic scientific advances to benefit individual patients.



In a groundbreaking new approach focused on developing precision-guided diagnoses and treatment of sight-threatening diseases, we are more formally integrating the work of our basic scientists, ophthalmic specialists, genetic counselors, and care coordinators. This initiative, made possible by the generous philanthropy of the Jonas Family Fund and Anne Stean Corneal Research Fund in New York City, leverages the combined power of genetic testing and sequencing, proteomics, and detailed phenotypic testing to develop the detailed understanding of individual patients and families necessary for truly personalized care.

TTC 64 ATTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCATTT

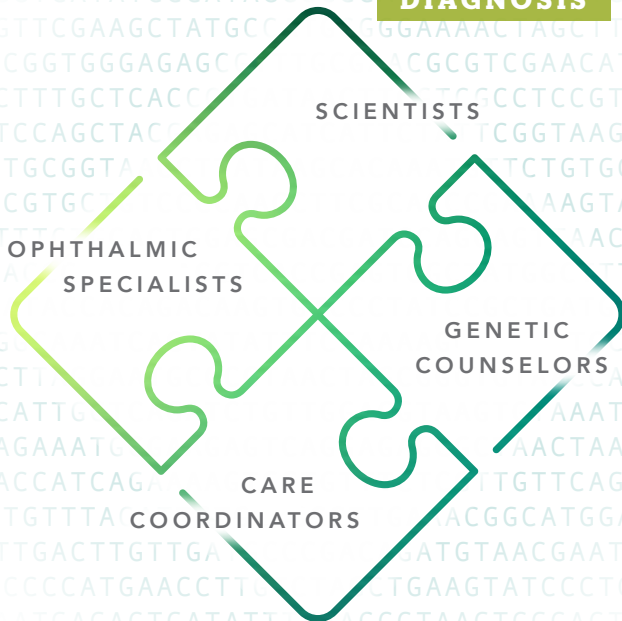
Most importantly, the program seeks to harness the power of multidisciplinary clinical collaboration and research necessary to successfully meet the daunting challenges and opportunities that Precision Ophthalmology™ poses. Our new biobank will store blood and tissue samples and provide a trove of information for investigations by our research teams. Our focus on the rapid, easy and candid exchange of information between scientists and clinicians at the University, nationally, and around the world is reflected in our numerous extramural grants, top-tier publications, and ongoing important discoveries. We strongly believe that the most effective way to achieve our goals in Precision Ophthalmology™ is through the development and expansion of these strong collaborative networks.

Overleaf: Everything you have read to this point—genetics, stem cell biology, imaging, bio-informatics and Big Data, and therapeutic innovation—converges in integrated, personalized, multidisciplinary clinical vision care. This is the ultimate promise of Precision Ophthalmology.™

JONAS CHILDREN'S VISION CARE

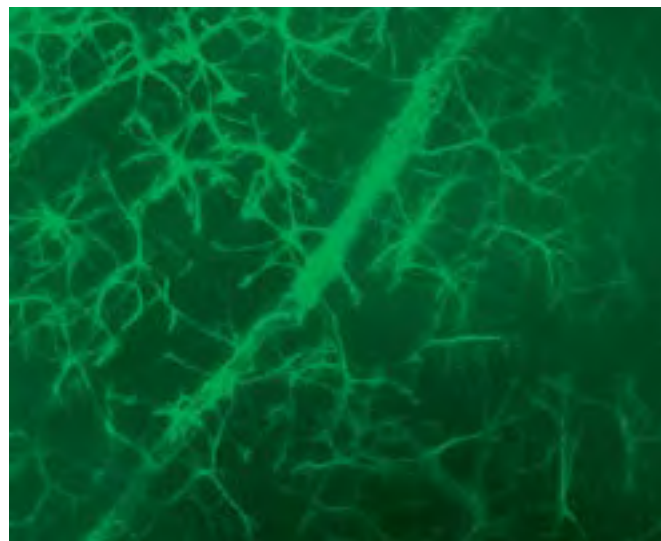
PRECISION-GUIDED

DIAGNOSIS



The concept of **multidisciplinary clinical care**, and its relationship to Precision Ophthalmology,TM is well illustrated by the recently launched initiative by the Department of Ophthalmology at Columbia. This novel program represents a joint effort by the Department and the generous philanthropy of the **Jonas Family Fund in New York City**. The goals of the program are to unite basic scientists, ophthalmic specialists, genetic counselors, and care coordinators in a far-reaching initiative focused on developing precision-guided diagnoses and treatment of sight-threatening diseases of childhood such as retinopathy of prematurity.

Retinopathy of prematurity (ROP) is a potentially blinding disorder affecting premature infants. Understanding the molecular and cellular mechanisms responsible is critical to developing effective strategies for prevention and treatment. Retinal astrocytes are an important population of cells involved in providing guidance for developing retinal vessels. When these are injured, normal retinal vascular development and repair cannot occur, and blindness may ensue. **The photomicrograph (right) shows the appearance of healthy astrocytes** in a mouse model of ROP during the reparative phase of the disorder. The astrocytes are labeled with a green fluorescent marker.



Steven Brooks, MD

Anne S. Cohen Professor of Ophthalmology (in Pediatrics) at CUMC



Lama Al-Aswad, MD, MPH

Associate Professor of
Ophthalmology at CUMC

Recognizing the multiple risk factors for blindness in the local community, Dr. Lama Al-Aswad, shown above interviewing a patient by videoconference, launched a free glaucoma screening project in 2007. From 2007 through 2014, 8,584 individuals from high-risk populations were screened for glaucoma across Washington Heights, Harlem, and the Bronx. The project was the first of its kind to provide free eye exams and evaluations, and recommendations for follow-up visits, staffed by bilingual eye health professionals. Approximately 25% of those screened tested positive for glaucoma; 56% had never seen an eye doctor in their lifetime. Led by Dr. Al-Aswad, Columbia Ophthalmology is now taking the fight against the leading causes

of blindness—glaucoma, diabetic retinopathy, macular degeneration and cataracts—out of the traditional clinic and onto the streets of New York City by dispatching what is believed to be the first-ever, mobile, “real-time tele-ophthalmology” unit into neighborhoods at high risk for eye disease. Equipped with state-of-the-art technology such as optical coherence tomography (OCT), the mobile unit will deliver free, high-quality care directly to individuals in their communities. This model has the potential to change the paradigm of healthcare, advancing population health management by targeting high-risk populations and screening them for eye diseases free of cost.

TTTC66ATTTCGGTTTACACGATCCAGAGTGCGGTAACCTTAACCTCAGCTACGAGAGCATCATTT

RESIDENCY PROGRAM



Bryan Winn, MD

Associate Professor of Ophthalmology at CUMC and Residency Program Director

To improve surgical outcomes and patient safety, the Harkness Eye Institute designed a new surgical curriculum consisting of structured surgical mentorship, accelerated participation in phacoemulsification steps during the first year of residency (a), reading assignments and online cognitive pretraining using COACH Ophthalmology (b), participation in an annual resident cataract symposium, wet lab training (c), with simulator eyes (d), surgical video review (e), Eyesi cataract surgery simulator (VRmagic, Mannheim, Germany) training (f), and implementation of a standardized surgical technique

with supervision by "core" cataract surgery instructors for the first 25 cases. After curriculum implementation, residents' surgical outcomes rose to levels rivaling those of highly experienced surgeons. This strongly suggests that developing and implementing a structured cataract surgical curriculum can substantially improve quality and patient safety related to resident surgical outcomes.

DEPARTMENT STATISTICS

6TH
in NIH funding



in 2015

22
best doctors



in national and regional rankings¹

205
abstracts



published in the last year

119
publications



published in the last year

BY THE NUMBERS

273

Total departmental staff and faculty

40

Full-time faculty

23

Part-time faculty

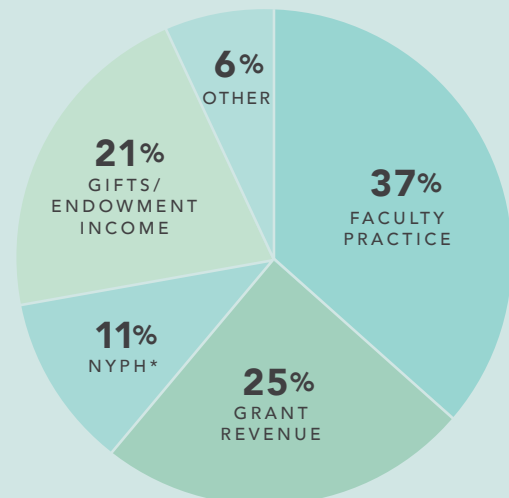
9

Clinical fellows

11

Ophthalmology residents

ANNUAL BUDGET



*NewYork-Presbyterian Hospital

RECENT ACCOMPLISHMENTS

- Discovered **new genes for retinal degenerations** — *RDH11*, *CWC27*, *RGS22* (Allikmets, Tsang with ERDC)
- Discovered new genes/loci for **age-related macular degeneration (AMD)** — *TIMP3*, etc. (Allikmets with AMD consortium)
- Developed and refined imaging modalities — qAF, NIR-AF, OCT, ultrasound, AO-SLO — allowing much more **detailed clinical characterization of patients** (Sparrow, Silverman, Greenstein, De Moraes, Hood)
- Developed **small molecule treatment** for Stargardt disease and AMD with RBP4 antagonists; clinical trial slated for 2017 (Petrukhin)
- Implicated **MDM2/MDMX genes** in ophthalmic disorders (Zhang)
- Defined *APLP2* gene as a **therapeutic target in myopia** (Tkatchenko)
- Determined **how drusen evolve** in the aging monkey retinal epithelium (Gouras)
- Edited a point mutation in the *RPGR* gene by CRISPR/Cas9 in **fibroblast-derived iPSCs** from a patient (Tsang)

>70,000
patient visits



served last year,
including >15,000 new
patient visits

>4,000
surgeries



performed
annually

57
projects



sponsored by
grants²

25%
grant funding



of the department's
annual budget³

10 NAMED LECTURESHIPS

Stanley Chang, MD Lectureship
Arthur Gerard DeVoe, MD Lectureship
Zacharias Dische, MD Lectureship
John H. Dunnington, MD Lectureship
Max Forbes, MD Lectureship
David Pearce, MD Memorial Lectureship
George K. Smelser, MD Lectureship
Abraham Spector, MD Prize Lectureship
Florence Epstein Teicher Lectureship
Ulrich Ollendorff, MD Lectureship

MAJOR FUNDED PROGRAMS

Acquavella Scholar Fund
The Russell Berrie Diabetic Retinopathy Research Unit
Bernard and Shirlee Brown Glaucoma Research
Laboratory
Robert Burch Family Eye Center
Burch Scholar Fund
Flanzer Eye Center
Gloria and Louis Flanzer Vision Care Center
Gloria and Louis Flanzer Amphitheatre
Louis V. Gerstner Jr. Clinical Research Center in Vision
Gerstner Scholar Fund
Irving Vision Research Laboratory
Jonas Children's Vision Care
Jonas Vision Research Laboratory
Kirby Fellow
Edith and Denton McKane Memorial Fund
Stephen M. Ross Pediatric Eye Center
Jean and Kent Sheng Glaucoma Fellowship
C.V. Starr Scholarship Fund
The Starr Foundation Retinal Research Unit
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Design: hgDesign NYC

Writing: Gina Shaw

Printing: Epic Litho

Editors: Jane Heffner,
Bonnie Wang,
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Photography: John Abbott;
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Special thanks to
Ophthalmology Photography
and Imaging; Archives and
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