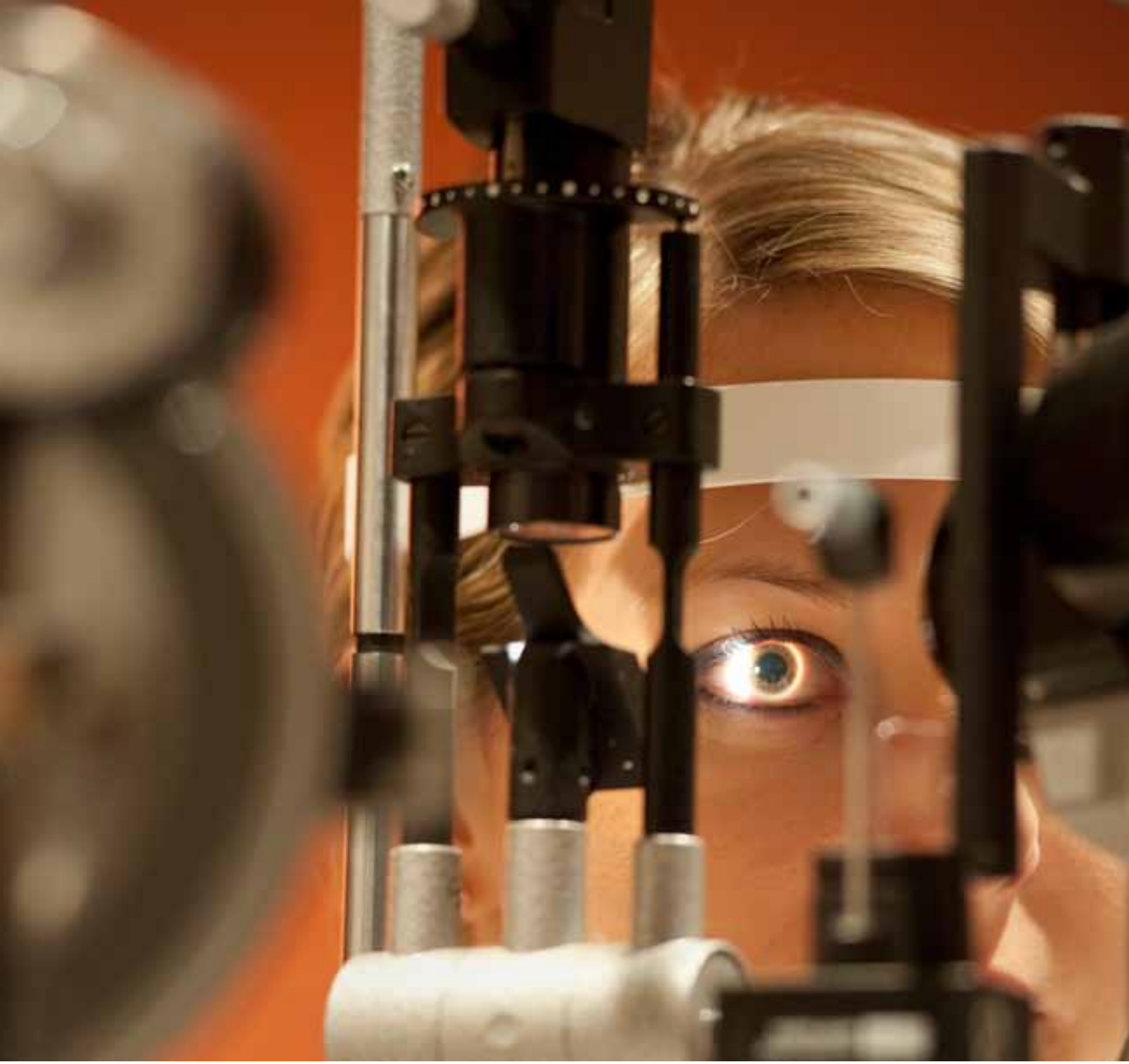

FRONTIERS IN OPHTHALMOLOGY

Harvard Medical School
Department of Ophthalmology

Harvard Medical School
Department of Ophthalmology
Frontiers in Ophthalmology 2011

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MESSAGE FROM THE CHAIR

Welcome colleagues, friends and supporters to the Harvard Medical School (HMS) Department of Ophthalmology's inaugural edition of Frontiers in Ophthalmology. I am proud and excited to share with you this first report, which highlights significant clinical, scientific, and educational milestones of the department's world-class affiliated hospitals and research institutions. Our report reflects on two decades of discovery and progress in the field of vision science, and the tools and technologies that are transforming the lives of people and patients across the globe.

From Boston to Bangladesh, improving ophthalmic care and its delivery to millions of people worldwide is a shared vision and singular goal of the HMS ophthalmic community. Advancing technology, expanded global connections, and thriving new alliances among HMS affiliates and across the broader scientific community are fueling gains in vision science, education, and medicine. As you'll read in the following pages, HMS scientists, physicians, and academics from all ophthalmic disciplines and across every subspecialty are brainstorming in the lab, the classroom, and the clinic. Their shared knowledge is driving ideas forward and, ultimately, improving care to patients.

Educating the next generation of leaders

The HMS Department of Ophthalmology has a proud history of teaching, training, and mentoring generations of students who become leaders in their field. In the last several years, we've reinvigorated, refined and retooled our educational program to challenge and inspire students at every level of their medical education.

Our training program features a newly restructured surgical curriculum for residents, which now integrates lectures and customized wet lab sessions supervised by attending physicians. Groundbreaking faculty efforts are reshaping resident education with the development of revolutionary, computer-simulated technologies that fine-tune surgical knowledge and skills outside the operating room. Innovative courses and conferences—including our nationally recognized cataract course and new vitreoretinal course—offer students added venues of scientific inquiry and learning, and attract prominent, international speakers. We continue to forge strong alumni ties through our expanded lecture series, a robust visiting professors program, a new AMD symposium, and a newly revamped and expanded three-day Annual Meeting & Alumni Reunion. Across the HMS community and abroad, our expanded alliances with affiliates and partners have sparked unprecedented opportunities for surgical, clinical, and research training. All of these endeavors offer an unparalleled educational experience for our brilliant young trainees.

Advancing science

Thanks to a paradigm shift in collaboration among basic researchers and clinician scientists, insights gained in the lab are accelerating bench-to-bedside discoveries faster than ever before. The last decade has seen groundbreaking advances in human genetics, regenerative medicine, and inflammation and immunology; these, in turn, have led to a host of new treatments, technologies, and therapies aimed at alleviating the suffering associated with eye diseases and blindness. HMS researchers have focused intensely on these areas, and are beginning to unravel some of the mysteries surrounding disease processes, and the biological mechanisms or environmental influences that may cause them to go awry.

For example, you'll read about advances in age-related macular degeneration (AMD) pioneered by the HMS Angiogenesis Research Group. The foundations of the group's work not only illuminated how new blood vessel formation in the eye (neovascularization) contributes to severe forms of AMD, but also spurred revolutionary clinical treatments that halt and sometimes reverse pathological blood vessel growth. Today, anti-VEGF inhibitors and therapies developed in our labs have saved or improved the sight of nearly a million people around the world. Recent and exciting results from a large-scale, phase 3 clinical trial for treating macular edema in diabetic patients showed dramatic visual improvement using the anti-VEGF drug Lucentis®. These groundbreaking efforts represent a quantum leap in treatment for patients with diabetes—the first in 25 years—and are rapidly establishing new standards of care.

In cornea, HMS faculty members are pursuing novel translational research that has shed new light on the roles of angiogenesis and inflammation in ocular disease. Clinical trials in these areas are providing a robust baseline of data—facilitating the development of therapies to combat these diseases. HMS cornea scientists are also leading industry efforts to harness powerful, new imaging technologies that more precisely target,

track, and treat corneal disease, and ultimately improve patient outcomes. You'll also read about advances to our Boston Keratoprosthesis (Kpro)—the most widely used corneal prosthesis in the world—coupled with aggressive outreach efforts to make it available to patients worldwide. To date, some 5,000 people in 50 countries, including the United States, are beneficiaries of our KPro programs.

In 2005, significant advances in whole-genome screening technologies, coupled with increasingly powerful computing capabilities, are enabling us to explore DNA inheritance with unimaginable precision and speed. For the first time, opportunities to examine gene-gene and gene-environment interactions will help us determine who may be at increased risk for specific diseases. Efforts within the department are already underway to exploit this potential: we are currently integrating information and expertise across the department through new centers of excellence, building a massive biorepository of donor tissue and DNA samples, integrating vast amounts of genetic and clinical information, and launching our new Ocular Genomics Institute. All of these efforts welcome a new era of personalized medicine—which ultimately means better care for everyone.

Pursuing excellence in patient care

The cornerstone of our mission is the quality of care we provide to patients. Significant efforts by HMS faculty are impacting our full spectrum of patient care—from prevention to treatment to rehabilitation. For example, cutting-edge technologies are giving us better prognostic information that enables us to diagnose and treat ocular diseases faster and more efficiently. More targeted and less invasive drug treatments and therapies are preventing, saving, and sometimes restoring sight in patients, young or old. Recent and exciting developments in lens technology—already helping to improve Kpro outcomes—may soon offer great therapeutic benefits across a broad range of eye disorders and diseases. Pioneering advancements in rehabilitative medicine are enabling site-challenged patients to maximize their vision—sometimes even restoring sight—with new tools, technologies, and therapies that improve their quality of life.

Physicians and faculty across the HMS ophthalmic community have a long tradition of collaborating on patient care, research, and academic activities. We've recently forged critical new alliances that have enabled unprecedented expansions in service to our patients and enhanced our quality of care. For example, we've boosted our presence in the Longwood Medical Area by launching a new outpatient practice at Joslin Diabetes Center's Beetham Eye Institute, and by adding emergency eye trauma coverage and inpatient consultation at Brigham & Women's Hospital. The Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital officially joined forces when Mass. Eye and Ear established a formal department of ophthalmology at Mass General, enabling highly coordinated patient care and expanding educational and research partnerships. Children's Hospital Boston and Mass. Eye and Ear have integrated their pediatric services, and now offer general pediatric ophthalmology and highly specialized pediatric strabismus care at both institutions. The recent merger between Schepens Eye Research Institute and Mass. Eye and Ear has created the world's largest ophthalmology research enterprise. We've also welcomed a cadre of bright, talented physicians and clinician scientists to support these important endeavors and to meet a steady rise in patient volume.

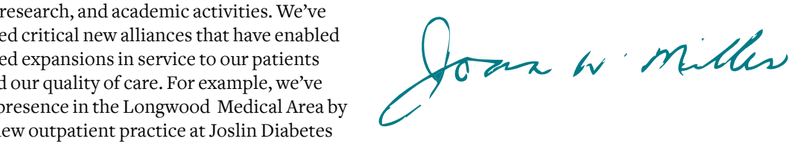
The future is now

The pace and progress of vision science is hurtling forward at momentous speed, spurred on by a host of exciting new research discoveries, an unprecedented culture of collaboration, and the unflagging efforts of our premier group of clinicians, researchers, and educators. As you'll read in these pages, our affiliate institutions that comprise the HMS Department of Ophthalmology have made remarkable gains in medical science and ophthalmic practice that are both broad in scope and high in impact.

Despite these gains, there is much to accomplish and a growing imperative to do so; as our population grows older, we can expect a significant rise in the number of people who become blind or visually impaired due to age-related diseases such as macular degeneration, glaucoma, and cataracts. An epidemic rise in the United States of type 2 diabetes is also triggering a surge in diabetic retinopathy—another leading cause of blindness in American adults. According to a study sponsored by the National Eye Institute, blindness or low vision affected 3.3 million Americans age 40 or older in 2004; by 2020, that number is projected to rise to 5.5 million Americans. These are sobering statistics that underscore the relevance of our mission and the call to action for continuing investments in vision science.

Thanks to you, our generous friends and supporters, our quest for innovation continues unabated across the HMS ophthalmic community. As you read on, I hope you'll share our excitement about the significant progress made to date and of the discoveries yet to come. It's a marvelous, inspiring, and empowering time to be at the forefront of vision science.

Welcome to our world of vision.



Joan W. Miller, MD
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Joan W. Miller, MD

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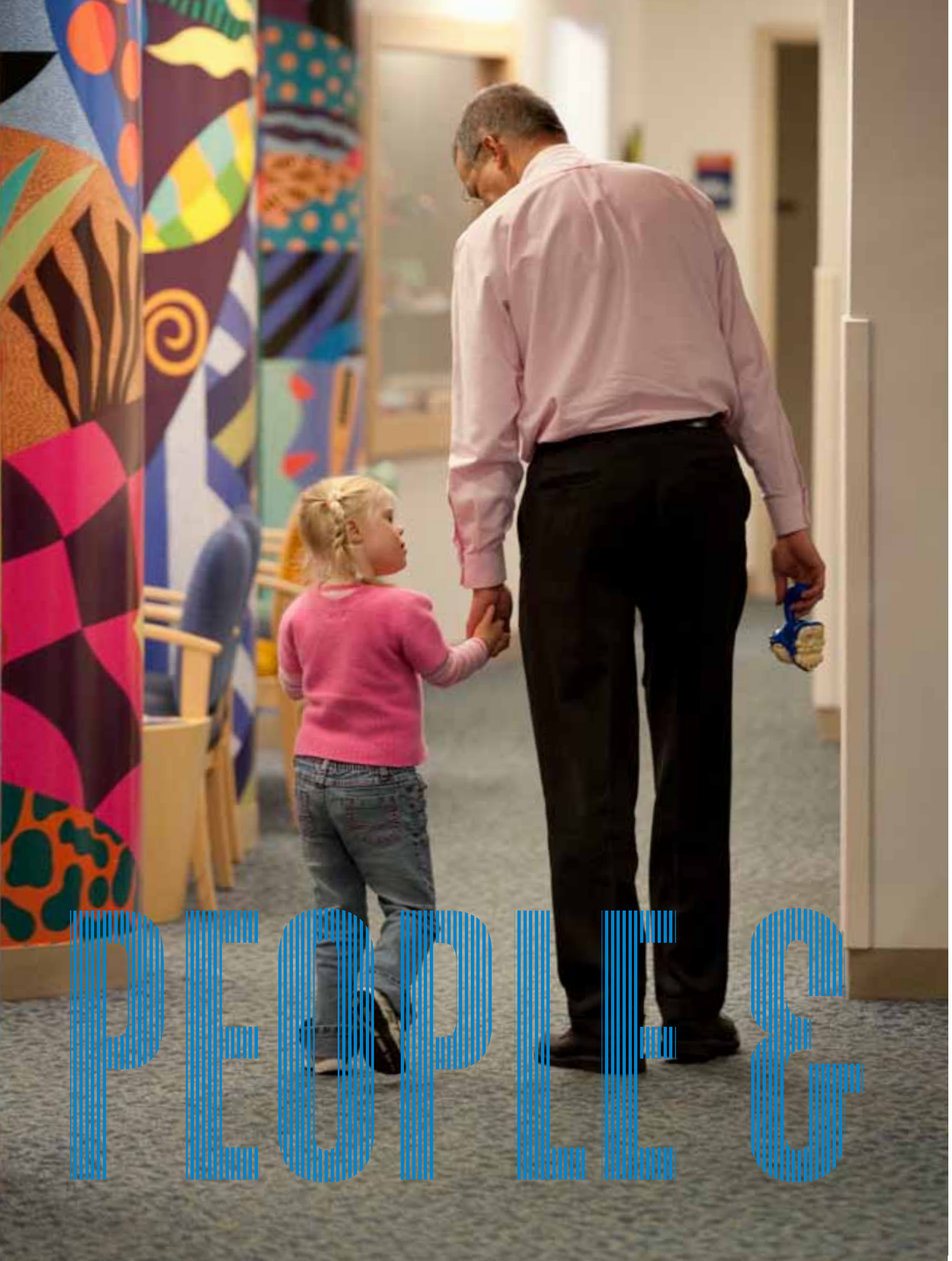
Dr. Joan Whitten Miller was born in Toronto, Ontario, Canada and is a graduate of Massachusetts Institute of Technology and Harvard Medical School. She completed her ophthalmology residency and vitreoretinal fellowship at Massachusetts Eye and Ear Infirmary. Dr. Miller joined the HMS faculty in 1991. She became the first women physician to attain the rank of HMS Professor of Ophthalmology and, in 2003, became the first woman to serve as chair of the department. Additionally, Dr. Miller is director of Mass. Eye and Ear's Angiogenesis Laboratory and a vitreoretinal surgeon in the Retina Service.

Dr. Miller is a preeminent leader in the field of retinal research, and her seminal contributions have helped save the sight of countless individuals suffering from age-related macular degeneration (AMD) and diabetic retinopathy. Her main research interests focus on ocular neovascularization and retinal disease; besides elucidating the molecular mechanisms of angiogenesis and neuroprotection, she leads studies that contribute the development of effective therapies and drug delivery systems. She and her colleagues at Mass. Eye and Ear pioneered the development of photodynamic therapy (PDT) using verteporfin (Visudyne®), the first pharmacologic therapy for AMD able to reduce and slow vision loss. The group also identified the importance of vascular endothelial growth factor (VEGF) in neovascular AMD, and helped develop the prominent anti-VEGF therapies, pegaptanib and ranibizumab—the latter able to improve vision in about one-third of patients with neovascular AMD. While these approaches have improved the outlook for patients with AMD, Dr. Miller and her colleagues continue investigations to elucidate the pathophysiology and to develop next-generation therapies for AMD.

Throughout her tenure as Chair, Dr. Miller has sought vigorously to grow and diversify the core missions of the HMS Department of Ophthalmology, and to establish the department as the undisputed global leader in ophthalmic medicine, education, and research. She has fostered numerous initiatives that have unified and built upon the intellectual and innovative force of the faculty. Substantial investments in leadership and resources, expanded educational and training venues, new research initiatives, and the establishment of new healthcare alliances have all contributed to the department's strong growth and increasing national and international presence. In 2008, Dr. Miller created five HMS Vice Chair positions to lead the areas of basic research, academic programs, centers of excellence, medical education, promotions, and reappointments. This new leadership structure has helped integrate the efforts of HMS affiliates and partners—promoting communication and multidisciplinary collaborations in all three mission-critical areas.

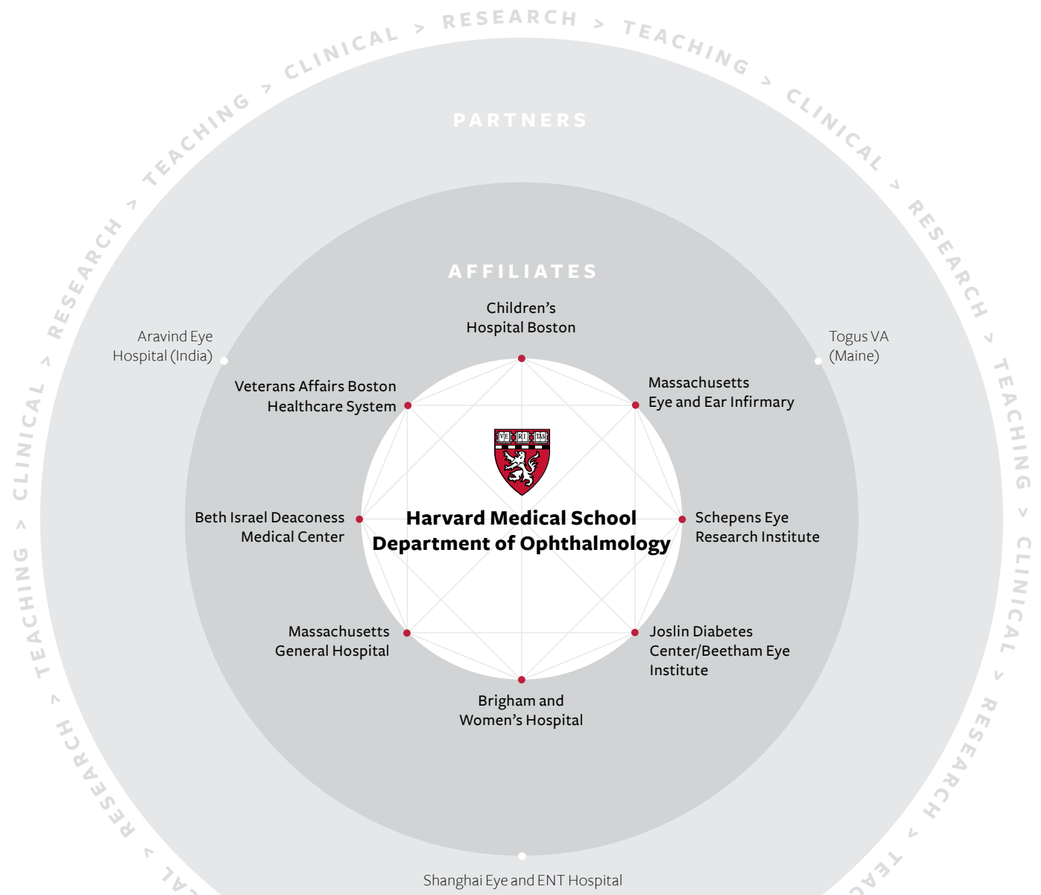
Dr. Miller is emphatically committed to supporting the incredible talent and dedication of HMS faculty. She has championed numerous administrative supports that have created a progressive and rewarding 21st century work environment. Dr. Miller has vigorously promoted superb faculty funding and mentoring programs, a renewed emphasis on promotions and appointments, and new venues for professional advancement and recognition; she also received national recognition for her strong advocacy efforts as the 2010 recipient of the Women in Ophthalmology (WIO) Suzanne Veronneau-Troutman Award. WIO president, Jennifer Lim, MD, lauded Dr. Miller as a "pioneer in enhancing the position and involvement of women in ophthalmology locally and nationally. Women have achieved parity guided by your gender-neutral policies, efforts to encourage women…to leadership positions in patient-care, teaching, research and administration and your support of their academic achievement…You stand out as a strong female voice in the ophthalmology community."

A committed teacher and mentor, Dr. Miller has supervised more than fifty clinical and research fellows, most of whom now hold positions in academic ophthalmology around the world. Her outstanding contributions to retinal science make her a sought-after lecturer in the United States and abroad. She has published more than 140 peer-reviewed papers and 55 book chapters and review articles. She is co-editor of Albert and Jakobiec's Principles and Practice of Ophthalmology, 3rd ed. and a named inventor on nine U.S. patents. She has been honored with numerous awards, including the Rosenthal Award and Donald J. Gass Medal of the Macula Society, the Retina Research Award from the Club Jules Gonin, the Alcon Research Institute Award, the ARVO/Pfizer Ophthalmic Translational Research Award, the Founder's Award from the American Society of Retinal Specialists, the HMS 2010 Joseph B. Martin Dean's Leadership Award for the Advancement of Women Faculty, the Suzanne Veronneau-Troutman Award from Women in Ophthalmology, and the Paul Henkind Memorial Award from the Macula Society.



PEOPLE OF

"Academic medical institutions like the HMS Department of Ophthalmology attract an intellectually curious faculty—individuals who push the boundaries of medicine and science in their often tenacious pursuit of answers."
—Janey Wiggs, MD, PhD, Associate Director of the Howe Laboratory, Massachusetts Eye and Ear Infirmary



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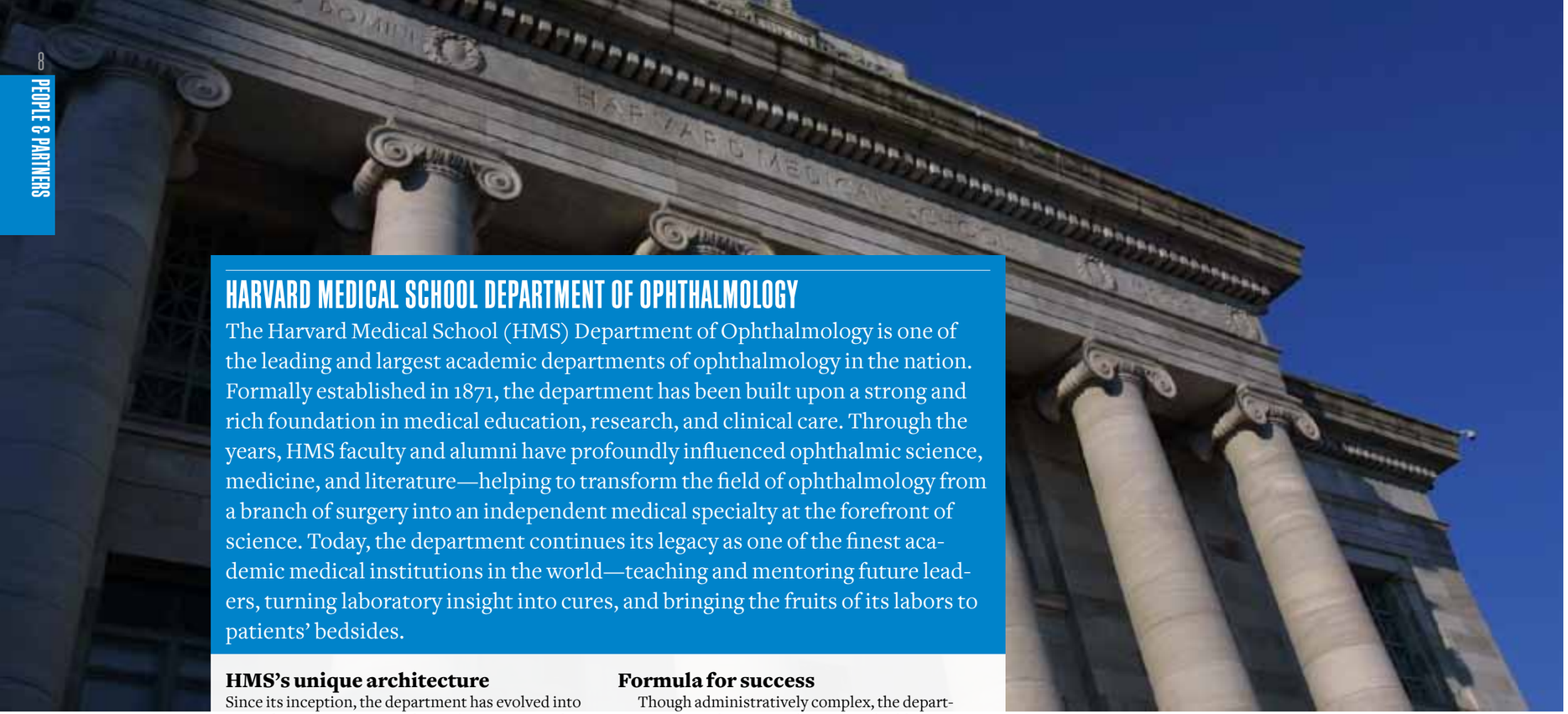


Photo: Harvard Medical School

HARVARD MEDICAL SCHOOL DEPARTMENT OF OPHTHALMOLOGY

The Harvard Medical School (HMS) Department of Ophthalmology is one of the leading and largest academic departments of ophthalmology in the nation. Formally established in 1871, the department has been built upon a strong and rich foundation in medical education, research, and clinical care. Through the years, HMS faculty and alumni have profoundly influenced ophthalmic science, medicine, and literature—helping to transform the field of ophthalmology from a branch of surgery into an independent medical specialty at the forefront of science. Today, the department continues its legacy as one of the finest academic medical institutions in the world—teaching and mentoring future leaders, turning laboratory insight into cures, and bringing the fruits of its labors to patients' bedsides.

HMS's unique architecture

Since its inception, the department has evolved into an academic institution with a multi-institutional structure and a broad base of clinicians and scientists. This decentralized structure is unique among other U.S. academic medical schools, which are typically integrated—physically and financially—into their affiliated universities. Unlike other medical schools, HMS does not own a teaching hospital; instead, the school comprises a network of formal hospital and research affiliations that provide the teaching, training, and research facilities for medical and graduate education. Through a system of faculty titles and cross-appointments, the hospitals and the school are closely linked.

The HMS Department of Ophthalmology is comprised of 140 full-time faculty members who carry out the majority of the department's teaching, research, and patient care activities. An additional 95 faculty members (mostly private practitioners) hold part-time HMS faculty appointments in ophthalmology and participate in various academic endeavors of the department.

Throughout the years, the department's ophthalmic network has grown in both scope and intellect. The department has recruited some of the finest clinician scientists in ophthalmology, and established key affiliations with many of the world's leading academic medical schools and research institutions. These affiliations have added significant depth and breadth to the department's core capabilities, and have created a rich and robust infrastructure steeped in multidisciplinary investigations, educational collaborations, and clinical enterprises.

Formula for success

Though administratively complex, the department's network structure has proven highly successful for a variety of reasons. Affiliates and partners are firmly united in their commitment to educational excellence. Stimulating residency and fellowship opportunities abound throughout the HMS network—offering broad clinical and surgical exposure, as well as rewarding mentorship opportunities, to the faculty and trainees. The collaborative environment also supports a wide array of preclinical and clinical research, and inspires robust scientific partnerships among divergent yet complementary research programs; these unified efforts have led to landmark advances in patient care, many of which are highlighted in this report. Collectively, the broad clinical expertise and deep fund of knowledge allows the Department of Ophthalmology to provide sophisticated diagnostic and therapeutic care for patients, thus ensuring the best possible outcomes.

The Department of Ophthalmology also wholeheartedly embraces the vast diversity of the HMS community, which forms the intellectual backbone of the department. Students and faculty, who represent a myriad of geographical and cultural backgrounds, and are selected based on their accomplishments and future potential. Women represent 45 percent of the full-time faculty, and fill numerous senior-level positions within the department, including Chair. In no small way, the cultural and academic diversity of the HMS community prepares the students and faculty to lead with fresh vision and purpose as they take on the challenges of an increasingly global healthcare environment.

HMS Ophthalmology historic milestones

1869 Henry Willard Williams, AM, MD, presents at HMS the first course of lectures ever given in an American medical school by an ophthalmologist. Two years later, he is appointed to Professor of Ophthalmology, marking the formal establishment of the HMS Department of Ophthalmology in 1871.

1891 Williams' successor, Oliver Fairfield Wadsworth, AM, MD, joins the staff of the Massachusetts Charitable Eye & Ear Infirmary (established in 1824). Soon after, the hospital becomes the hub of Harvard's ophthalmic training.

1891 Benjamin Joy Jeffries, AM, MD, establishes one of the first ophthalmic pathology laboratories in the U.S., at Mass. Eye and Ear. In 1982, the lab is dedicated to renowned HMS ophthalmologist and alumnus, David G. Cogan, MD.

1926 Frederick H. Verhoeff, MD, HMS Professor of Ophthalmology and Mass. Eye and Ear's first full-time researcher and pathologist, establishes the first endowed ophthalmic research unit, the Howe Laboratory, at Mass. Eye and Ear.

1949 The world's first retina service, and first retinal disease fellowship, is established at Mass. Eye and Ear by famed HMS retinal pioneer and innovator, Charles L. Schepens, MD. Dr. Schepens is also credited with establishing the vitreoretinal subspecialty.

1958 Claes H. Dohlman, MD, PhD, considered to be the founder of modern corneal science, establishes the world's first organized cornea subspecialty, and the first structured cornea fellowship program at Mass. Eye and Ear.

1966 Deborah Pavan-Langston, MD becomes the first woman to be accepted into the HMS Ophthalmology residency program. Unlike her male colleagues, Dr. Langston is required to complete a two-year pre-residency fellowship. In 1973, she is appointed the first woman director of Mass. Eye and Ear's Cornea and External Disease Service.

1974 The Berman-Gund Laboratory for the Study of Retinal Degenerations formally opens. The laboratory was conceived as a multi-disciplined research effort between Mass. Eye and Ear and Harvard with the goal of understanding the disease mechanisms involved in retinitis pigmentosa and the more than 30 related diseases that affect the retina.

2003 Joan W. Miller, MD, is named Chair of the HMS Department of Ophthalmology and Chief of Ophthalmology at Mass. Eye and Ear. She is the first woman to hold this dual role.

HMS OPHTHALMOLOGY VICE CHAIRS

John I. Loewenstein, MD

Vice Chair for Medical Education, Department of Ophthalmology, Harvard Medical School

Associate Professor of Ophthalmology, Harvard Medical School

Director, Department of Ophthalmology Residency Training Program, Harvard Medical School

Associate Chief for Graduate Medical Education and Associate Clinical Chief of Ophthalmology, Massachusetts Eye and Ear Infirmary

A graduate of Massachusetts Institute of Technology, Dr. John Loewenstein received his medical degree from the State University of New York at Buffalo and completed his ophthalmology residency at Boston University (BU) School of Medicine. This was followed by a two-year clinical and research fellowship at BU. He initially joined the HMS Department of Ophthalmology as a part-time member of the Retina Service at Mass. Eye and Ear while continuing to practice privately in the Boston area. After a decade, he missed teaching and the academic environment, and in 1994, was invited to join Mass. Eye and Ear/HMS as a full-time faculty member of the Retina Service. He quickly became an integral part of the training program for medical students, residents, and fellows.

In 1996 and 2001, Dr. Loewenstein earned high accolades from HMS ophthalmology residents who honored him as Teacher of the Year. He was also a 2007 nominee for the HMS Prize for Excellence in Teaching. In 2002, with the vigorous support and unanimous approval from residents and administration alike, Dr. Loewenstein was named Director of the Residency Program. A gifted teacher, clinician, surgeon, and manager, Dr. Loewenstein has used his exceptional abilities to enhance the residency program in numerous ways. He has modified and streamlined residency rotations to improve continuity of experience, and to maximize clinical and surgical teaching. He has collaborated with colleagues at the Boston Veterans Administration Hospital to enhance the resident experience, and strengthened communication and feedback among HMS' affiliated teaching hospitals. He is also a strong advocate of achieving progress through collaboration; in this regard, he chairs a biweekly Residency Steering Committee meeting, which provides residents and faculty with a forum where they may address concerns and brainstorm about continuous improvements to the program.

Together with Associate Residency Program Director, Carolyn Kloek, MD, Dr. Loewenstein has created a structured surgical curriculum that enhances the overall training experience for residents. This invigorated curriculum includes faculty-proctored wet labs in cataract surgery, retinal surgery, glaucoma surgery, cornea surgery, and oculoplastics surgery. A step-wise introduction to phacoemulsification (cataract surgery) boosts cognitive learning and reduces resident stress, and a state-of-the-art virtual reality eye surgery simulator enables residents to practice and hone their surgical skills.

In 2008, Dr. Loewenstein was appointed Vice Chair for Medical Education. In this expanded educational role, he continues to cultivate and fine-tune the HMS Residency Program and works closely with the Fellowship Committee Chair to coordinate fellowships across HMS affiliate sites. He also collaborates with the Director of Medical Student Education and the Vice Chair of Academic Programs to identify new educational initiatives and program improvements. Since becoming Vice Chair, he has pursued a strategic vision that ensures a cohesive, challenging, and inspiring experience for students at every level of their medical education.

Dr. Loewenstein has pioneered revolutionary teaching tools to improve surgical competency in ophthalmology. Beginning in 2003, he collaborated with colleagues and experts in cognitive psychology, computer programming and ophthalmology to develop an interactive, computer program for teaching the complex art of cataract surgery. This virtual surgical tool, called the Mass. Eye and Ear Cataract Surgery Mentor, allows residents to gain critical cognitive skills in a safe, forgiving environment and eliminates risk to patients. So far, eight of 10 modules on phacoemulsification have been completed. Current efforts focus on developing the remaining modules and establishing licensing agreements to distribute the program to residents nationwide.

Dr. Loewenstein's newest initiative in resident education development is a formal study of the effect of trainee fatigue on surgical learning. Working with Drs. Carolyn Kloek, James Gordon, Director of the Gilbert Program in Medical Simulation at HMS, and Charles Czeisler, Stephen Lockley, and Brian Abaluck from the sleep medicine program at HMS and Brigham and Women's Hospital, he is evaluating retention of surgical learning in rested and sleep-deprived states using a commercial, virtual reality eye surgery simulator. He is also developing a computer-based training tool to teach residents, fellows, and practicing ophthalmologists how to screen for retinopathy of prematurity (ROP), a disease that can cause premature infants to go blind. For this effort, he is collaborating closely with Dr. Rodrigo Alvarez and other clinicians who have expertise in ROP, and leveraging the techniques used to develop the Mass. Eye and Ear Cataract Surgery Mentor.

Reza Dana, MD, MPH, MSc

Vice Chair for Academic Programs, Department of Ophthalmology, Harvard Medical School

Claes H. Dohlman Professor of Ophthalmology, Harvard Medical School

Associate Chief for Academic Programs and Director of Cornea and Refractive Surgery Service, Massachusetts Eye and Ear Infirmary

Co-Director of Research, Senior Scientist, and W. Clement Stone Scholar, Schepens Eye Research Institute

Dr. Reza Dana is a leading international expert in corneal and ocular inflammation, and his studies have greatly elucidated the cellular and molecular mechanisms of ocular surface biology. Dr. Dana has made substantial contributions to the bodies of knowledge in both basic science and clinical research.

After receiving college-preparatory education at St. Paul's School in Concord, New Hampshire, Reza Dana pursued his baccalaureate degree at Johns Hopkins University School of Arts and Sciences, where he was elected to Phi Beta Kappa. Dr. Dana continued his postgraduate training at Johns Hopkins, where he received both his MPH and MD degrees. He performed his residency in ophthalmology at the Illinois Eye and Ear Infirmary in Chicago, followed by a clinical fellowship in cornea and external diseases at Wills Eye Hospital in Philadelphia. Dr. Dana then received additional fellowship training in immunology and uveitis at Mass. Eye and Ear, and in ocular immunology and transplantation at Schepens Eye Research Institute.

Dr. Dana was appointed Instructor in the Department of Ophthalmology at HMS in 1995; he ascended to the rank of Assistant Professor in 1997, Associate Professor in 2000, and Professor and Claes Dohlman Chair in Ophthalmology in 2007. At Schepens, Dr. Dana was appointed as Associate Scientist in 2000, the W. Clement Stone Scholar in 2002, and Senior Scientist in 2004. With numerous ongoing projects in his laboratory and multiple collaborations with other researchers, Dr. Dana is rapidly expanding his list of scientific accomplishments and publications—with over 270 publications, including 175 peer-reviewed articles to date. In addition to leading laboratory research, Dr. Dana has served on the Cornea and Refractive Surgery Service of Mass. Eye and Ear since 1996.

In 2005, Dr. Dana earned his MSc degree in Health Care Management from Harvard University; this, complemented by his scientific and clinical expertise, gives Dr. Dana a unique capacity for leadership. As Director of the Cornea and Refractive Surgery Service at Mass. Eye and Ear, a position he has held since 2006, Dr. Dana leads the world's largest and most esteemed group of clinician-scientists dedicated to cornea research and treatment. Dr. Dana became Vice Chairman of Academic Programs in the Department of Ophthalmology at HMS in 2008, and was named Co-Director of Research at Schepens in 2009. With leadership appointments at both Mass. Eye and Ear and Schepens, Dr. Dana has promoted collaborative efforts in translational research between the two institutions. Committed to the advancement of clinician scientists, Dr. Dana is a Principal Investigator of the Harvard Vision Clinical Scientist Development Program funded by the NIH, and has helped provide unparalleled training opportunities for junior investigators.

In addition to publishing numerous original research articles in top-tier scientific journals such as *Nature Medicine, Proceedings of the National Academy of Sciences,* and *Journal of Clinical Investigation*, Dr. Dana is dedicated to the dissemination of scientific knowledge. He serves on the editorial board of journals such as *Cornea, Investigative Ophthalmology and Visual Science, Ophthalmologica,* and *The Ocular Surface*. He has served as Editor of the Eye and Systemic Disease volume of *The Principles and Practice of Ophthalmology*, and as Senior Editor of *The Encyclopedia of the Eye,* published in 2010 by Elsevier.

Dr. Dana has delivered more than 120 invited and named lectures, and has been the recipient of multiple awards, including the William and Mary Greve Special Scholar Award and the Physician-Scientist Merit Award from Research to Prevent Blindness (RPB). In 2009, he was honored with the Lew R. Wasserman Award from RPB. Dr. Dana's honors also include the Achievement Award of the American Academy of Ophthalmology, the Cogan Award of the Association for Research in Vision and Ophthalmology, and the Alcon Research Institute Award.

Patricia D'Amore, PhD, MBA

Vice Chair for Basic Research, Department of Ophthalmology, Harvard Medical School

Professor of Ophthalmology, Harvard Medical School

Professor of Pathology, Harvard Medical School

Co-Director of Research, Senior Scientist, and Ankeny Scholar of Retinal Molecular Biology, Schepens Eye Research Institute

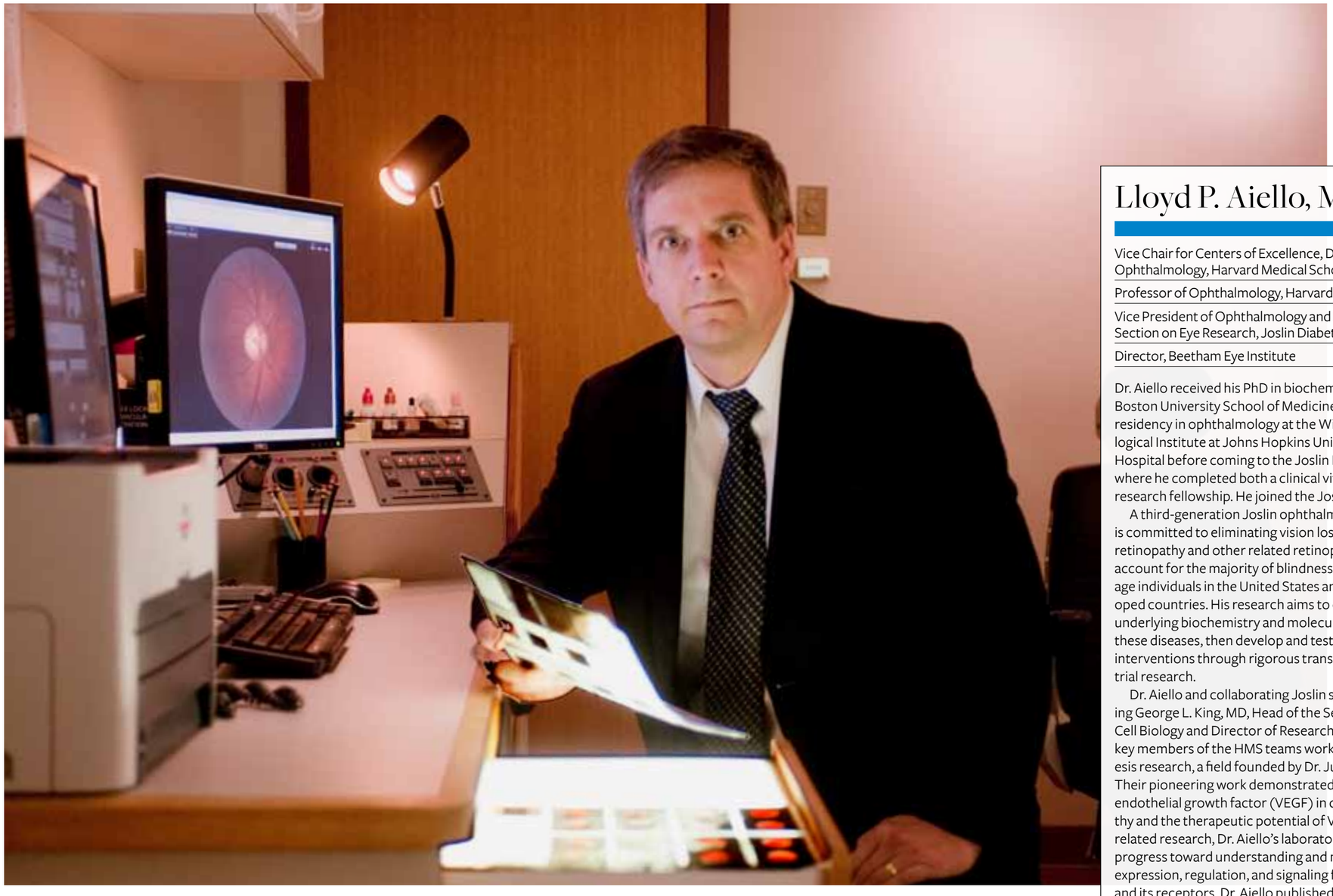
Dr. Patricia D'Amore is an internationally recognized expert of vascular growth and development, and has been at the forefront of angiogenesis research for over three decades. Investigations conducted in her laboratory have helped form the foundations of vascular-targeting therapies, which are currently used to treat various cancers and vascular diseases of the eye. Dr. D'Amore's studies have also uncovered important physiological roles of vascular growth factors—yielding crucial insight into the safe use of antiangiogenic therapies.

Dr. D'Amore received her PhD in biology from Boston University in 1977. She went on to conduct postdoctoral research in the Department of Ophthalmology and the Department of Physiological Chemistry at Johns Hopkins University School of Medicine. There, she was appointed Instructor in 1979 and Assistant Professor in 1980. Dr. D'Amore returned to Boston in 1981 to join Dr. Judah Folkman at Children's Hospital, where she has since served as a Research Associate in the Department of Surgery. At HMS, Dr. D'Amore became Associate Professor of Pathology in 1989, and was promoted to Professor of Ophthalmology (Pathology) in 1998. Dr. D'Amore also joined Schepens Eye Research Institute as a Senior Scientist in 1998, where she is the Ankeny Scholar of Retinal Molecular Biology.

To complement her scientific achievements, Dr. D'Amore obtained her MBA degree from Northeastern University in 1987, and has parlayed her knowledge and superb management skills into numerous leadership roles. Since 2001, Dr. D'Amore has served as Co-Chair of the Program in Development in Angiogenesis, Invasion & Metastasis at the Dana Farber/Harvard Cancer Center. At Schepens, she was appointed Associate Director of Research in 2002, and assumed the role of Co-Director of Research in 2009. In 2008, Dr. D'Amore became HMS Ophthalmology Vice Chair of Basic Research.

Over 50 predoctoral students and postdoctoral fellows have benefitted from the outstanding teaching and thoughtful mentorship of Dr. D'Amore. At HMS, Dr. D'Amore serves on numerous committees that promote educational and research opportunities for future and established scientists; these include but are not limited to the Minority Recruitment Committee, Joint Committee on the Status of Women, Faculty Committee on Student Research, Summer Honors Undergraduate Research Program (SHURP), Henry K. Beecher Prize in Medical Ethics Committee, Selection Committee for the Eleanor and Miles Shore Fellowship Program for Scholars in Medicine, and the Faculty Diversity Committee. Since 2003, Dr. D'Amore has served as Co-Director Director of the Leder Human Biology & Translational Medicine Program at HMS. For her efforts in training future leaders in research, Dr. D'Amore was honored in 2006 with the A. Clifford Barger Excellence in Mentoring Award.

Dr. D'Amore is also committed to fostering scientific discussion and communication. She founded the Boston Angiogenesis Meeting, now in its 13th year; this meeting continues to be a highly regarded forum for presenting new findings and promoting collaboration, understanding, and advancement in angiogenesis research. She has held editorial roles for many scientific journals, including Executive Editor of *Experimental Eye Research*, Associate Editor of *American Journal of Pathology*, and Editor-in-Chief of *Microvascular Research*. For her scientific and academic achievements, Dr. D'Amore was elected to The Academy at Harvard Medical School in 2004, and received the Senior Scientific Investigator Award from Research to Prevent Blindness in 2006. In 2009, she was elected a Gold Fellow by the Association for Research in Vision and Ophthalmology. Dr. D'Amore delivered the 2010 Isner Lecture for the Jeffrey M. Isner Endowed Memorial Lectureship, a venue for cutting-edge, thought-provoking discussions on basic and translational research. She is also the recipient of the 2012 Rous-Whipple Award from the American Society of Investigative Pathology.



Lloyd P. Aiello, MD, PhD

Vice Chair for Centers of Excellence, Department of Ophthalmology, Harvard Medical School

Professor of Ophthalmology, Harvard Medical School

Vice President of Ophthalmology and Head of Joslin's Section on Eye Research, Joslin Diabetes Center

Director, Beetham Eye Institute

Dr. Aiello received his PhD in biochemistry and MD from Boston University School of Medicine. He completed residency in ophthalmology at the Wilmer Ophthalmological Institute at Johns Hopkins University and Hospital before coming to the Joslin Diabetes Center, where he completed both a clinical vitreoretinal and a research fellowship. He joined the Joslin staff in 1994.

A third-generation Joslin ophthalmologist, Dr. Aiello is committed to eliminating vision loss due to diabetic retinopathy and other related retinopathies, which account for the majority of blindness among working-age individuals in the United States and other developed countries. His research aims to determine the underlying biochemistry and molecular mechanisms of these diseases, then develop and test novel therapeutic interventions through rigorous translational and clinical trial research.

Dr. Aiello and collaborating Joslin scientists—including George L. King, MD, Head of the Section on Vascular Cell Biology and Director of Research at Joslin—were key members of the HMS teams working on angiogenesis research, a field founded by Dr. Judah Folkman. Their pioneering work demonstrated the role of vascular endothelial growth factor (VEGF) in diabetic retinopathy and the therapeutic potential of VEGF inhibitors. In related research, Dr. Aiello's laboratory made significant progress toward understanding and manipulating the expression, regulation, and signaling functions of VEGF and its receptors. Dr. Aiello published the first evidence that protein kinase C-beta (PKC-beta) is involved in excessive blood vessel growth and vascular leakage in diabetic retinopathy. The team went on to develop a PKC-beta inhibitor that interrupts the actions of this protein—thus opening a new therapeutic avenue for diabetic and other retinopathies.

Dr. Aiello is recognized internationally for his leadership in diabetic retinopathy research. In 2002, he founded and served as the inaugural chair for the Diabetic Retinopathy Clinical Research Network (DRCR.net), a national collaborative network dedicated to facilitating multi-center clinical research for diabetic retinopathy, diabetic macular edema, and related disorders. Funded by the National Eye Institute, DRCR.net is now comprised of 150 centers nationwide representing academic medical institutions and private practice groups.

In 2008, Dr. Aiello was named Vice Chair for Centers of Excellence (COE) in the HMS Department of Ophthalmology. These centers are designed to coordinate the department's efforts in patient care, research, and training in key areas of ophthalmology in order to leverage the expertise and core strengths of faculty across affiliates. As Vice Chair, Dr. Aiello brings a wealth of collaborative insight, experience and energy to this role. Initial COE targets include diabetic eye disease, AMD, cornea, and glaucoma.

Dr. Aiello is the author of over 130 original papers and 215 publications, including contributions to the *New England Journal of Medicine, Nature Medicine, PNAS, Journal of Biological Chemistry, Journal of Clinical Investigation, Diabetes, Lancet*, and many others covering a wide range of topics in diabetic eye disease. Dr. Aiello has received 40 national and international awards and honors, including the Alcon Research Institute Award, the ARVO/Pfizer Ophthalmics Translational Research Award, the Award of Merit in Retina Research from the Retina Society, the Senior Achievement Award from the American Academy of Ophthalmology, the Charles Schepens Award in Research, the Outstanding Foreign Investigator Award from the Japan Society of Diabetic Complications, and the Novartis Award in Diabetes. The Research to Prevent Blindness Foundation has awarded Dr. Aiello the Dolly Green Scholar Award, the Special Research Scholar Award, and the Lew R. Wasserman Merit Award; from the Macula Society, Dr. Aiello has received the Rosenthal Foundation Award and the Paul Henkind Memorial Award.

David G. Hunter, MD, PhD

Vice Chair for Promotions and Reappointments, Department of Ophthalmology, Harvard Medical School

Professor of Ophthalmology, Harvard Medical School

Richard Robb Chair of Ophthalmology, Children's Hospital Boston

Ophthalmologist-in-Chief, Children's Hospital Boston

Dr. Hunter received his MD and PhD degrees at Baylor College of Medicine, and completed an ophthalmology residency at Mass. Eye and Ear Infirmary/HMS. Dr. Hunter furthered his training with a pediatric ophthalmology fellowship at Wilmer Eye Institute of Johns Hopkins Medical School, where he joined the faculty in both Ophthalmology and Biomedical Engineering. He returned to HMS in 2002 as Ophthalmologist-in-Chief of Children's Hospital.

During his tenure, Dr. Hunter has encouraged both clinical excellence and research innovation within the Ophthalmology division at Children's. He created the first International Fellowship in Pediatric Ophthalmology, and led the development, initiation, and funding of the Children's Hospital Boston Visiting Professorship lecture series. Since its establishment in 2006, this lecture series has brought four to six internationally recognized visiting professors to Boston each year.

A devoted mentor and teacher, Dr. Hunter was nominated for the Harvard Medical Student Teaching Award in 2004, and received the Robert Petersen Pediatric Ophthalmology teaching award in 2005. As HMS Vice Chair for Promotions and Reappointments, Dr. Hunter facilitates the academic advancement of department faculty across all HMS affiliates. He also has added to the wealth of academic strength and collaboration within the Department by rigorously recruiting faculty with dual fellowship training—combining pediatric ophthalmology and subspecialty training in neuro-ophthalmology and oculoplastics.

Dr. Hunter is best known for his expertise in complex strabismus (misalignment of the eyes) in adults and children. He is exploring and publishing innovative techniques in strabismus surgery, including the "short tag noose" adjustable suture and transposition procedures for paretic strabismus. His research also focuses on developing more accurate ways to help pediatricians identify eye problems in children.

In collaboration with Elizabeth Engle, MD, HMS Professor of Neurology and Ophthalmology, Dr. Hunter has established new clinical systems and protocols for studying the genetics of common strabismus disorders, including simple esotropia, exotropia and anisometropic amblyopia. These new protocols—which include clinical exams and sampling of affected and non-affected family members to ensure proper phenotyping—will serve as models for ongoing and future genetic studies at HMS affiliates.

A preeminent expert in optics and refraction, Dr. Hunter delivers lectures worldwide and via podcast; he has also authored numerous scientific articles, editorials, and book chapters. He co-authored *Last Minute Optics,* a widely used optics review book, and serves as Editor-in-Chief of *Journal of the American Association for Pediatric Ophthalmology and Strabismus*. For his outstanding contributions to clinical ophthalmology, Dr. Hunter has received numerous honors, including the Richard Starr Ross Clinician Scientist Award from Johns Hopkins University and the Research to Prevent Blindness Lew R. Wasserman Merit Award.

AFFILIATES & PARTNERS

MASSACHUSETTS EYE AND EAR INFIRMARY

Founded in 1824, the Massachusetts Eye and Ear Infirmary is a pre-eminent specialty, teaching, and research hospital caring for disorders of the eye, ear, nose, throat, head, and neck. Mass. Eye and Ear is the main primary and tertiary care facility of the HMS Department of Ophthalmology, and the hub of its teaching and research activities. The hospital's dedicated staff provides a full range of primary and subspecialty medical and surgical care to nearly 225,000 patients each year, and serves as a major referral center throughout the northeast. With a medical staff that tops nearly 130 full-time physicians and some 325 community-based physicians, Mass. Eye and Ear encourages multi-disciplinary and interdisciplinary pursuits across patient care, education, and research. Seminal contributions to these three mission-critical areas span nearly a two hundred year history and have shaped the hospital's reputation and success as a national and global center of excellence in ophthalmology and otolaryngology.

In 2011, the Schepens Eye Research Institute became a member of the Massachusetts Eye and Ear Foundation—forming the world's largest and most robust basic and clinical ophthalmology research enterprise. Both institutions are long-time collaborators in vision research,with complementary areas of expertise and technology. Together, this scientifically rich and diverse union is uniquely primed to solve the problems of and to find cures for blinding diseases.

Educating future leaders in ophthalmology

As the flagship academic center for the HMS Department of Ophthalmology, Mass. Eye and Ear is deeply committed to providing a superb education and an exciting, fruitful learning experience to the next generation of ophthalmology health care leaders. Innovative medical training programs prepare young physicians and scientists to excel as leaders in today's increasingly complex and global health care environment. Broad clinical and surgical exposure, a first-rate mentoring program, and unparalleled research opportunities combine to offer a world class medical education experience. Each year, the department's progressive training programs attract 600+ of the highest-caliber physician applicants from around the world to match its eight residency and 14 fellowship positions.

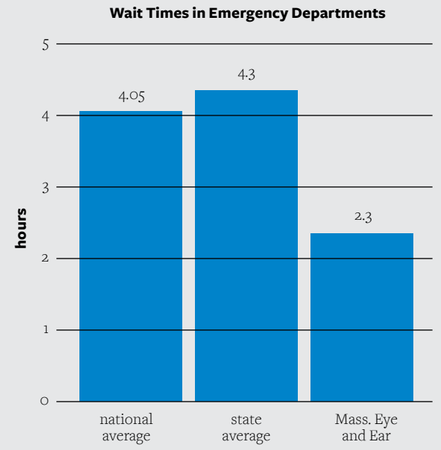
Graduates of the department's training programs are well prepared to be tomorrow's leading clinicians, researchers, and academicians. In fact, a significant number of graduating residents—nearly 60 percent—pursue academic careers after fellowship rather than establishing a full-time private practice. Today, about one in six ophthalmology chairmen in academic institutions across the United States and Canada are HMS postdoctoral alumni—striking testimony to the caliber of the department's graduates and the strength of its programs.

Thriving patient care

Mass. Eye and Ear strives to enhance every patient's quality of life by providing the best possible care. Central to this mission is the hospital's highly skilled and compassionate team of physicians, many of whom are global leaders in their fields of specialty. Every physician specializes in at least one area of ophthalmic care; some physicians are cross-trained in multiple specialties, and nearly all have completed subspecialty fellowship training. Most conduct active laboratory and/or clinical research programs; this knowledge contributes immeasurably to their clinical, surgical, and diagnostic expertise. The talented faculty, together with scientifically advanced medical care and dedicated support staff, keeps Mass. Eye and Ear at the forefront of care.

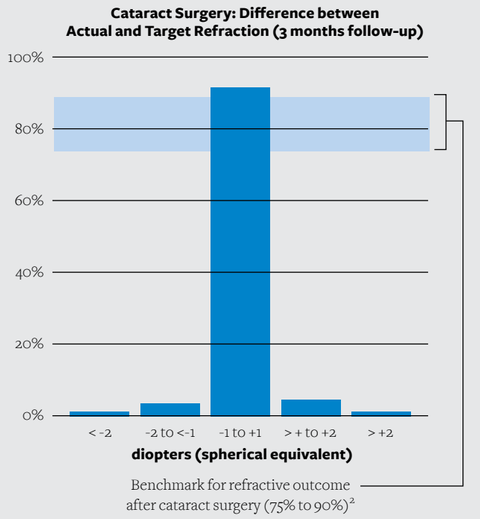
Mass. Eye and Ear's 2010 Quality and Outcomes report highlights several benchmark standards for patient care.

Mass. Eye and Ear's 24/7 dedicated **Eye Emergency Department** (**ED**) is the only specialized facility of its kind in New England, and provides care to over 12,000+ patients every year for a wide array of urgent ophthalmic issues. The ED has earned a stellar reputation as one of the most efficient emergency departments in the country. Compared to data from the 2009 Press Ganey Emergency Department Pulse Report, the average wait time at Mass. Eye and Ear to see an ophthalmologist in the ED is almost half the average of state and national wait times.



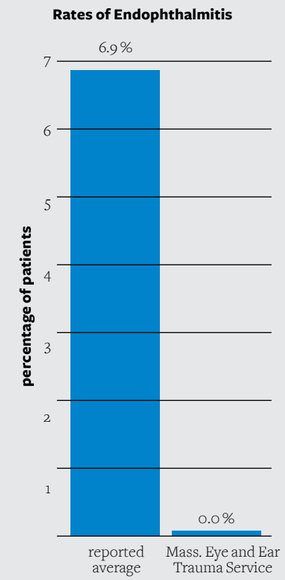
N = 12,239

The Comprehensive Ophthalmology and Cataract Consultation Service (**COS**) handles more than 20,000 patient visits each year. In addition to serving walk-in patients, COS serves as a key resource for ophthalmic referrals from the HMS network of 17 hospitals and affiliates, as well as referrals from private practitioners from all over New England. The service specializes in cataract extraction with intraocular lens implantation. Between July 2008 and June 2009, COS performed 974 cataract surgeries at Mass. Eye and Ear's main Boston campus. Surgical results exceeded national and international benchmarks (*Cataract and Refractive Surgery Today* Europe, May 2009, and Cole Eye Institute, Outcomes 2008) with 92 percent of patients achieving within 1 diopter of target refraction after surgery.



N = 974

Mass. Eye and Ear's **Eye Trauma Service** has developed highly successful, standardized protocols for treating emergency eye injuries. According to a recent review of all open globe injury cases treated at Mass. Eye and Ear from January 2000 to July 2007, the post-surgical infection rate of endophthalmitis was less than 1 percent. By comparison, the endophthalmitis rate in the United States is 6.9 percent after open globe repair, according to the U.S. National Eye Trauma Registry. The service also has exceeded benchmark outcomes with some of the lowest enucleation (eye removal) rates nationwide, and some of the lowest rates reported for sympathetic ophthalmia—a devastating and vision-threatening complication that can occur in the non-injured eye after open globe surgery.



N = 95

Best-of-class services spur best outcomes

As a preeminent center of ophthalmic care, Mass. Eye and Ear establishes global standards for quality patient care while pushing the envelope internally to achieve the highest levels of excellence. In 2010, the hospital published its first Quality and Outcomes report, which documented clinical and surgical outcomes data for 13 subspecialty procedures. The initial impetus for this effort was to determine the quality of care and how well the patient experience is managed; ultimately, however, the report also showed that the hospital is leading the medical community in the development of outcomes measures in ophthalmic care.

Reaching out to patients and partners

In 2008, Mass. Eye and Ear launched a strategic and collaborative plan for growth, which was designed to streamline services and expand its expertise and resources to as many people as possible. Since that time, the hospital has forged several highly successful alliances with its HMS affiliates and partners that will directly benefit patients by nurturing an environment for improved patient care, research activities, and educational programs.

Mass. Eye and Ear has added ophthalmic services in multiple satellite offices beyond Boston's city limits, providing thousands of patients with easy access to world-class care. Mass. Eye and Ear has also established its first teleretinal imaging program in MGH's Chelsea Health Center to screen patients for diabetic eye disease. Numerous expansions and modernizations to its physical facilities—including a new state-of-the-art surgical center, renovated pediatric and rehabilitation suites, and a renovated radiology department with significant equipment upgrades—have added capacity and comfort for patients. In 2010, the hospital kicked off an ambitious expansion plan that will add approximately 50,000 square feet to its central Charles Street clinical facility and a 90,000 square foot research center to its main Boston campus. Additionally, an outpatient surgical center will be developed in Boston's Longwood Medical Area. To support its new service partnerships and department expansions, the hospital has added more than a dozen esteemed physicians and researchers to its full-time staff in just the last two years. Aggressive recruitment efforts are ongoing at Mass. Eye and Ear to keep pace with its accelerated growth.

Advancing ophthalmic science & discovery

For nearly two centuries, Mass. Eye and Ear faculty members have pioneered advances in ophthalmic medicine and research, many of which have set standards of care in the United States and abroad. The pursuit of knowledge has driven numerous groundbreaking discoveries; scientists have developed new drugs and devices, perfected new techniques, identified disease-causing genes, and translated groundbreaking laboratory research into clinical treatments that benefit scores of people. Today, the department remains at the forefront of discovery, aggressively tackling new areas of research and developing next-generation tools and technologies to combat blinding diseases. Mass. Eye and Ear provides a first-rate setting for scientists who facilitate a broad and aggressive program of basic, translational, and clinical research. Key areas of study focus on retinal degenerations, (including age-related macular degeneration and retinitis pigmentosa), glaucoma, Keratoprosthesis, corneal infections and ocular tumors. During the last several years, the department also has made significant inroads in the specialty areas of ocular genetics, regeneration, and repair.

Bringing personalized medicine to Mass. Eye and Ear

Delivering highly targeted care to patients based on their unique genetic makeup is now an exciting possibility thanks to modern genomics and powerful new computing technologies. At Mass. Eye and Ear, transforming the hope of personalized medicine into a 21st century reality is now a vigorous focus of the department. In 2011, the department launched the Ocular Genomics Institute, which combines clinical information from a patient's electronic medical records and clinical samples from Mass. Eye and Ear's expanding biobank. Relating clinical information to tissue and DNA samples, coupled with advanced DNA sequencing and analysis technologies, will allow investigators to unravel disease mechanisms and develop new interventions at an accelerated pace. The department's ten-year goal is to have personal genome sequences embedded into the electronic medical records of the nearly 200,000 patients treated annually at Mass. Eye and Ear.

Eric Pierce, MD, PhD

Lecturer on Ophthalmology, Harvard Medical School

Associate Director, Berman-Gund Laboratory for the Study of Retinal Degenerations, Massachusetts Eye and Ear Infirmary

Director, Ocular Genomics Institute, Massachusetts Eye and Ear Infirmary

Dr. Pierce, a clinician, educator, and preeminent leader in the area of retinal degenerations, recently joined Mass. Eye and Ear and HMS as Associate Director of the Berman-Gund Laboratory for the Study of Retinal Degenerations. As Director of the new Ocular Genomics Institute, he will direct the Genetic Therapies Program—accelerating the department's growth into advanced studies in genomic research and gene therapy. Dr. Pierce is working in close collaboration with Berman-Gund Laboratory Director Eliot L. Berson, MD, and Janey Wiggs, MD, PhD, who directs the Genetic Diagnostics section of the Institute.

Dr. Pierce's scientific efforts have resulted in groundbreaking ways to address retinal degenerations using genetic sequencing and gene therapy methods. Recently, he has used next-generation DNA sequencing to identify new retinal degeneration disease genes and to improve genetic testing for patients with inherited retinal degenerative disorders. He has also demonstrated that it is critical to functionally test DNA sequence variants to accurately identify specific disease-causing mutations. Dr. Pierce is also applying his genetic expertise to therapeutic discovery and helped demonstrate the safety and efficacy of gene therapy for the RPE65 genetic form of Leber congenital amaurosis, an early onset form of retinal degeneration.

Dr. Pierce earned a PhD in biochemistry at the University of Wisconsin-Madison and his MD at HMS/MIT Health Sciences and Technology Division. He completed his ophthalmology residency at Mass. Eye and Ear/HMS, followed by a combined research-clinical fellowship in pediatric ophthalmology at Children's Hospital Boston. He joined the faculty of Children's Hospital Boston working in clinical care and angiogenesis research for three years before being recruited to the University of Pennsylvania. In 1999, Dr. Pierce joined the F.M. Kirby Center for Molecular Ophthalmology in the Scheie Eye Institute of the University of Pennsylvania School of Medicine. He focused his work on retinal degenerations and was a member of the Division of Ophthalmology at Children's Hospital of Philadelphia, where he attained an appointment as Associate Professor of Ophthalmology.

SCHEPENS EYE RESEARCH INSTITUTE

In 1947, World War II hero Charles L. Schepens, MD, joined the HMS Howe Laboratory as a research fellow. Recognizing the need for a dedicated eye research organization, Dr. Schepens established the Retina Foundation in 1950, representing a handful of researchers working out of a modest Boston tenement. This collaboration was renamed the Eye Research Institute of Retina Foundation in 1974 to better represent its active research program, and became formally affiliated with HMS in 1991. Today, the Institute bears the name of its influential founder, who is regarded as "the father of retinal surgery." In a cutting-edge facility just a short walk from the main campuses of Mass. Eye and Ear and Massachusetts General Hospital, Schepens researchers advance the understanding of eye disease and facilitate the transfer of scientific knowledge into clinical use. Since its inception, Schepens has trained over 600 postdoctoral fellows and produced nearly 5,000 scientific papers and books on the eye. Schepens Eye Research Institute became a subsidiary of the Massachusetts Eye and Ear Foundation in 2011.

Leadership

In 1993, J. Wayne Streilein, MD, joined Schepens Eye Research Institute as Ankeny Director of Research. He became President in 1995, and was responsible for the Institute's substantial growth in size and impact. After Dr. Streilein's sudden passing in 2004, renowned microbiologist Michael Gilmore, PhD, was recruited as President and Ankeny Director of Research. Dr. Gilmore led the Institute for five years before joining the Howe Laboratory at Mass. Eye and Ear to focus on research. In 2009, Kenneth Fischer, MBA, was named President and Chief Operating Officer. Co-Directors of Research, Patricia A. D'Amore, PhD, MBA; Reza Dana, MD, MPH, MSc; and Eli Peli, OD, MSc, form the Institute's triumvirate research directorate.

Unique centers of excellence

Scientific endeavors carried out at Schepens span all levels of research, from developing novel concepts to conducting clinical testing in various forms of eye diseases. Extensive preclinical investigations carried out by Schepens researchers often dovetail with ongoing basic and translational efforts at other HMS affiliates. These collaborations have led to innovative pathways for ocular disease therapies.

To advance these efforts, Schepens has formed distinct Centers of Excellence to streamline the transfer of scientific knowledge to clinical application:

The Mobility Enhancement and Rehabilitation Center

Directed by Dr. Peli, an expert in vision rehabilitation, the Mobility Enhancement and Rehabilitation Center aims to improve eyesight in visually impaired patients. Researchers are developing novel and innovative techniques to enhance vision—and thus quality of life—for people with various forms of vision loss, including strabismus, amblyopia, age-related macular degeneration (AMD), and hemianopia.

Center for Corneal & External Eye Disease Research

The interdisciplinary research in the Center for Corneal & External Eye Disease Research focuses on multiple conditions that affect the cornea, such as dry eye disease, corneal dystrophies, infections, and injuries. Dr. Dana, a renowned immunologist and forerunner in corneal research, directs this center, which has helped develop numerous pharmacological treatments and innovative therapeutic methods.

Center for Age-Related Macular Degeneration (AMD) Research

Among retinal diseases, AMD is of particular concern as it becomes more and more prevalent with increasing life expectancies. Led by Dr. D'Amore, a world-renowned authority in AMD, the Center of Excellence for AMD Research brings together outstanding scientists, engineers, and clinicians to decipher the mechanisms of AMD and combat this growing cause of vision loss.

Minda de Gunzburg Center for Ocular Regeneration

The Minda de Gunzburg Center for Ocular Regeneration forms an arena for developing revolutionary methods to regenerate eye tissues. Michael Young, PhD, a leading expert in tissue and stem cell transplantation, leads the effort to develop regenerative therapies for various diseases, including AMD, glaucoma, corneal disease, and ocular cancer.

CHILDREN'S HOSPITAL BOSTON

A leader in pediatric healthcare for more than 130 years, Children's Hospital Boston first opened in 1869 as a 20-bed facility in Boston's South End. Since then, scientists at Children's Hospital have made important contributions in eradicating some of the major illnesses that have threatened young lives. Today, the hospital stands out as a preeminent institution for pediatric care by utilizing cutting-edge research from disciplines such as genomics, proteomics, and informatics. Children's Hospital has also revolutionized treatment options for infections, congenital disorders, and other childhood diseases.

The Department of Ophthalmology at Children's Hospital Boston is the largest group of full-time practicing pediatric ophthalmologists in the United States. Here, children and families receive the most advanced testing and treatment available for all types of visual impairments. Specialized services are available for misaligned eyes (strabismus), cataract and retinal degenerative conditions, as well as comprehensive evaluation and treatment of patients with eye muscle problems or refractive concerns. The Department of Ophthalmology is a collaborative environment that includes clinicians at the top of their field, award-winning principal investigators, and trainees from around the world.

Innovative treatments for pediatric eye disorders

Led by Ophthalmologist-in-Chief David G. Hunter, MD, PhD, the Ophthalmology Department is known internationally for its innovative techniques in treating difficult pediatric vision problems. Ophthalmologists at Children's Hospital have extensive experience performing cataract extraction and intraocular lens implantation in infants and children. In some cases, Botox (botulinum toxin A) is used in young children to correct strabismus instead of eye muscle surgery. When eye muscle surgery is needed, ophthalmologists can use adjustable sutures, which allow for adjustments to be made in the position of the eye after surgery. Children's is also at the leading edge of treatment for complex strabismus in children, and recently presented a webcast for management of Duane syndrome using transposition surgery and adjustable sutures.

Multidisciplinary programs

Collaboration is central to the success of Children's Hospital, and multidisciplinary programs allow teams of physicians and scientists with training in different scientific fields to work together to address specific medical problems. Located in the John F. Enders Pediatric Research Laboratories and in the Karp Family Research Laboratories, the Multidisciplinary Programs uniquely position Children's Hospital to be a pioneer in the applications of vascular biology, bioinformatics, genomics, clinical research, neurobiology, translational research, and stem cell research.

Expanding partnerships: a model for growth

In 2009, the Department of Ophthalmology of Children's Hospital Boston began a formal relationship in patient care with Mass. Eye and Ear Infirmary and Children's Hospital Ophthalmology Foundation (CHOF). This unique arrangement furthers the mission of both institutions to increase access to patient care in a seamless fashion and integrate training and research programs.

World-changing research

The research mission of Children's Hospital encompasses clinical research, basic research, postdoctoral training of new scientists and community service programs. With over $225 million in annual funding, Children's Hospital Boston is home to the world's most dynamic research enterprise at a pediatric center. Significant ophthalmologic advancements have been made at Children's in the field of retinopathy of prematurity, revealing the important role of growth factors in this vision-robbing childhood disease. Studies conducted in collaboration with Mass. Eye and Ear have shed new light on the etiology of vision loss in glaucoma, revealing the chain of molecular and cellular events that damage the optic nerve. During the last two decades, intense research at Children's has uncovered some of the genetic underpinnings of strabismus, revealing the underlying genetics of seven inheritable forms of the disorder.

BEETHAM EYE INSTITUTE AT THE JOSLIN DIABETES CENTER

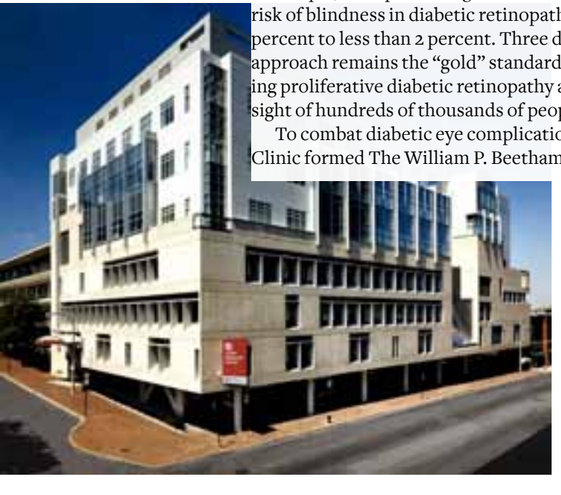
Joslin Diabetes Center is the world's premier diabetes research and clinical care institution, and is dedicated to improving the lives of people with diabetes. Joslin Diabetes Center owes its existence to Elliott Proctor Joslin, MD, who is widely considered to be the pioneer of modern diabetes management. When Dr. Joslin began his private practice in 1898, he became the first physician in the United States to specialize in diabetes—which was still a poorly understood disease with few treatment options. In 1952, Dr. Joslin's practice became formally known as the Joslin Clinic, which moved to its current location in the Longwood Medical Area in 1956.

With the discovery of insulin in the 1920s came substantial growth in the life span of patients with diabetes. Unfortunately, increased life expectancy also brought an increased risk of vascular complications—including diabetic retinopathy. By the 1950s, diabetic retinopathy had become the leading cause of blindness in the United States.

Combating diabetic eye complications at the Beetham Eye Institute

In the 1960s, Joslin physicians Lloyd M. Aiello, MD, and William P. Beetham, MD, noticed that retinal scarring (from causes other than diabetes) could prevent retinal blood vessels from proliferating, bleeding and detaching—and thus prevent vision loss—in patients with diabetic retinopathy. Drs. Aiello and Beetham developed a method that used lasers to create scars in retinas. This technique, laser photocoagulation therapy, reduced the risk of blindness in diabetic retinopathy from over 75 percent to less than 2 percent. Three decades later, this approach remains the "gold" standard of care for treating proliferative diabetic retinopathy and has saved the sight of hundreds of thousands of people worldwide.

To combat diabetic eye complications, the Joslin Clinic formed The William P. Beetham Eye Institute (BEI), a dedicated on-site eye research center that fosters close partnerships between physicians and scientists at Joslin and BEI. Through the years, this model of collaboration has accelerated bench-to-bedside therapies for patients. Beetham researchers were some of the first to define complications from diabetic eye disease, and have led preeminent discoveries and improvements in diabetes eye care that have preserved vision for more than nine million people worldwide. Today, the Institute participates in virtually every major medical trial for diabetic retinopathy in the United States, some 24-26 trials at any given time.



A new wave of discoveries

Despite advances in eye care, some patients with diabetes still suffer visual loss. Today, Joslin clinicians and researchers from the BEI continue their quest to develop new and improved methods to prevent diabetes-related eye complications. HMS Professor of Ophthalmology, Dr. Lloyd P. Aiello, MD, PhD, is Head of Joslin's Section on Eye Research and Director of the Beetham Eye Institute. In recent years, Dr. Aiello and other BEI members have been at the forefront of several key discoveries that may soon yield better treatments and therapies. These include the development of inhibitors to prevent proliferation, bleeding, and detachment of blood vessels in the back of the eye, as well as the development of treatments that block the activation of a molecule called protein kinase C (PKC). Previously, BEI researchers found PKC to be a major signaling pathway that, when activated, can trigger early cellular changes in the eye leading to diabetic retinopathy. Investigators have also identified several key risk factors for diabetic eye disease—such as the thickness of the retina and changes in blood flow in the back of the eye—that may enable clinicians to better predict who may be at risk for the disease.

Preventing blindness through patient participation

Dr. Elliott P. Joslin believed that patient participation and empowerment were vital in the effort to control diabetes. Fulfilling this vision is the Joslin Vision Network (JVN), implemented by Joslin researchers in 1990. This initiative uses advanced video technology to detect abnormal retinal blood vessels, and not only allows regular and noninvasive screenings of diabetic retinopathy (at over 70 sites in the United States and abroad), but also allows patients in the network to participate in clinical trials. Through its 50-Year Medalist program, the Joslin Diabetes Center also recognizes individuals who live with diabetes for 50 years or longer without apparent complications. Many Medalists are participating in a long-term study that is yielding important clues into the prevention of diabetic retinopathy.

MASSACHUSETTS GENERAL HOSPITAL

Massachusetts General Hospital consistently ranks in the top 1 percent of the nation's medical institutions and is second in U.S. News & World Report's most recent, "America's Best Hospitals Survey." Working collaboratively within Harvard's broad network, the clinicians and researchers in this world-class institution are bringing scientific breakthroughs to ophthalmic practice.

Allies in comprehensive eye care

In close collaboration with multiple HMS affiliate and partner institutions, Massachusetts General Hospital (MGH) offers comprehensive and expert care for a broad range of eye conditions. In 2009, the hospital teamed with Mass. Eye and Ear to establish the Mass. Eye and Ear/Massachusetts General Hospital Department of Ophthalmology, an innovative alliance that formalized the centuries-old clinical and academic partnership between the two world-class institutions. The department is staffed by Mass. Eye and Ear physicians under the direction of HMS Ophthalmology Chief and Chair, Joan W. Miller, MD. Deeper collaboration and joint programmatic planning is enhancing the quality of care, research, and teaching at both institutions. Patients, in particular, will benefit from this closer connection with seamless access to the most innovative care available anywhere in the world.

The proximity to Mass. Eye and Ear also allows access to advanced diagnostic tests, such as optical coherence tomography, optic nerve imaging, and fundus tomography. The Mass General Hospital for Children provides pediatric services in collaboration with ophthalmologists from Children's Hospital Boston—both primary pediatric teaching sites for HMS. These valuable alliances allow the ophthalmology specialists at MGH to determine the best possible course of treatment for each patient.

Neuro-ophthalmology consultation

Because visual function is closely integrated with neurological function, many conditions that affect the brain may also affect vision. Through a streamlined consultation process, physicians from Mass General's neurology, neurosurgery, and inpatient services work jointly with Mass. Eye and Ear's Neuro-Ophthalmology Service to provide unparalleled services to patients with neuro-visual complications, as well as patients with primary neurological conditions that may cause visual disturbances. This service is widely recognized for handling rare neuro-ophthalmic conditions, and receives many referrals from general ophthalmologists and optometrists. In addition, the service coordinates ophthalmic inpatient consultation for urgent patient care.

Cooperative pathology programs

The Mass General Hospital Surgical Pathology Service and Mass. Eye and Ear's David G. Cogan Laboratory of Ophthalmic Pathology collaborate extensively to provide enhanced diagnostic services. The staff and full spectrum of diagnostic methods from MGH's surgical pathology services are available to facilitate the diagnostic and research work undertaken in the Cogan Laboratory. Cooperative programs between MGH and ophthalmic pathology specialists also support clinico-pathology research projects and enhanced educational and training initiatives throughout the HMS Ophthalmology campus.

Teleretinal screening program

Another vital alliance between Mass General Hospital and Mass. Eye and Ear was realized in 2008 when a teleretinal imaging program was established at MGH's Chelsea Health Center. The program provides expanded, preventive care to high-risk patients with diabetes. Retinal images are sent electronically to Mass. Eye and Ear and screened for diabetic retinopathy and other pathologies, enabling early intervention and potential sight-saving diagnosis and treatment. This program also provides primary care practices with key diabetes screening results that are central to meeting major performance measures of health care insurers.

VETERANS AFFAIRS BOSTON HEALTHCARE SYSTEM

The Veterans Affairs Boston Healthcare (VHA) System —one of 171 VA health care facilities across the country —is a full-service tertiary care center that provides a broad spectrum of medical, surgical, and rehabilitative care to veterans across New England and the Veterans Integrated Service Network 1. The medical center encompasses three main campuses and five outpatient clinics located within a 40-mile radius of Boston.

Providing world-class care to veterans

Affiliated with Boston University and Mass. Eye and Ear/HMS, the VA Boston Ophthalmology Department provides veterans with a full complement of eye care and services with specialization in vitreoretinal diseases, glaucoma, neuro-ophthalmology, oculoplastics, cataract, strabismus, and cornea/external eye diseases. In recent years, under the leadership of Chief of Ophthalmology, Mary K. Daly, MD, the department's reputation for delivering excellence in patient care has flourished; today, it is a premier provider of ophthalmic care within the VA national network. The busy department offers 24/7, on-call access to more than 20,000 patients every year; a number that has steadily climbed in recent years along with an influx of ophthalmic referrals from other VA centers across the country. The department continually strives for innovation and, for example, is one of a handful of VA medical centers nationwide that offers certain highly specialized procedures such as the Boston Type I Keratoprosthesis (KPro) surgery pioneered by HMS Emeritus Professor, Claes Dohlman, MD, PhD; other innovative procedures include Descemet's stripping endothelial keratoplasty and treatments for choroidal melanoma.

Training partners

The VA Boston Healthcare System has a strong educational partnership with Mass. Eye and Ear and HMS. Residency training is a key mission area of VA ophthalmology. Guided by Dr. Daly, the department has significantly improved the quality and depth of its training program in just the last few years, which has evolved into a highly structured curriculum comprised of surgical conferences, weekly faculty lectures and journal clubs, with greater participation from residents. HMS residents complete one six to seven week block rotation at the VA each year of residency with exposure to general and subspecialty clinical care in retina, cornea, glaucoma, oculoplastics, and neuro-ophthalmology, as well as hands-on surgical training. Third-year residents receive intensive cataract training and serve as primary surgeons on a large volume of cataract and glaucoma surgeries. The department utilizes state-of-the-art equipment, including two Eyesi virtual reality simulators to help residents hone their surgical skills.

Supporting innovations in research

Historically, the U.S. Department of Veterans Affairs has supported innovative R&D efforts in many areas of healthcare to improve the lives of Americans. This same spirit of purpose drives ongoing research efforts at the VA Boston. Since 2001, the VA has supported the efforts of HMS Professor of Ophthalmology, Dr. Joseph Rizzo III, MD, in the Boston Retinal Implant Project. In this endeavor, Dr. Rizzo leads a team of physicians, scientists, and engineers to develop an implantable microelectronic retinal prosthesis that can eventually restore some vision to people blinded by retinitis pigmentosa and age-related macular degeneration (AMD). This highly challenging and multidisciplinary research is being carried out by the Center for Innovative Visual Rehabilitation located at the VA.

Veteran's Affairs Boston Healthcare System, Jamaica Plain campus

Mary K. Daly, MD

Lecturer on Ophthalmology, Harvard Medical School

Associate Professor of Ophthalmology, Boston University School of Medicine

Chief of Ophthalmology, Veterans Affairs Boston Healthcare System

Associate Director, HMS Ophthalmology Residency Training Program, Veterans Affairs Boston Healthcare System

Dr. Mary K. Daly obtained her BA from Harvard College in 1994 and her MD degree from Johns Hopkins University in 1998. After completing an ophthalmology residency at the Wilmer Eye Institute at Johns Hopkins in 2002, she conducted fellowship training in cornea and external eye disease at Moorfields Eye Hospital, London. Dr. Daly specializes in complex cataract, anterior segment, and corneal surgery including keratoprosthesis and Descemet's stripping endothelial keratoplasty.

Since 2005, Dr. Daly has championed transformative changes within the Department of Ophthalmology at the Boston VA, boosting continuity and quality of patient care, expanding research efforts, and creating an enhanced training rotation for HMS residents. Under her guidance, the department's staff, programs, and services continue to grow at a rapid clip. She has recruited superb clinical and research talent to the department, including clinician scientists from Mass. Eye and Ear and the Boston University School of Medicine, tripling the number of full-time staff in the last two years. She credits VA Boston Leadership—including Dr. Kamal Itani, Chief of Surgery; Dr. Michael Charness, Chief of Staff; and Mr. Michael Lawson, Medical Center Director—for their tremendous support of Ophthalmology at VA Boston and for always putting the patients first. "Today, I'm proud to say that our staff and capabilities are at the leading edge of technology, and we are providing premier ophthalmic services to our veterans. It's unbelievably rewarding to work here and with this particular patient population," says Dr. Daly. "I know everyone, including the residents, consider themselves lucky to be taking care of this wonderful group of people."

Dr. Daly is a valued member of the Veterans Affairs Boston Integrated Ethics Committee, which strives to ensure ethical practices in the Veterans Healthcare Administration and foster a strong ethical environment and culture through ethical leadership.

Dr. Daly is also a clinical champion of the Ophthalmic Surgical Outcomes Data Committee (OSOD) under the direction of Mary Lawrence, MD, Deputy Director of the Vision Center of Excellence. The VA Boston is one of five OSOD pilot sites tracking ophthalmic surgery data in order to establish a prospective outcome-based program for comparative assessment and enhancement of the quality of cataract surgery across the VA system.

MARK C. KUPERWASER, MD

BETH ISRAEL DEACONESS MEDICAL CENTER

Beth Israel Deaconess Medical Center (BIDMC) is one of the nation's preeminent academic medical centers, committed to providing excellence in clinical care, teaching, research, and community outreach. A major teaching hospital of Harvard Medical School with more than 1,250 full-time medical staff, BIDMC is ranked each year as a "Best Hospital" by U.S. News & World Report in multiple specialties. BIDMC's focus on safe and quality patient care has helped establish them as a national leader in health care quality, safety and transparency. BIDMC's thriving research programs, state-of-the-art clinical care and unparalleled medical education are recognized worldwide.

The BIDMC Division of Ophthalmology

Located within the Longwood Medical Eye Center, the BIDMC Division of Ophthalmology provides comprehensive medical and surgical treatment of eye diseases. Dr. Frank Berson, Chief of the Division of Ophthalmology, leads an exceptionally trained team of ophthalmologists, all of whom hold academic appointments in the HMS Department of Ophthalmology. In research and clinical care, the Division collaborates with other HMS affiliates, including Beetham Eye Institute at Joslin Diabetes Center and Mass. Eye and Ear.

Under the direction of Jorge G. Arroyo, MD, MPH, the Retina Service serves an international patient base, and handles some of the most complex vitreoretinal cases utilizing a complete array of state-of-the-art equipment and intraocular instruments. Dr. Arroyo is a sought-after authority in complex vitreoretinal and other surgical techniques and has participated in research studies on age-related macular degeneration (AMD), retinal detachment, and diabetic retinopathy.

Converging disciplines

In conjunction with the Department of Ophthalmology, the Neuro-Ophthalmology Service, under the direction of Nurhan Torun, MD, employs a wide range of ophthalmologic and neurologic evaluative techniques to provide care for patients with neurological difficulties. The Eye Movement Laboratory provides quantitative assessment of difficulties with eye movements and visual perception, both for research and for patient care needs.

BIDMC partners with the nearby Joslin Diabetes Center, a preeminent diabetes research and clinical care organization, to provide patients with a spectrum of multidisciplinary care for diabetes and endocrine disorders in both inpatient and outpatient settings. The BIDMC/Joslin Collaborative Eye Care Program offers diabetes-specific ophthalmic care focused on preventing and treating eye disease. Ophthalmologists in this program are specially trained to treat complex eye conditions associated with diabetes.

Highly lauded teachers and mentors

Using outstanding depth of knowledge and experience, BIDMC's esteemed team of mentors, educators, and clinicians play a key role in the education of HMS ophthalmology residents and fellows. All second-year residents rotate through BIDMC and participate in comprehensive ophthalmology and subspecialty clinics, including retina, glaucoma, and neuro-ophthalmology. Surgical experience is also a primary focus of this rotation, and residents spend a significant amount of time participating in cataract, retina, and glaucoma surgeries. Drs. Berson and Arroyo, and Mark Kuperwaser, MD, have received teaching awards from Mass. Eye and Ear/ HMS ophthalmology residents, most recently Dr. Kuperwaser in 2010.

Frank G. Berson, MD

Associate Professor of Ophthalmology, Harvard Medical School

Chief, Division of Ophthalmology, Beth Israel Deaconess Medical Center

As Chief of the Division of Ophthalmology at BIDMC, Dr. Berson is an integral member of the world-renowned surgical staff in the HMS Department of Ophthalmology. He holds an academic appointment as Associate Professor in Ophthalmology at HMS. Dr. Berson was recently recognized by BIDMC for his milestone anniversary of 30 years of service.

Board-certified in ophthalmology, Dr. Berson received his MD degree from HMS in 1971. After completing an internship in surgery at Beth Israel Hospital, he went on to complete his residency and fellowships in ophthalmology at Mass. Eye and Ear. Dr. Berson's clinical interests are focused on glaucoma and cataracts. For more than two decades (1982–2004), he served as Director of Medical Student Education for Mass. Eye and Ear/HMS Department of Ophthalmology. From 1982 to 1992, he was the Director of the HMS Ophthalmology Residency Training Program.

Dr. Berson currently serves on the Executive Committee and the Subcommittee for Promotions and Reappointments in the HMS Department of Ophthalmology. At BIDMC, he is a member of the Board of Overseers and Treasurer of the Beth Israel Surgical Foundation.

BRIGHAM AND WOMEN'S HOSPITAL

Brigham and Women's Hospital (BWH) is committed to upholding the best practices in eye care. Centrally located in Boston's Longwood Medical Area, BWH has established a strong partnership with the Mass. Eye and Ear Department of Ophthalmology to ensure that their patients have convenient and direct access to best-in-class eye care providers and services.

The hospital's guiding philosophy is to utilize an exceptionally trained and experienced team of eye care providers, resources, and technology to achieve an optimal outcome for every ophthalmology patient.

Comprehensive care through collaboration

BWH offers comprehensive ophthalmology services and most subspecialty eye care through this clinical affiliation with Mass. Eye and Ear, which offers world-renowned expertise and diagnostic and treatment capabilities unmatched in the region.

As the result of a comprehensive partnership, Mass. Eye and Ear began providing inpatient subspecialty ophthalmic care and emergency eye trauma coverage to BWH patients in 2009. Trauma care at BWH is coordinated by the director of the Mass. Eye and Ear Ophthalmic Trauma Service and is reinforced by its unique around-the-clock, dedicated eye Emergency Department. This creative alliance has helped to streamline and boost quality of care for patients who can now receive 24/7 on-site treatment at BWH from an outstanding group of physicians who rank as one of the leading eye trauma management teams in the country.

Integrated clinical services and training

A second innovative alliance in 2009, led by Mass. Eye and Ear and the Beetham Eye Institute at Joslin Diabetes Center, has enabled continuity of follow-up care (post discharge) for BWH patients with the establishment of a new, outpatient comprehensive ophthalmology service (COS) at One Joslin Place. Located in the heart of the Longwood Medical Area the service is directed by Lloyd Paul Aiello, MD, PhD, and staffed by Mass. Eye and Ear ophthalmologists with participation from Joslin retina specialists and BWH neuro-ophthalmologist director, Dr. Don Bienfang. The service provides BWH with outpatient services, as well as inpatient consultations and marks yet another important milestone in collaborative service development among HMS affiliates. Patients can receive routine annual eye and vision exams as well as spectacle and lens correction. Comprehensive evaluation and treatment of complex and systemic disorders, such as cataract, glaucoma, diabetes, macular degeneration, retinal detachment, conjunctivitis, and dry eye are also provided.

The Neuro-Ophthalmology service of the Brigham and Women's Hospital Department of Neurology diagnoses and treats disorders involving the visual pathways and eye movements. A number of neurological conditions affect the areas of the brain devoted to vision. Disturbances of these important visual areas may produce debilitating symptoms, and often require high-quality, specialized care.

ARAVIND EYE HOSPITALS

The Aravind Eye Care System of India is the world's largest provider of eye care services, encompassing five hospitals, three managed eye hospitals, an international research foundation, an ophthalmic product manufacturing center, and a training center. Committed to the prevention of needless vision loss, the Aravind Eye Hospitals are revolutionizing the concept of efficient and sustainable eye care across the developing world.

Upon his retirement in 1976, Govindappa Venkataswamy, MD, established the GOVEL Trust to support an alternate health care model. Under this Trust, the Aravind Eye Hospitals were created as a self-sustaining system that not only provides affordable high-quality care for millions of individuals, but also serves as a model example of sustainable health care. For its remarkable impact, the Aravind Eye Care System has been honored with several prestigious awards, including the 2007 The António Champalimaud Vision Award, the 2008 Gates Award for Global Health, and the 2010 The Conrad N. Hilton Humanitarian Prize.

International partnership

Since 1988, HMS senior residents have had the option of an elective rotation at Aravind Eye Hospital in Madurai. This unique training experience offers residents an unparalleled learning experience in international eye care, and the opportunity for hands-on clinical and surgical exposure to many ophthalmic conditions rarely encountered in the United States. Since the program's inception, more than 100 seniors have opted to experience an Aravind rotation.

Expanding on this educational partnership, HMS Ophthalmology and Aravind leadership recently conducted two joint grand rounds teleconferences. These interactive, high-tech events have allowed faculty from both institutions the opportunity to present grand rounds cases in real time, and share observations and insights.

Research and development

Several Aravind programs, catering to all levels of ophthalmic teaching and training, are designed to meet the demands of a growing ophthalmic health care system. More recently, Aravind has expanded its research facilities and created PhD programs for medical and non-medical graduates. In 2010, there were 26 research projects being conducted in the department, with significant growth predicted for coming years.

Telemedicine: remote care and communication

As part of its comprehensive success, Aravind utilizes telemedicine to reach out to remote rural areas using computers, video conferencing and the Internet. Through these technological services, eye care service is made accessible and affordable by reducing travel cost and time for the patients. In addition, telemedicine provides a network for eye care providers to share their knowledge and expertise.

SHANGHAI EYE AND ENT HOSPITAL

Founded in 1952, the Shanghai Eye and ENT Hospital of Fudan University is a leading specialty hospital, which integrates medical care, education and research, providing patient care for the health of eye, ear, nose, throat, head, and neck. This 430-bed hospital is also a post-graduate teaching center of the Medical School of Fudan University, and offers subspecialty training to ophthalmologists and otolaryngologists across China.

Beginning an international dialogue

HMS Ophthalmology faculty and Chinese colleagues from Shanghai Eye and ENT Hospital have begun a dialogue aimed at exploring potential research and educational opportunities. This endeavor began in earnest in December 2010, when several HMS faculty members traveled to Shanghai Hospital on a five-day international outreach trip. The group received a tour of the institution and presentations on its clinical and research efforts. Faculty gained a solid perspective of the hospital's ophthalmology training process, as well as the needs of the population they serve; today, for example, there are only 600 phacoemulsion/cataract surgeons to serve the country's population of 1.3 billion. During their visit, HMS faculty provided an overview of ongoing research efforts within the HMS Ophthalmology Department, as well as details about the organization, structure of the HMS Department of Ophthalmology Residency Training Program, and innovations to the curriculum.

Collaborations aim to advance science and education

This initial exchange proved highly successful, and HMS Ophthalmology reciprocated in the spring of 2011 when the faculty welcomed to Boston a five-member ophthalmology team from Shanghai. The two-month visit gave team members first-hand exposure to a full range of learning opportunities, including general ophthalmology and subspecialty training practices. With specialties in glaucoma, retina, cornea, and cataracts, each Shanghai physician shadowed a faculty mentor from Mass. Eye and Ear in the operating room and clinic. Another goal of the team was to learn about the department's residency training program. Shanghai ophthalmologists attended educational programs and lectures, and met with investigators to explore potential research collaborations.

Ultimately, faculty members from both institutions look forward to a productive relationship, which will advance academic programs and scientific endeavors in various subspecialty fields in China.

TOGUS VETERANS AFFAIRS MEDICAL CENTER

Togus Veterans Affairs Medical Center strives to advance health care through research and education, with an emphasis on preventive, primary, and specialty interventions in both outpatient and inpatient settings. The dedicated staff at Togus VAMC provides high-quality and timely care to better serve veterans.

History

On March 21, 1866, Congress established the National Homes for Disabled Volunteer Soldiers (NHDVS) to provide care for wounded soldiers; soon thereafter, the Eastern Branch of NHDVS in Togus, Maine was established. In 1930, the Togus NHDVS became a part of the Veterans Administration, which provides benefits to veterans and their dependents. Since its inception in 1866, Togus VAMC has grown to be recognized locally, regionally, and nationally as a leader in quality patient care. Today, the Department of Veterans Affairs Medical and Regional Office Center has an operating bed capacity of 176 beds, with a staff of approximately 900 full-time and part-time employees.

Ophthalmic care

As a regional referral center for ophthalmology in the state of Maine, Togus VAMC provides various clinical services, including general surgery, ophthalmology, neurosurgery, pain management, and optometry. Here, senior residents work with staff ophthalmologists in surgical procedures for a broad range of ocular disease (including cataracts and glaucoma) as well as retina laser procedures. Togus VAMC is an academic affiliate of Mass. Eye and Ear and the New England College of Optometry.

Telemedicine: medical care at a distance

Togus VAMC contributes greatly to the growing success of telemedicine programs, such as the Joslin Vision Network (JVN). Implemented in 1990, the JVN uses advanced digital video technology to detect abnormal retinal blood vessels. In 2005, over 1,200 patients from Togus VAMC were selected to participate in a clinical trial through JVN. This study demonstrated the utility of JVN for identifying the severity of wide-ranging ocular conditions, thus determining the appropriate treatment priorities for eye care and allowing clinicians to provide "care at a distance."

HMS Instructor in Ophthalmology, Joseph Ciolino, MD, and Mass. Eye and Ear Clinical Fellow, Houman Hemmati, MD, PhD, at the Massachusetts Institute of Technology (MIT). Drs. Ciolino and Hemmati are collaborating with Professor Robert S. Langer (David H. Koch Institute Professor), Daniel Kohane, MD, PhD (MIT and Children's Hospital), Claes Dohlman, MD, PhD (Mass. Eye and Ear), and others on the development of long-term drug delivery systems for use in a wide range of ophthalmic conditions.

HMS Department of Ophthalmology researchers and clinician scientists are continuously turning insights into cures that benefit scores of people. Many discoveries and developments, past and present, are helping to enhance the knowledge and practice of ophthalmology worldwide. Here are some of these outstanding achievements:

DISCOVERIES MAKING A DIFFERENCE

RETINA

- Isolated the gene governing retinoblastoma, a potentially fatal eye tumor affecting young children. This gene is also a prototype for an entire class of genes relating to cancers of the breast, bone, bladder, and lung.
- Pioneered the use of proton beam therapy for successfully treating intraocular malignant melanoma with minimal or no damage to surrounding tissue.
- Isolated the gene that causes a form of retinitis pigmentosa, a hereditary and degenerative blinding disease of the retina.
- Made the first diagnosis of retinopathy of prematurity, a form of blindness caused by excessive amounts of oxygen given to premature babies.
- Introduced scleral buckle surgery for retinal detachments (to North America).
- Developed laser photocoagulation therapy, which revolutionized the diagnosis and treatment of diabetic retinopathy, and has remained the gold standard of therapy for more than 25 years.
- Developed photodynamic therapy (PDT) with verteporfin (Visudyne®), the first FDA-approved drug treatment for neovascular "wet" age-related macular degeneration (AMD).
- Discovered the role of vascular endothelial growth factor (VEGF) in ocular neovascularization in two of the most common causes of blindness: AMD and diabetic retinopathy.
- Participated in the development of anti-VEGF drugs for treating AMD and diabetic retinopathy. Given by intraocular injection, this new class of inhibitors has been shown in clinical trials to help 90 percent of patients avoid moderate vision loss, while one-third experienced gains in vision.
- In collaboration with Swedish colleagues, developed an algorithm called WINROP; based on measures of postnatal weight gain, this algorithm can predict retinopathy of prematurity nine weeks before development of disease.
- Identified the role of environmental factors in promoting AMD, and how nutritional factors may lower the risk of AMD.
- Demonstrated the utility of vitamin A palmitate in retinitis pigmentosa.
- Implanted the first microelectronic retinal prosthesis in a human eye (an array of 100 microelectrodes) to stimulate residual elements of the retina in a patient with advanced retinal degeneration.
- Validated and implemented the first ocular telemedicine program—the Joslin Vision Network (JVN)—for early detection of diabetic retinopathy. JVN nonmydriatic images have been validated for diabetic retinopathy severity grading against the Early Treatment Diabetic Retinopathy Study protocol, which involves fundus photographs and clinical examinations.
- Identified genetic pathways that increase the risk of advanced diabetic retinopathy. A collaboration with the University of San Diego demonstrated that a polymorphism in the promoter region of the erythropoietin gene increases the risk for proliferative diabetic retinopathy.
- Developed (with MIT and MGH researchers) optical coherence tomography, the most widely used and non-invasive imaging modality in retina.

CORNEA

- Developed the Boston Keratoprosthesis (Kpro), the world's first and most popular artificial cornea, with more than 5,000 implantations to date in 50 countries.
- Discovered the first drug to cure the virus infection, Herpes Simplex, which causes severe damage to the cornea.
- Elucidated the molecular and physiological mechanisms of corneal swelling and edema that contribute to corneal clouding. These discoveries laid the groundwork for many techniques currently used to restore corneal clarity and visual acuity in patients.
- Elucidated the role of VEGFR3 as the mechanism by which the cornea remains avascular (without blood vessels). This body of work formed the basis for ongoing clinical studies of novel therapies to treat graft rejection and other inflammatory disorders, including dry eye disease, which affects millions of people worldwide.
- Demonstrated the protective role of certain molecules (called mucins) to prevent infections on the cornea and surrounding tissue. This key discovery had multiple crossovers to other areas of investigation, including human reproduction and infectious diseases.

STRABISMUS

- Discovered seven different forms of strabismus arising from a variety of genetic errors in brainstem motor neuron development. This body of work defined a new category of congenital disorders that leave children unable to move their eyes in specific directions.
- Discovered that earlier intervention in unilateral coronal synostosis (by way of endoscopic strip craniectomy) can prevent sight-threatening strabismus and astigmatism.

OPTIC NERVE/GLAUCOMA

- Paul A. Chandler, MD, and W. Morton Grant, MD, describe clinical features of glaucoma, and form definitive concepts in the management of the disease. Their book Chandler and Grant's Glaucoma remains an authoritative reference text since its first publication in 1965.
- Identified several genetic and molecular mechanisms underlying the pathology of pediatric glaucoma.
- Demonstrated (in postnatal mice) successful full-length regeneration of the optic nerve.
- Identified several genetic, hormonal, and environmental factors associated with various forms of glaucoma, a diverse group of conditions that can potentially damage the optic nerve.
- Identified novel targets for potential neuroprotective strategies in glaucoma management.

COLLABORATING TO CURE

HMS Ophthalmology Centers of Excellence drive collaboration

From novel clinical and research partnerships to new educational venues, many exciting initiatives in recent years are transforming "business as usual" within the HMS Department of Ophthalmology. Contributing to this momentum, the HMS Department of Ophthalmology has launched Centers of Excellence (COEs) in key subspecialty areas that draw on the exceptional talent and resources of the HMS community. These efforts are advancing scientific discovery, expand training opportunities, and bringing new innovations into the clinic. COEs are underway in the areas of diabetic eye disease, age-related macular degeneration (AMD), cornea, and glaucoma.

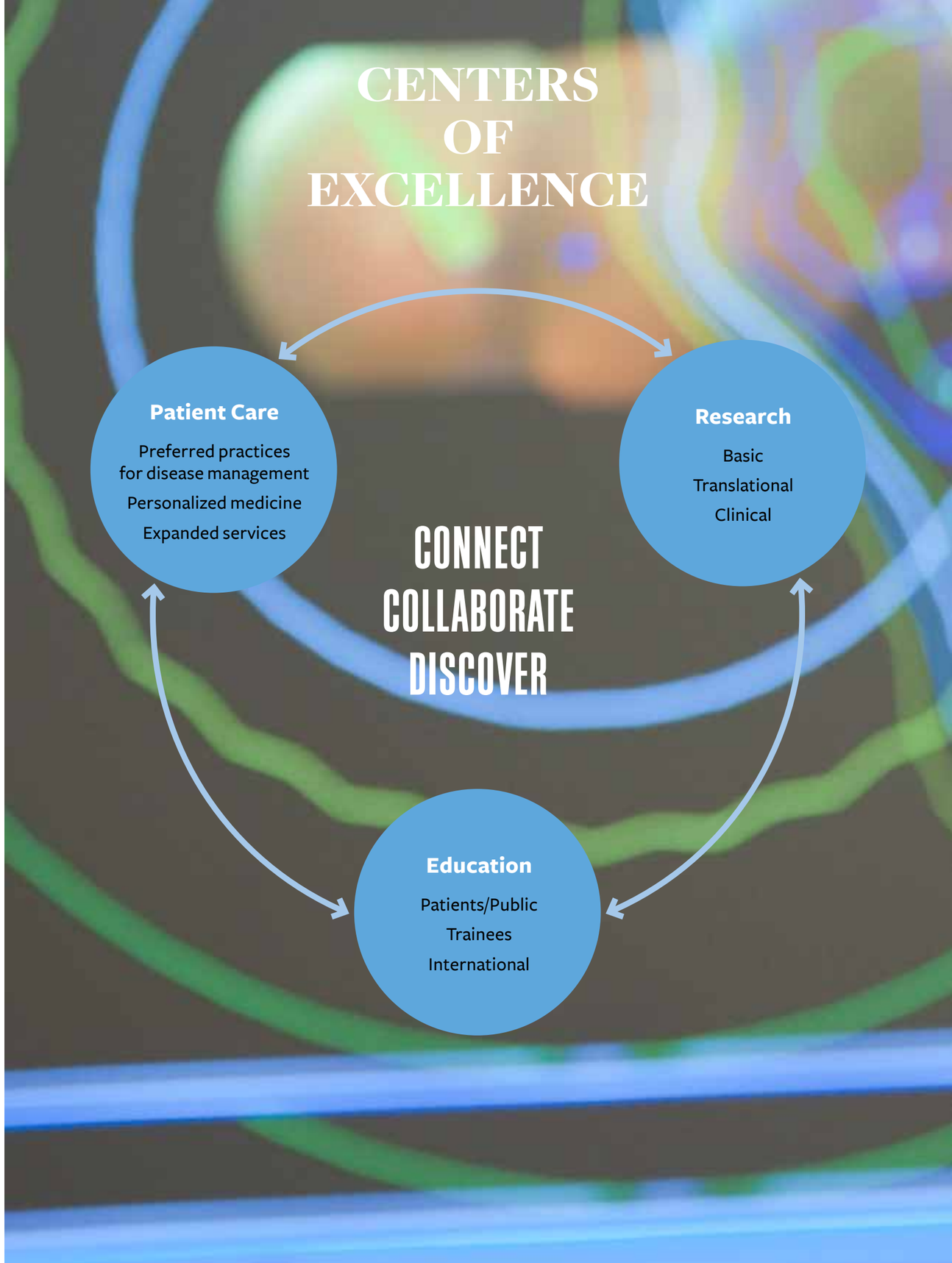
"Momentous leaps in science, biotechnology, and medicine in the last decade have brought the future of healthcare to our doorstep—creating unprecedented opportunities for advancement," says Lloyd P. Aiello, MD, PhD, HMS Ophthalmology Vice Chair for Centers of Excellence and Director of the Beetham Eye Institute at Joslin Diabetes Center. "Centers of Excellence allow us to lead by design and create communities of collaborators that will bring the next generation of advances to fruition. COEs also provide the framework for moving information and ideas across campus with improved speed and access, helping us to accelerate progress in all aspects of our mission."

COEs integrate the clinical, research, and academic objectives of HMS's six ophthalmology affiliates and broad faculty base of 140 full-time clinicians, scientists, and academicians—creating an information network that links ideas, resources, and people in pursuit of common goals. Each center is a catalyst for collaboration—creating a multidisciplinary "think tank" that identifies new training opportunities, broadens the scope of research at every juncture, and elicits the highest benchmark standards in all aspects of clinical care.

Core Concepts

- Utilize inherent leadership and expertise to build the key structure, components, and mechanisms of each center for maximum results.
- Identify communication strategies that integrate academic, clinical, and research objectives, and spark cross-institutional involvement.
- Develop unified and readily accessible standards and metrics to improve patient care across the HMS campus and to lead national benchmark standards of care.
- Establish, maintain, and share preferred practice patterns through an ongoing clinical quality program that utilizes robust, evidence-based surgical and outcomes review.
- Facilitate vital research, educational, and clinical partnerships within HMS and in collaboration with community and academic institutions across the United States.
- Expand training opportunities and boost recruitment efforts through stimulating and supporting mentorship, resident, and fellowship programs.
- Create a focus for new funding opportunities that attract sponsorship from government, industry, foundation, and private donors.

As the HMS COEs continue to evolve, department Chair Joan Miller, MD, anticipates that they will be a global resource for innovation. "As our world becomes increasingly connected, we need to embrace strategic partnerships that advance collaboration and connections in our three mission-critical areas," she said. "COEs represent a scalable healthcare model that will help forge these synergies and usher in advancements that resonate here and around the world."



CENTERS OF EXCELLENCE

CENTERS OF EXCELLENCE HIGHLIGHTS

Diabetic eye disease
- BEI clinical research program (DRCR.net)
- Joslin Vision Network (model for preferred practice patterns)
- Latino diabetes initiative

Age-related macular degeneration (AMD)
- Public symposia and outreach
- Biennial AMD International Symposium
- Experimental models for ocular research

Cornea
- Translational research center
- Ocular Surface Imaging Center
- Monthly cornea conference

Glaucoma
- Clinical/research faculty focus groups
- State-of-the-art glaucoma laboratory
- Glaucoma COE newsletter

Optimizing eye care

The use of evidence-based data helps identify the best eye care delivery systems. The Diabetes COE, for example, is using data-driven management practices for its acclaimed international imaging program, the Joslin Vision Network (JVN), to evolve standards across other areas of diabetic eye disease. Lessons learned from the JVN can now be used to improve screening techniques, rigorously validate imaging methods, establish detailed metrics, and engage in multi-institutional collaboration. All of this information can be fed continuously to other faculty engaged in related research within HMS and with outside collaborators.

Delivering care in real time

In just one year, patient referrals to the department's new Ocular Surface Imaging Center (OSIC) have increased ten-fold thanks to high-tech imaging equipment and enhanced diagnostic methods developed by OSIC Director, Pedram Hamrah, MD. These optimized tools and techniques enable real-time and non-invasive imaging, allowing our physicians to diagnose, monitor, and track disease progression and treatments with unprecedented speed and precision. These methods also eliminate the need for invasive biopsies and slow cultures, and reduce the wait time for results from three to seven days to less than 24 hours. In many cases, results can be read during the patient's visit. For thousands of patients each year, this means better diagnosis, treatment, and outcomes.

Tools of the trade

Nidek Confoscan 4.0 and the Heidelberg-HRT 3 Rostock Cornea Module confocal microscopes; Haag-Streit IM 900 digital slit lamp camera, and a Optovue Ocular Coherence Tomographer with cornea module.

Focus for funding

COEs create new funding opportunities in every aspect of the mission of the Department of Ophthalmology. For example, researchers in the AMD Center of Excellence conduct preclinical investigations using a variety of animal models, and carry out small-scale clinical trials to establish a foundation for proof-of-concept in humans In recent years, work with these models has led to revolutionary treatments for macular degeneration, including the photodynamic therapy and a number of antiangiogenic agents. Today, HMS investigators use models for angiogenesis, diabetic retinopathy, retinal detachment, glaucoma, intraocular tumors, and uveitis to develop novel pharmaceutical, biological, and gene-therapy approaches to treat eye diseases. Investigators are also developing the first dry AMD primate model to better understand the pathophysiology of the disease, as well as potential therapeutic targets. To learn more, contact Kim Fechtel at kim_fechtel@meei.harvard.edu.

Tear down those walls!

COEs engender a disease-driven approach that break down traditional research silos, and engage basic researchers and clinicians scientists in direct and focused dialogue. Pertinent clinical opportunities can then be identified and moved from bench to bedside with greater speed. "At any given time, ophthalmology faculty members are leading investigations for 50 to 75 clinical trials in various phases, and pursuing vital grant research," notes Dr. Joan Miller, HMS Ophthalmology Chair. "COEs simplify our communication structure and open the floodgates for scientific inquiry and discovery across the department in complimentary areas. What's happening in AMD research, for example, may yield critical insight into diabetic eye research, and vice versa. It may also embolden scientists to take their research in entirely new directions."

Making connections:

COEs provide a scalable platform for expanding collaboration, education, and training opportunities. For example, a monthly glaucoma focus group was the flashpoint for merging the research efforts of Louis Pasquale, MD, from Mass. Eye and Ear and Emmanuel Buys, PhD, from Mass General. During a recent meeting, Dr. Buys spoke to the group about his research on a knockout mouse model that turned out to have direct relevance to Dr. Pasquale's epidemiology research on primary open-angle glaucoma. Finding common ground, they teamed up with Schepens scientists Bruce Ksander, PhD, and Meredith Gregory-Ksander, PhD, to validate that the mouse model is applicable to POAG in humans. The group has submitted an R21 grant application to NIH. "This cross-fertilization of ideas is an exciting hallmark of the glaucoma Center of Excellence," says Dr. Pasquale. "We learn first-hand about ongoing work across the department, and how our clinically relevant findings may have direct application to what our colleagues are discovering in the lab."

One size does NOT fit all

Ten years ago, the Human Genome Project provided a genetic blueprint of the DNA code that ushered in a revolution in personalized medicine. The goal at HMS is to capture genetic variations that contribute to human disease and use it to improve patient care for every disease we treat. COEs provide an integrated framework for delivering personalized medicine to every patient. By merging clinical data (electronic medical records) with a biorepository of donor DNA and tissue samples, HMS clinician scientists can draw unprecedented insights as to how diseases manifest, and the best route to intervention based on a patient's unique genetic and biological make-up.

CHILDREN'S HOSPITAL OPHTHALMOLOGY FOUNDATION AND MASS. EYE AND EAR FORM A PEDIATRIC POWERHOUSE

In August 2009, Massachusetts Eye and Ear Infirmary and the Children's Hospital Ophthalmology Foundation (CHOF) combined their pediatric services, creating one of the most comprehensive pediatric ophthalmology networks in the country. Under this new partnership, general pediatric ophthalmology and strabismus care at Mass. Eye and Ear is being provided by Children's ophthalmologists, while Mass. Eye and Ear physicians offer subspecialty care in glaucoma and cornea disease at Children's Hospital Boston. Both HMS affiliates have long cooperated on patient care, research and academic activities; this innovative clinical partnership streamlines patient care while broadening access to services, and more tightly integrates training and research activities.

"Delivering the best possible care to every patient is always our first priority," notes HMS Ophthalmology Chief and Chair, Joan Miller, MD. "Children's Hospital Boston has built one of the country's premier practices in ophthalmology. Integrating their depth of experience into our core services enables us to deliver seamless and integrated care to our most vulnerable patients."

"This partnership is a significant milestone in keeping us a top-tier pediatric care provider," said David Hunter, MD, PhD, Ophthalmologist-in-Chief at Children's Hospital Boston. "It reinforces our already deep commitment to quality patient care by making our world-class services increasingly accessible to patients, including treatment for the most complicated eye and vision problems."

Raising the bar on research

By pooling resources and a patient base that combines pediatric eye and adult strabismus cases, the new alliance also enhances investigative teamwork carried out internally, and brings more opportunity for the department—and patients—to participate in benchmark clinical studies on an international scale. Melanie Kazlas, MD, Medical Director of the Children's Hospital Ophthalmology Foundation at Mass. Eye and Ear, describes one such study that involves the Pediatric Eye Disease Investigative Group (PEDIG), a collaborative network funded by the National Institute of Health that facilitates multicenter clinical research in strabismus, amblyopia and other eye disorders that affect children.

HMS Instructor in Ophthalmology, Suzanne Johnston, MD, is Principal Investigator of a randomized clinical trial comparing observation vs. occlusion therapy for intermittent exotropia. Using rigorous study protocols, the study aims to better understand the natural history and progression of intermittent exotropia (wandering eye) and determine the best method of managing the disease in young patients. Until now, there have been no studies to verify the efficacy of current treatments," says Dr. Kazlas. "Studies like this provide important public health implications because they help establish standards for solving common childhood problems in eye disease using evidenced-based medicine."

Currently, more than 60 sites comprising 120 pediatric ophthalmologists and optometrists in the United States, Canada, and the United Kingdom participate in the PEDIG network on various studies.

"Forward-thinking consortiums like PEDIG help generate new ideas that can then be pursued in a collaborative, well-designed study. Integrating Mass. Eye and Ear and CHOF pediatric services gives us the sizeable patient base required to participate, as well as the vital research resources and support staff we need to carry out a long-term study," noted Dr. Kazlas.

Patient empowerment

Bringing CHOF to Mass. Eye and Ear also affords patients more opportunities to participate in ongoing investigations. Some patients, for example, have contributed clinical information in the form of blood, tissue, and DNA samples that have helped to elucidate the genetics of common forms of strabismus. Study participation is empowering for many patients whose vital contributions can help pave the way for new treatments or lead to a cure for their disease.

Enhancing resident education

The clinical alliance between CHOF and Mass. Eye and Ear also has enhanced resident education with added exposure to important pediatric ophthalmology and strabismus topics through lectures at both institutions. The Pediatric Ophthalmology Visiting Professor Lecture Series, organized by Dr. Anne Fulton, HMS Professor of Ophthalmology, invites faculty who are leaders in the field of pediatric eye disease and strabismus to lecture and interact with faculty, residents, and students. These lectures are televised remotely to Mass. Eye and Ear's main campus and CHOF's Waltham location.

DRCR.NET PROVES THE POWER OF PARTNERSHIP

Launched in September 2002, the Diabetic Retinopathy Clinical Research Network (DRCR.net) was a timely development. In prior decades, vigorous scientific investigations conducted by researchers in the HMS Department of Ophthalmology and in laboratories across the globe had led to exciting breakthroughs elucidating the role of vascular endothelial growth factor (VEGF) in neovascular (wet) age-related macular degeneration (AMD). Integral to these studies was the groundbreaking work of scientists at the Beetham Eye Institute (BEI) at the Joslin Diabetes Center. At BEI, research focuses on unraveling the molecular mechanisms responsible for diabetic eye diseases, and finding potential therapeutic targets that may lead to successful clinical treatments for patients with diabetic retinopathy, diabetic macular edema, and related disorders. Numerous studies followed—conducted at BEI and elsewhere—implicating VEGF and other pivotal compounds in the disease process.

Despite the milieu of scientific discovery, there was no mechanism in place to quickly move data from hypotheses and laboratory studies into multicenter clinical trials. Lloyd P. Aiello, MD, PhD, HMS Professor of Ophthalmology and Director of BEI, realized the critical need for a standardized infrastructure and support system, which could be used to mine and evaluate rapidly accumulating data, then conduct clinical trials using rigorous scientific protocols. He founded the DRCR.net, a national collaborative network dedicated to facilitating multicenter clinical research for diabetic eye disease.

Supported through a cooperative agreement from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, the DRCR.net has grown to include 150 participating sites nationwide, including international participation from sites in India, Scotland, and Denmark. Nearly 300 investigators from academic medical institutions as well as private community practice groups participate in the network, including one out of every three retinal specialists across the country. In its brief history, the DRCR.net has rapidly emerged as the premier clinical trial group in diabetes—mentioned in the U.S. Congressional Record—and lauded by the National Institute of Health as establishing the paradigm for collaborative clinical trials.

"Clinically rigorous testing requires large numbers of patients and participation from large numbers of centers," says Dr. Aiello, who has been recognized internationally for his leadership in diabetic retinopathy research and served as the network's inaugural chair. "The DRCR network enables us to tap this vast pool of resources and, in short order, identify key clinical areas that need to be addressed, recruit patient volunteers, and carry out high quality multicenter trials. In less than a decade, this powerful means of collaboration has led to remarkable clinical gains that have refined our knowledge of diabetic eye disease and how we manage patients."

Melanie A. Kazlas, MD

Instructor in Ophthalmology, Harvard Medical School

Medical Director, Children's Hospital Ophthalmology Foundation, Massachusetts Eye and Ear Infirmary

Dr. Melanie Kazlas received her BS degree cum laude at Rensselaer Polytechnic Institute in 1987. Following completion of her MD in 1989 and an internship in 1990, both at Albany Medical Center, Dr. Kazlas completed her residency in ophthalmology at Manhattan Eye, Ear and Throat Hospital (MEETH). She went on to complete an ophthalmology and strabismus fellowship at MEETH in 1994. She served as Acting Director of the Pediatric Ophthalmology and Strabismus Service at Mass. Eye and Ear from 2006 until 2009, at which time she was appointed Medical Director of the Children's Hospital Ophthalmology Foundation at Mass. Eye and Ear.

Dr. Kazlas provides comprehensive evaluation and treatment for babies, children, and adults of all ages with strabismus (otherwise known as misaligned eyes or crossed eyes). In addition to pediatric and adult strabismus, Dr. Kazlas specializes in amblyopia (commonly known as lazy eye), retinopathy of prematurity, and all other areas of pediatric ophthalmology. Exceptionally trained in delicate surgical techniques required for difficult cases of strabismus, Dr. Kazlas has earned a stellar reputation for her compassionate and innovative diagnostic and treatment approaches.

Dr. Kazlas is an active health educator, and serves as a leading expert in strabismus and pediatric ophthalmology for ABCNews.com. Dedicated to providing the pediatric community with the best care possible, Dr. Kazlas has teamed with Mass. Eye and Ear's Outreach staff to provide eye screenings to at-risk pediatric populations at Boston's Camp Harbor View and Neighborhood House Charter School. A member of the New England Ophthalmologic Society, Dr. Kazlas has also co-authored several papers including historical and current practices in pediatric intraocular lens implantation, ocular injuries in shaken baby syndrome, and diplopia after surgical repair of facial trauma.

DRCR.net:
A model clinical research program

Tier 1 recruiter for multiple consecutive years, and #1 nationally in quality in multiple consecutive years (2010 statistics):

- 100% completion of primary outcome visits
- 99% patient retention
- 99% visit completion
- 93% on-time study visit completion
- .02 protocols deviations per visit (average)

UNITED STATES AND INDIA PARTNER TO ADVANCE VISION RESEARCH

As the world becomes increasingly connected, there is a greater need to build viable global healthcare partnerships. In 2005, an initiative funded by the National Institute of Health led to one such collaboration: the US INDO Joint Working Group, a vision research partnership between the U.S. National Eye Institute (NEI) and the Indian government's Department of Biotechnology (DBT). Co-Chair of the initiative is Janey Wiggs, MD, PhD, Associate Director of the Howe Laboratory of Ophthalmology, Associate Chief for Clinical Research at Mass, Eye and Ear Infirmary, and Director of the Genetics Diagnostics section of the department's new Ocular Genomics Institute. As Co-Chair, Dr. Wiggs oversees the U.S. effort, which includes research projects from physicians and researchers from academic medical institutions throughout the U.S.

The exploratory vision science group first met in India in 2005 to identify and facilitate research opportunities between the two countries. The group visited three institutions that deliver high quality eye care and conduct active, vibrant research programs: Aravind Eye Hospital in Madurai, the largest eye care provider in the world and a long-standing educational partner of the HMS Department of Ophthalmology; Sankara Nethralaya in Chennai; and LV Prasad Eye Institute in Hyderabad. Through a series of meetings and workshops, the U.S. team and Indian colleagues paired research interests and skills, which spanned several areas of the molecular genetics of eye disease, including clinical aspects and harmonization of clinical measurement techniques and terminology. Additional areas included translational physiology and the identification, development, and exchange of research resources.

Today, several projects are well underway. For her part, Dr. Wiggs teamed with David Friedman, MD, MPH, PhD, from Johns Hopkins University and Ronnie George, MD, a clinician scientist from Sankara Nethralaya, to study the application of consanguineous pedigrees to mapping of complex genetic traits.

In 2008, Dr. Wiggs received a grant for a National Eye Institute study entitled India-US Genetics Study of Ocular Quantitative Traits. The purpose of the project is to determine the viability of consanguinity for quantitative trait mapping, and to identify genes that are associated with specific ocular characteristics that are risk factors for common, complex eye diseases. During the last several years, Drs. Wiggs and George have worked together to develop project logistics and strategies and to execute each phase of the study, from identifying study participants, to collecting blood samples and analyzing data.

The underlying hypothesis of the study is that consanguineous families—compared to nuclear families—may provide a more powerful way to identify genetic factors responsible for quantitative ocular traits. For example, optic nerve size is a quantitative trait that is passed from generation to generation, and larger optic nerves may carry an increased risk of developing glaucoma. In the long term, this information may provide a rich source of genotype/phenotype data that can be mined for genetic insights into blinding diseases such as glaucoma. Analysis of data gathered from the study is currently underway.

Besides having the potential for advancing vision science, the study demonstrates the growing importance of cross-border collaboration. "If our underlying hypothesis proves correct—that consanguineous pedigrees do, indeed, provide a more robust genetic roadmap for flushing out faulty genes—then we'll have the information needed to accomplish two important goals: helping to pave the way for new diagnostic and therapeutic capabilities, and applying that knowledge to reduce the burden of blindness worldwide," notes Dr. Wiggs. "It's a win-win for the U.S. and India, with positive global consequences."

Members of the U.S. Indo Joint Working Group

"TFOS embraces Harvard's 1650 Charter and mission statement, in that it strives to create knowledge, to advance the sciences, to educate leaders and to pursue excellence in a spirit of productive cooperation."
—Dr. David Sullivan, TFOS President

THE TEAR FILM & OCULAR SURFACE SOCIETY BUILDS A GLOBAL EYE RESEARCH COMMUNITY

During the past several decades, a significant international research effort has focused on understanding the composition and regulation of the ocular surface tear film. This effort was motivated by the recognition that the tear film is critical for maintaining corneal and conjunctival integrity, protecting against microbial challenge, and preserving visual acuity. In addition, research has been stimulated by the knowledge that deficiency of the tear film—commonly called "dry eye"—occurs in innumerable individuals throughout the world and over 40 million people in the United States alone. Dry eye may lead to desiccation of the ocular surface—potentially resulting in visual disability and vision loss.

To promote further progress in this field of vision research, David A. Sullivan, PhD, HMS Associate Professor in Ophthalmology, founded and created a global eye research community that became known as the Tear Film & Ocular Surface Society (TFOS). The mission of TFOS, which was incorporated as a non-profit organization in 2000, is to advance the research, literacy, and educational aspects of the field of tear film and ocular surface. Since incorporation, TFOS has launched numerous initiatives, including:

- Organization of International Conferences on the TFOS in Maui in 2000, Puerto Rico in 2004, Taormina in 2007, and Florence in 2010.
- Organization of a special experts' meeting, entitled "Global Treatments for Dry Eye Syndrome: An Unmet Need," in Florence in 2010. This meeting addressed accepted and emerging clinical endpoints of dry eye with regulatory authorities from around the world.
- Publication of a 1,385-page book (Adv Exp Med Biol 2002, vol 506), to provide an educational foundation and scientific reference for research on the tear film, ocular surface, and dry eye disease.
- Organization of the International Dry Eye Workshop (DEWS), and publication of the DEWS report in The Ocular Surface (TOS). The DEWS Report updated the definition, classification, and diagnosis of dry eye disease, and assessed its etiology, mechanism, global impact, management, and therapy. This report, termed the "Regulatory Bible" in Europe, required a 3-year effort of more than 65 experts—21 who are associated with the HMS Department of Ophthalmology.

Dry Eye WorkShop Steering Committee (left to right): front row, Drs. Michael Lemp (USA), Anthony Bron (USA), Kazuo Tsubota (Japan) and David A Sullivan (USA); row 2, Janine Clayton (USA), Gary Foulks (USA), Murat Dogru (USA); row 3, Kelly Nichols (USA), Ilene Gipson (USA), Debra Schaumberg (USA) and Stephen Pflugfelder (USA); row 4: Alan Tomlinson (UK) and J.Daniel Nelson (USA)

- Creation of TFOS TV, which features many important diagnostic procedures cited in the DEWS Report.
- Sponsorship of TOS, and facilitation of its growth into the 3rd highest ranked ophthalmic journal in the world.
- Organization of the International Workshop on Meibomian Gland Dysfunction (MGD), and publication of this TFOS MGD report in March 2011 in IOVS. The TFOS MGD Report provides an evidence-based evaluation of meibomian gland structure and function in health and disease. MGD is very likely the most frequent cause of dry eye. The report required over 2 years of effort from more than 50 leading clinical and basic research experts and is being translated into 12 languages.
- Collaboration with the ARVO, EVER, MEACO, ICO, AAOpt, AOptA, BCLA, British Royal Society of Ophthalmology, Japanese Dry Eye Society, Asia Pacific Academy of Ophthalmology, International Symposium on Ocular Pharmacology and Therapeutics, and São Paulo Federal University in organizing scientific sessions.
- Awarding of more than 120 Young Investigator Travel Awards.

Dr. Sullivan, TFOS President, notes that "TFOS activities have significantly helped to promote increased international awareness of external eye diseases, enhance governmental funding for tear film and ocular surface research, stimulate the development of therapeutic drugs and diagnostic devices, and influence the design and conduct of clinical trials of new and unique treatments for ocular surface disorders." At present, TFOS has a distribution to thousands of basic scientists, clinical researchers and industry representatives in more than 80 countries. For more information, visit: www.tearfilm.org.

"I am still in awe of what I see every day! As a visual artist and photographer, everything I do is about light and the way it reflects off an object. This operation has given me my creative life back; my sight, I feel, is that of a newborn's sight, but with a lifetime's experience in which to use what I now see in artistic ways. I am forever grateful to Dr. Daly and her staff for the professionalism they have shown, and the follow-up care they have given me. Your system works amazingly well. Thank you!"

–Joseph Puleo, Navy Veteran, Photographer and Visual Artist

TURNING INSIGHT INTO CURES

LIFE-TRANSFORMING CARE

The brain receives more environmental input from the eyes than from any other sensory system. While most of us enjoy healthy vision, 314 million people around the world live each day with blindness or low vision. For many individuals, loss of vision can have devastating social and economic consequences, leading to a significant loss of independence, mobility, and productivity. In some cases, vision loss is accompanied by significant eye pain or discomfort.

In the United States, blindness or low visual acuity affects 1 in 28 Americans older than 40, or 3.3 million people, according to a 2004 study of age-related eye disease sponsored by the National Eye Institute (NEI). Authors of the study project a significant increase in age-related ophthalmic disease—including cataracts, macular degeneration (AMD), glaucoma, and diabetic retinopathy—as the population ages. By 2020, the number of blind persons in the U.S. is projected to reach 5.5 million—a 70 percent jump—with a similar projection for low vision.

Dr. Mary Daly checks the vision of patient, Mr. Edward Cahalane, a United States Air Force Veteran of the Korean War.

Beyond individual suffering, the economic backlash of blindness and low vision on societies around the world is staggering. In April 2010, AMD Alliance International released a landmark report with the first-ever estimates of the global cost of vision loss—nearly $3 trillion dollars (USD) in 2010 for the millions of people worldwide living with low vision and blindness. According to the study, these costs will rise dramatically through 2020, unless effective prevention and treatment strategies are adopted worldwide.

Dedicated stewards of vision health

Working the front lines of vision care every day, HMS Department of Ophthalmology physicians understand the extent to which blindness and low vision can compromise a patient's quality of life. Fueled by this knowledge, HMS clinicians practice exacting standards of care along the vision health continuum—from well-visits to rehabilitation—combining their expertise with innovations that aim to prevent, mitigate or cure blinding eye diseases. Each year, the HMS network of physicians draws thousands of patients from around the country and the world seeking treatment for some of the most challenging and complex eye diseases. Collectively, they form a clinical ophthalmic powerhouse, offering an extensive array of the world's best tertiary and specialty care for patients of all ages and across every ophthalmic subspecialty.

The preceding section of this report, People & Partners, highlights the unique attributes, expertise, and strengths of HMS affiliates and partners. This section focuses on their inspiring clinical innovations and treatments, which have given hope and sight to millions of people around the globe, and credence to the possibility that one day blinding diseases will be relics of the past.

"I recently have become some 20 years younger thanks to the remarkable skills of Dr. Mary Daly. I want to thank you and the VA Boston for giving me sight again."
—First Lieutenant Theodore Scott Simpson, World War II and Korean War Air Force veteran

Advanced Clinical Resources

The HMS Department of Ophthalmology continually invests in people, technology, and resources to facilitate a full spectrum of clinical services, advance quality of care, and enhance every patient's experience.

Clinical teams

Each clinical area is staffed by a team of highly skilled ophthalmic professionals, including dedicated faculty, fellows, residents, nurses, technicians, and clinical coordinators.

Dedicated eye emergency department

Mass. Eye and Ears 24/7 Emergency Department is a unique Center of Excellence that offers unparalleled resources for emergency ophthalmic eye care and trauma.

Morse laser center

The center performs advanced laser procedures using state-of-the-art refractive, glaucoma, retinal, and anterior segment lasers.

Enhanced imaging and diagnostics centers

HMS Ophthalmology affiliates utilize highly sophisticated imaging and diagnostic equipment for precision diagnostic capabilities.

- At Mass. Eye and Ear, the Ocular Surface Imaging Center is equipped with confocal microscopes that enable rapid, non-invasive, corneal biopsies, and potentially earlier detection and treatment of disease. The department's Electroretinography Service performs hundreds of high-tech evaluations annually for patients with retinal degenerative diseases who are referred for diagnosis, prognosis, genetic counseling, and treatment.
- Children's Hospital Boston uses child-focused, sophisticated diagnostic exams to test for a wide range of eye conditions and visual impairment.
- The Joslin Vision Network (JVN), the nation's foremost teleophthalmology program, utilizes unique custom software and a digital retinal imaging device to screen and evaluate diabetes patients for diabetic eye disease. To date, the service has evaluated nearly a million retinal images.

The David G. Cogan Laboratory of Ophthalmic Pathology

The Cogan Laboratory was the first ophthalmic pathology service in the nation, and provides enhanced diagnostic services and pools resources with Massachusetts General Hospital's Surgical Pathology service.

Biobank

Plans are underway to develop a centralized data registry and tissue repository of DNA samples that will be collected from patients and stored electronically. Genetic information will be merged with clinical information via electronic medical records, enabling clinicians to compare and contrast genetic differences for a host of ocular diseases.

International programs

HMS affiliate hospitals offer extensive medical and non-medical coordination services to ensure a friendly and seamless experience for international patients. Services range from assistance with appointments, transportation and accommodations, to language translation assistance.

Contact lens services

Mass. Eye and Ear's full-service center specializes in therapeutic fits, bandage lenses, and a range of specialty contact lens uses that address numerous eye diseases and conditions, including astigmatism, bifocal, dry eye, and prosthetics. Children's Hospital Boston also provides complete contact lens care for newborns and infants, and specializes in fittings for children with cataract removal, keratoconus, astigmatism, and other conditions.

Around-the-clock pharmacy

Mass. Eye and Ear's 24/7 pharmacy specializes in ophthalmic medications.

Dedicated social work department

The Social Work and Discharge Planning Department at Mass. Eye and Ear is staffed by licensed clinical social workers and nurses registered in continuing care. Services are designed to help families cope with medical, psychological, social, and practical concerns related to their illness and treatment.

Around the world, an adult goes blind every five seconds and a child goes blind every minute.
— National Eye Institute

JOAN W. MILLER, MD

$3,000,000,000,000 (U.S. dollars) The estimated cost of global vision loss today.
— AMD Alliance

FOCUS:

AGE-RELATED MACULAR DEGENERATION

Revolutionary AMD therapies reshape the landscape of patient care

Age-related macular degeneration (AMD) is the leading cause of blindness in adults over age 55 in the United States, and affects some 10 million Americans. The disease causes the macula, the central portion of the retina, to progressively deteriorate; left untreated, it eventually robs patients of their central vision.

There are two types of AMD. Dry AMD makes up about 90 percent of all cases, and involves the degeneration of the retinal pigment epithelium (RPE), which is a thin layer of supportive cells beneath the macular photoreceptors. This corresponds with atrophy of the macular photoreceptors and loss of central vision. Although dry AMD is a less common cause of significant vision loss, it is associated with an increased risk of developing the more severe "wet" form.

The process of new blood vessel growth in the body is called angiogenesis. "Wet" or neovascular AMD occurs when there is abnormal angiogenesis in the choroid, a layer of blood vessels that grows under and into the retina beneath the macula. The new blood vessels tend to be immature and leaky, which can rapidly destroy the photoreceptors. Wet AMD causes about 90 percent of vision loss in all AMD cases combined. In decades past, clinical interventions for wet AMD were limited to observation, laser photocoagulation (which often damaged surrounding healthy tissue), and sometimes surgery; however, none of these options offered patients long-term hope for arresting the disease's relentless march.

The status quo began to change in the 1970s when angiogenesis pioneer, Judah Folkman, MD, first proposed the groundbreaking concept that angiogenesis is central to the development and growth of tumors. Dr. Folkman theorized that it was possible to identify specific factors that induce and inhibit angiogenesis, thus providing a way to arrest tumor growth and develop new treatments for cancer. In the decades to follow, Dr. Folkman and other scientists conducted intensive research to identify specific promoters driving angiogenesis. In particular, the efforts of the nine-member HMS Angiogenesis Research Group (HMSARG , see footnote on page 88), led to key studies that elucidated the role of vascular endothelial growth factor (VEGF) in ocular neovascularization, and its potential as a target pathway for treating neovascular AMD.

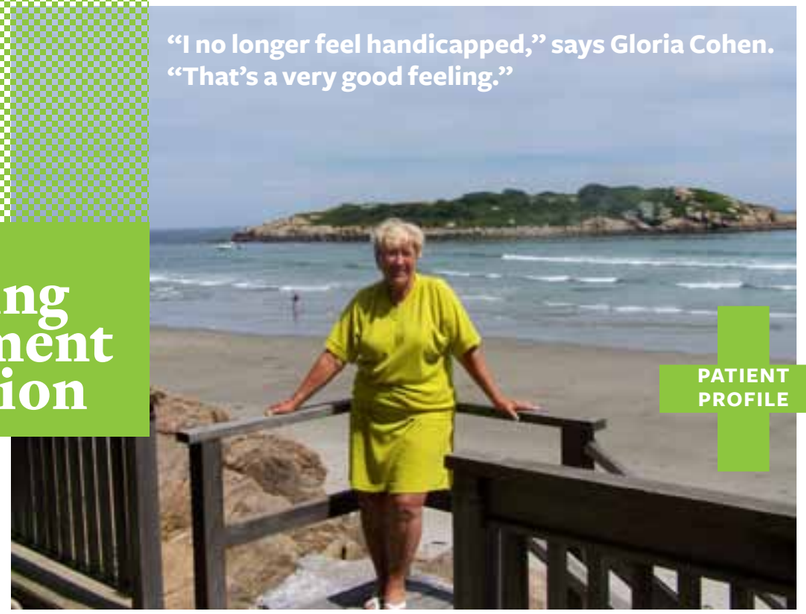
Studies directed by Joan Miller, MD, and Evangelos Gragoudas, MD, in the Mass. Eye and Ear Retina Research Institute and HMSARG led to the first FDA-approved drug treatment for neovascular (wet) AMD: photodynamic therapy (PDT) with Visudyne®. Now a decade in use, Visudyne® was a revolution in patient care. Injected systemically and activated by light, the drug targets and destroys pathogenic blood vessels in the eye. A relatively painless and quick treatment, Visudyne® marked a significant milestone in patient care by slowing and limiting vision loss without damaging surrounding healthy tissue.

Photodynamic therapy laid the foundation for the second wave of pharmacologic treatments that soon followed. Anti-VEGF drugs Macugen®, Avastin®, and Lucentis® represented a novel attack on the underlying cause of wet AMD. Given by intraocular injection, this class of inhibitors prevents specific VEGF proteins from binding to receptors, thus thwarting the growth and leakage of destructive new blood vessels that can lead to the disease. These new therapies represent a quantum leap in patient care—not only saving but restoring vision in many patients. In particular, clinical trials of Lucentis®, approved by the FDA in 2006, showed nine out of 10 patients avoided moderate vision loss, while one-third of patients experienced gains of three lines or more on an eye chart. Forty percent of these patients achieved vision of 20/40 or better on a monthly treatment regimen lasting one year.

Today, these pioneering discoveries—coupled with a passion and persistence to translate them into vision-saving therapies—have ushered in a new era of patient care for treating wet AMD. Physicians now have powerful anti-VEGF therapies at their disposal that can slow or arrest vision loss in patients—or even markedly improve vision in some cases. In the last decade, nearly one million AMD patients around the globe have avoided vision loss thanks to these therapies.

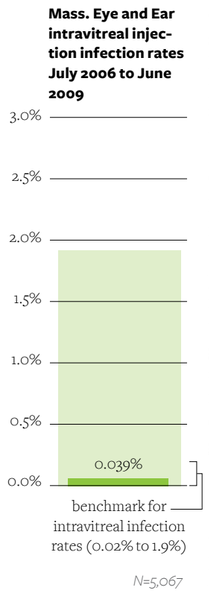
The unprecedented and rich tapestry of angiogenesis and translational work pursued by HMS clinician scientists has established new paradigms of patient care. It has given hope—and sight—to millions of people, and set forth a promising precedent that is helping to shape the vision of the future. Research efforts continue at full throttle as the HMS Department of Ophthalmology continues the quest to solve some of the most complex genetic and epidemiologic puzzles in retinal science. "We've made some dramatic gains in AMD research and clinical care that gives us an exciting platform of discovery on which to forge ahead," said department chief and chair, Joan Miller, MD. "Our research mantra today of 'follow the biology' takes aim at several different AMD targets that potentially could lead to better therapies and preventive measures in the years ahead."

Transforming AMD treatment restores vision



"I no longer feel handicapped," says Gloria Cohen. "That's a very good feeling."

PATIENT PROFILE



Gloria Cohen, an avid tennis player and golfer and now a youthful 72, was diagnosed with AMD at the age of 49. Reading one evening, she noticed that the words on the page were blurred. Gloria made an appointment with an optometrist to get reading glasses. During her exam, the optometrist noticed tiny accumulations of drusen (deposits) beneath the retina—an early finding of AMD. The optometrist referred Gloria to the Mass. Eye and Ear Infirmary for further examination, and she was diagnosed with dry AMD.

Thankfully, Gloria's vision did not change for many years. Then, in 2004, some two decades after her diagnosis of dry AMD, she noticed while playing golf one day that another person on the tee appeared to have "squiggly" legs. Soon afterwards she realized that she was not seeing objects that were in her center of vision. "When I met with a retina specialist, I learned my condition had changed from dry to wet AMD," Gloria said. This progression occurs only in 15 percent of all AMD cases. The retina specialist suggested that she undergo laser treatment to destroy the blood vessels and stop the leakage.

Uncomfortable with this suggestion, Gloria decided to research other options. She read an article in AARP Magazine about Dr. Joan Miller, a retina specialist who was working with a new drug called Lucentis®. In November, 2004, Dr. Miller examined Gloria and found that her visual acuity had decreased to 20/200 on the eye chart. Dr. Miller recalls, "When I met Gloria, I was conducting a clinical trial investigating Lucentis® here at Mass. Eye and Ear. Gloria was a good candidate for the treatment." The studies found that Lucentis® slowed or helped prevent vision loss in patients. According to Dr. Miller, "A substantial number of patients showed significant vision improvement. In fact, 30 percent of the patients who were given Lucentis® gained three or more lines of vision improvement on an eye chart. Forty percent of patients achieved driving vision of 20/40 or better."

The U.S. Food and Drug Administration (FDA) approved the new drug in June 2006. Lucentis® is administered in small-doses, injected directly into the eye through the sclera (white coating) of the eye. Gloria remembers the procedure. "The treatment was quick and I didn't feel a thing."

"We haven't seen any serious side effects with Lucentis®," Dr. Miller says. Gloria was given three injections of Lucentis® over a three-month period. "When I saw Dr. Miller after the third injection, I had a wonderful surprise," she said. "My vision had been restored to 20/25 with correction. I hadn't noticed the vision improvement because it happened slowly." Two months later, she had a fourth injection and her vision improved to 20/20.

"Lucentis®," Dr. Miller notes, "is the first treatment that, taken monthly, can maintain the vision of more than 90 percent of patients with wet AMD." This is good news for the 155,000 Americans who are diagnosed each year with the disease. However, Lucentis® is expensive and some people are not covered by insurance, or they are burdened with high co-pays. For others, getting to a doctor's office for treatment each month can be difficult. "To make treatment easier," Dr. Miller says, "we are looking at ways to slowly release Lucentis® into a patient's eye without injections as well as combination therapies with other drugs that might lead to good results with fewer treatments. We're also part of a multicenter trial (Comparison of AMD Treatments Trials) to compare Lucentis® and Avastin®, a less expensive anti-VEGF agent."

Lucentis® treatments and excellent ophthalmic care from Dr. Miller have transformed Gloria's life. "I no longer feel handicapped," she says. "That's a very good feeling."

HMS scientists forge ahead

Crucial gains in AMD research and treatment, pioneered by an eminent team of HMS scientists during the last two decades, mean that millions of people diagnosed with neovascular AMD will potentially retain their vision for life.

While this is exciting and remarkable progress, much work remains. In the United States, wet AMD is still the leading cause of blindness in older adults, and is expected to rise dramatically as the population ages and adults live longer. Also, there are currently no FDA-approved treatments for treating the atrophic or "dry" form of AMD, though studies have shown vitamin and mineral supplementation in certain patients can help to delay or prevent dry AMD from advancing to the neovascular form.

Thus, while important milestones have been achieved, AMD laboratory and translational research remain a top priority in the department. Efforts continue unabated with an aggressive, multi-pronged attack that aims to improve current therapies, refine diagnostic tools, and develop future therapies that "follow the biology" through epigenetics and gene-based models. Some exciting avenues of research and study include:

- Making current anti-VEGF treatments more "patient-friendly" by 1) reducing the frequency of intraocular treatments while optimizing their effects, and 2) developing drug-eluting contact lenses that may allow for topical delivery of anti-VEGF drugs, thereby reducing or eliminating the need for intraocular injections or eye drops.
- Developing new combination therapies that slow or reverse vision loss, including photodynamic therapy and steroids, or PDT in combination with current anti-VEGF drugs.
- Targeting new disease pathways for additional potential therapies by pinpointing genetic and environmental factors that make some people more susceptible to AMD.
- Developing neuroprotective agents in combination with anti-VEGF therapies to prevent photoreceptor death—the ultimate cause of vision loss in both wet and dry AMD.
- "Reawakening" dead or damaged photoreceptors (rods and cones) through neuro-regeneration techniques, as well as stem cell therapy, which has been shown effective in animal models.
- Refining diagnostic tools and optical methodologies for detecting early signs of AMD, so patients can be tracked and treated sooner to minimize or prevent vision loss.

Anti-VEGF therapies redefining diabetic macular edema treatment

For the first time in 30 years, some people suffering from central retinal swelling, or diabetic macular edema (DME), may be able to substantially improve their vision thanks to novel pharmacologic therapies already FDA-approved for treating the "wet" form of age-related macular degeneration. A recent landmark clinical trial, sponsored by the Diabetic Retinopathy Clinical Research Network (DRCR.net), has shown that the anti-vascular endothelial growth factor (VEGF) medication ranibizumab (Lucentis®)—combined with either prompt or deferred laser treatment—significantly improved vision in many patients with DME, and is quickly emerging as a potential and powerful first-line treatment for people with the disease. The lead author of the study is Lloyd P. Aiello, MD, PhD, Director of the Beetham Eye Institute at Joslin Diabetes Center, and the inaugural chair of the NIH-funded DRCR network.

Nearly three decades ago, Dr. Lloyd P. Aiello's grandfather, William P. Beetham, MD, and his father, Lloyd M. Aiello, MD, pioneered laser photocoagulation, the first treatment shown to be effective at preventing or improving vision loss from proliferative diabetic retinopathy and diabetic macular edema, common ocular complications of diabetes and a leading cause of vision loss in the working-age population. Since the introduction of laser photocoagulation for diabetic eye complications, millions of people worldwide have benefited from this treatment, which can preserve vision and reduce the risk of blindness in 90 percent of patients. Now, findings from the DRCR.net study demonstrate that anti-VEGF therapies may prove even more beneficial than standard laser therapy by further reducing diabetes-associated swelling in the retina.

The ongoing, five-year study involves a total of 854 eyes of 691 people diagnosed with type 1 or 2 diabetes and diabetic macular edema involving the center of the retina (macula). At one year of follow-up, participants who received anti-VEGF therapy gained an average of nine letters (nearly 2 lines) in visual acuity—a three-fold improvement over laser treatment alone. The percentage of patients who achieved at least two lines of vision gain also jumped dramatically, from 28 to approximately 50 percent with anti-VEGF treatment (with prompt or deferred laser) compared to laser treatment alone. Conversely, the number of individuals treated with anti-VEGF medication versus laser alone who experienced two or more lines of vision loss also fell sharply from 13 percent to fewer than 5 percent of patients, representing a significant reduction in the number of people who experienced adverse effects.

Few participants experienced eye-related complications, and there were no serious systemic events such as heart attack or stroke associated with treatment. Results from the trial were published online April 2010 in Ophthalmology. Two-year follow-up data are available for 57 percent of study participants, and these results are consistent with the one-year findings.

"The results from this clinical trial demonstrate that anti-VEGF therapies for treating diabetic macular edema can be remarkably effective, providing substantial improvements in vision and substantial reductions in vision loss," said Dr. Lloyd P. Aiello. "Anti-VEGF treatments represent a full bench-to-bedside cycle of translational research and, for the first time in more than a quarter-century, offer a new and powerful method for restoring sight to perhaps millions of people whose vision might otherwise be compromised by diabetic macular edema."

Initially designed as a three-year study, involving 52 sites within the DRCR network, the trial—now in year three—has been extended to five years, and is supported by the National Eye Institute and the National Institute of Diabetes and Digestive Kidney Diseases.

PATIENT PROFILE

New diabetic macular edema therapy is saving sight

Kevin England, a 32-year-old participant in the DRCR.net-sponsored diabetic macular edema (DME) study, was diagnosed with type 1 diabetes at the age of five. In October of 2007, he first sought the help of Drs. Jennifer Sun and Lloyd P. Aiello, ophthalmologists at Joslin's renowned Beetham Eye Institute. At the time, Kevin already had lost sight in his right eye due to complications from diabetic retinopathy. Substantial retinal swelling in his left eye, caused by DME, had reduced his vision to 20/200, the legal definition of blindness.

Fortunately, Kevin's left eye met the criteria for study participation and he was enrolled in the clinical trial the following January. He was randomly assigned to the study group receiving up to once-monthly injections of the anti-VEGF drug ranibizumab (Lucentis®) in combination with prompt laser therapy. Kevin remembers feeling hopeful that the treatment would arrest the ravaging progress of the disease and save the sight in his left eye. "Even though there were no guarantees, I was happy to be accepted," he said.

From the outset, participation in this study has involved rigorous evaluation and careful follow-up of patients. For the first 13 months of the study, Kevin traveled once or twice a month from his home in Connecticut to the Beetham Eye Institute to receive treatment and/or an eye exam to check his progress. In Kevin's case, Dr. Sun gave him intraocular injections during nine of his first 13 visits and Dr. Aiello performed laser treatment every four months.

Within two months of treatment, Kevin's vision began to improve. As the DME-induced swelling decreased in his eye, his vision continued to show dramatic improvement. Thirteen months into the study, Kevin's visual acuity had climbed an astonishing 15 lines on the eye chart giving him better than average "normal" vision of 20/16. According to Dr. Sun, his results mirrored overall results from the study – now in year three - with half the participants experiencing an average eight to nine letter gain. "Kevin's left eye has done remarkably well in this study and, despite minor variations month-to-month, his vision has remained strong and intact," she said. "And he hasn't experienced any serious side effects, which is consistent with the results from his treatment group."

For Kevin, who works in construction, the treatments have opened up a whole new world - literally. "I don't even remember how I managed before," he says. "I struggled to read a newspaper, watch TV, or see any distance. Now, life is just a whole lot easier."

Dr. Sun adds, "Our ultimate goal for all of our patients, including Kevin, is to maintain vision so that they're not limited by diabetic eye disease. The results in Kevin's case are especially exciting because he is a young person with many years ahead of him. Saving the vision in his left eye, hopefully, will give him maximum quality of life so he remains independent and continues to have a bright, productive future."

FOCUS

OCULAR ONCOLOGY

Ocular oncology involves the study and treatment of tumors that occur in or around the eye. These tumors may cause vision loss or even loss of the eye itself; some ocular tumors are potentially fatal, while others are benign yet severely disfiguring.

The HMS Department of Ophthalmology provides unparalleled care for patients with various forms of ocular tumors. Ocular oncologists at Mass. Eye and Ear regularly perform life-changing procedures, and researchers throughout the department are actively pursuing new and improved ways to treat tumors of the eye.

Proton beam therapy: the gold standard of treatment for uveal melanoma

Between the sclera (the "white" of the eye) and the retina lies the uveal tract, which consists of the iris, the ciliary body, and the choroid. Melanomas, which are tumors that arise from melanin-producing cells (melanocytes), sometimes develop in the uveal tract. Uveal melanoma is the most common type of eye cancer that affects adults, and about 25 percent of cases are fatal.

The earliest treatment for uveal melanoma was enucleation, or removal of the eye. Radiotherapy is now the standard of care, and can allow patients to retain their eyes as well as visual function. Proton beam therapy (PBT), a very precise form of radiation therapy that was developed by Dr. Evangelos Gragoudas at Mass. Eye and Ear, is particularly effective for treating tumors near critical parts of the eye, such as the optic disc (where the optic nerve joins the retina) or the macula (area of the retina that provides central vision).

Presently, with more than 30 years of follow-up, PBT has proven to have the lowest local recurrence rate of any radiation therapy. There are now 20 proton beam facilities in North America, Europe, South Africa, and Japan. More than 15,000 patients have been treated worldwide. Not surprisingly, the Mass. Eye and Ear Retina Service has become a major center for the treatment of this tumor, as well as a center of investigation for related areas of study in epidemiology, diagnosis, treatment, experimental models, new therapies, and basic research.

Dr. Gragoudas played a pivotal role in the development of PBT for uveal melanoma, and performed both preclinical studies and the first clinical studies in patients. For his invaluable contributions to the field of ocular oncology—as well to the development of vascular-targeting therapies for numerous eye disorders—Dr. Gragoudas received the esteemed Mildred Weisenfeld Award in 2006. In his Weisenfeld lecture entitled "Proton Beam Irradiation of Uveal Melanomas: The First 30 Years," Dr. Gragoudas describes the evolution of charged-particle tumor therapy from its conception in a Harvard physics laboratory in 1946 to its inaugural use for choroidal melanoma in 1975 at Mass. Eye and Ear. Despite the clinical success of this therapy, Dr. Gragoudas emphasized the need for further optimizing PBT—particularly for complicated tumors and for prevention of metastasis. Along with Drs. Ivana Kim and Demetrios Vavvas of Mass. Eye and Ear's Retina Service, Dr. Gragoudas continues to refine PBT, and has taken a multidisciplinary approach to developing new strategies for managing uveal melanoma. By investigating the epidemiology, genetics, and molecular biology of uveal melanoma, Dr. Gragoudas and colleagues may uncover innovative therapies and diagnostic methods for this prevalent and potentially deadly cancer.

"I was diagnosed with an ocular melanoma in May of 1992...and was treated by Dr. Gragoudas in July, 1992. I am an 18-year survivor, and I still have good vision in my eye. I come to the Mass. Eye and Ear every year for checkups... Thank you so much for all you do and for adding years to my life."

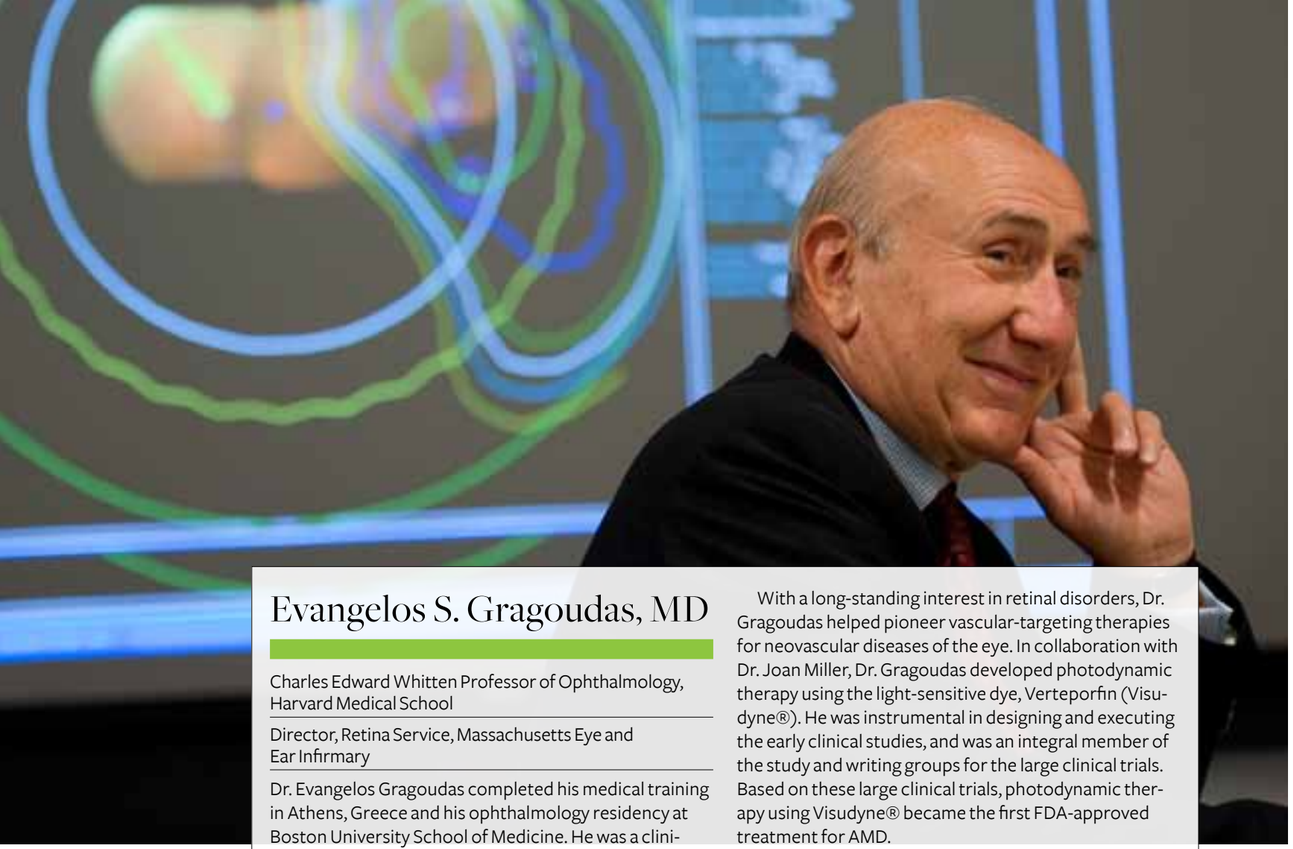
– Margaret Judy Poindexter

Uveal melanoma registry

The HMS Department of Ophthalmology has stood at the forefront of uveal melanoma research and treatment since 1975, when proton beam therapy (PBT) was first used to treat choroidal melanoma at Mass. Eye and Ear. In the early 1980s, Mass. Eye and Ear established the Uveal Melanoma Registry, which contains detailed demographic and clinical data for most patients treated by PBT. Multiple published studies have shown PBT to be a safe and effective treatment for uveal melanoma. A serum, plasma and DNA archive was added to the registry in the mid-1990s, and houses specimens from more than 1,600 patients with uveal melanoma. This information is used as a resource for biomarker and genetic research, and has enabled Mass. Eye and Ear researchers to conduct several studies of cancer susceptibility genes and biomarkers.

Uveal melanoma before proton therapy

Uveal melanoma after proton therapy



Evangelos S. Gragoudas, MD

Charles Edward Whitten Professor of Ophthalmology, Harvard Medical School

Director, Retina Service, Massachusetts Eye and Ear Infirmary

Dr. Evangelos Gragoudas completed his medical training in Athens, Greece and his ophthalmology residency at Boston University School of Medicine. He was a clinical fellow in diabetic retinopathy at the Elliot P. Joslin Research Laboratory at Harvard Medical School (HMS), and subsequently a retina fellow under Dr. Charles Schepens at Mass. Eye and Ear. In 1975, Dr. Gragoudas joined the full-time faculty at Mass. Eye and Ear. He was promoted to HMS Professor of Ophthalmology in 1994.

Director of the Retina Service since 1985, Dr. Gragoudas has helped transform the service into the preeminent academic and clinical service that it is today. Under his leadership, the service has grown from two clinicians to nine clinicians and clinician scientists pursuing vigorous research activities. The number of retina fellows also increased from two to six, and the fellowship expanded from one to two years. Dr. Gragoudas has trained more than 100 clinical retina fellows, many of whom have gone on to leadership roles in medicine, academics, and industry. The Retina Service also serves an important role in training the 24 residents in the Harvard Medical School Department of Ophthalmology Residency Training Program.

Dr. Gragoudas is an international authority in retinal diseases and intraocular tumors. His early translational work focused on uveal melanoma, for which he pioneered the use of proton beam irradiation—a highly successful treatment that has been used in over 15,000 patients to date as a proven and safe alternative to enucleation. Along with refining proton beam therapy, Dr. Gragoudas also has studied the epidemiology, genetics, and molecular biology of uveal melanoma to further improve diagnosis and treatment for this potentially fatal disease.

With a long-standing interest in retinal disorders, Dr. Gragoudas helped pioneer vascular-targeting therapies for neovascular diseases of the eye. In collaboration with Dr. Joan Miller, Dr. Gragoudas developed photodynamic therapy using the light-sensitive dye, Verteporfin (Visudyne®). He was instrumental in designing and executing the early clinical studies, and was an integral member of the study and writing groups for the large clinical trials. Based on these large clinical trials, photodynamic therapy using Visudyne® became the first FDA-approved treatment for AMD.

Dr. Gragoudas also was among the first to target vascular endothelial growth factor (VEGF) in the treatment of AMD. As a member of the HMS Angiogenesis Research Group, he worked with a group of ophthalmologists, including Drs. Joan Miller, Anthony Adamis, Patricia D'Amore, and others in collaboration with the laboratory of famed anti-angiogenesis proponent, Dr. Judah Folkman. This team first demonstrated the critical role of vascular endothelial growth factor (VEGF) in ocular neovascularization, and went on to develop therapies targeting VEGF.

Dr. Gragoudas has published over 200 articles in peer-reviewed journals, and authored more than 100 chapters, reviews, and books; he lectures nationally and internationally. His scientific discoveries in developing therapies for ocular malignancies and for retinal neovascular diseases have saved the sight and the lives of countless patients.

Dr. Gragoudas holds honorary doctorates from the University of Athens and the University of Patras, Greece. Some of his major honors and awards include the Academy Honor Award of American Academy of Ophthalmology, Retina Research Foundation prize of the Jules Gonin Lectureship, Senior Scientific Investigators Award from Research to Prevent Blindness, Senior Achievement Award of American Academy of Ophthalmology, J. Donald M. Gass Medal of the Macula Society, HMS Distinguished Alumni Award, the Arnall Patz Medal of the Macula Society, and the Mildred Weisenfeld Award for Excellence in Ophthalmology from The Association for Research in Vision and Ophthalmology.

Making treatments safer for retinoblastoma patients

Retinoblastoma is the most common primary ocular tumor that affects infants. This cancer develops in the retina, which is the light-collecting tissue at the back of the eye. In advanced cases, the affected eye must be removed; if the cancer spreads to other tissues, retinoblastoma can be fatal. If retinoblastoma is detected early enough, there is a good chance of survival, and it is often possible to save the eye as well as vision. Ongoing studies in the Department of Ophthalmology aim to improve existing approaches for retinoblastoma, as well as to develop new therapeutic strategies.

Chemotherapy is often used to treat retinoblastoma. Unfortunately, the existing chemotherapeutic treatments for retinoblastoma can be highly toxic, and may even increase the risks for other forms of cancer. Drs. Demetrios Vavvas, Joan Miller, and Evangelos Gragoudas set out to find safer treatments for retinoblastoma. They focused on a cellular protein called AMP-activated protein kinase (AMPK), which helps tumor cells grow and multiply. Along with colleagues, they found that they could inhibit retinoblastoma cells with a chemical that inhibits AMPK. This chemical, called 5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside (AICAR), holds enormous potential in treating retinoblastoma because it not only inhibits cancer cell growth, but also has very low toxicity. This study, published August 2010 in *The FASEB Journal*, provides evidence that safer, non-toxic treatments for retinoblastoma may soon be possible.

Several ongoing collaborations between several HMS affiliates are also aiming to improve the methods of treating retinoblastoma. Dr. Shizuo Mukai, a pediatric retinal specialist at Mass. Eye and Ear, has helped develop collaborations with Mass General Hospital, Dana Farber Cancer Institute, and Children's Hospital Boston to test combination chemotherapy and radiotherapy for retinoblastoma. In addition to fine-tuning proton beam therapy techniques, Dr. Mukai is also examining the possibility of inducing the body's own immune defenses to fight retinoblastoma. In a study led by Dr. Bruce Ksander of Schepens Eye Research Institute, Dr. Mukai and colleagues used the membrane-bound, pro-inflammatory form of Fas ligand (FasL) in a mouse model of intraocular tumors. FasL induced a potent inflammatory response in mice with tumors of the eye; this resulted in tumor rejection, reduced metastasis, and lower mortality. This study, reported July 2005 in the journal *Investigative Ophthalmology and Visual Science*, helped form the basis of potential immune-based therapies for retinoblastoma and other intraocular tumors.

Life-changing surgery for patients with vascular malformations

About 10 percent of all babies have vascular birthmarks that develop either before birth or during the first few weeks of life. The most common vascular birthmarks are known as hemangiomas, which are actually non-cancerous tumors made almost entirely of abnormal blood vessels. Hemangiomas are generally not harmful, and many go away without treatment. However, some hemangiomas continue to grow and develop into life-long deformities that may cause significant complications. Such was the case with Alicia Loshkin, a young girl who developed a hemangioma near her eye when she was an infant. When Alicia came to Mass. Eye and Ear in 2009 as a 17-month-old toddler, her hemangioma had grown so large that it almost completely blocked her vision in one eye. Alicia was treated by Dr. Aaron Fay of Mass. Eye and Ear's Ophthalmic Plastic and Reconstructive Surgery Service.

In collaboration with the Vascular Birthmarks Foundation, Dr. Fay donated his consultation and services to remove Alicia's hemangioma—thus restoring her vision. "When we intervene, it's almost like—overnight—they're back to normal," Dr. Fay says of the surgery. "You can't even put it in words; it's really a great feeling to be able to participate in that experience."

Dean Eliott, MD

Dr. Dean Eliott is Associate Director of the Mass. Eye and Ear Retina Service and a full-time clinical and research faculty member of the HMS Department of Ophthalmology. Dr. Eliott is an accomplished and nationally renowned vitreoretinal surgeon. He is active in clinical trials for retinal disease, with a strong interest in translational research on diabetic retinopathy, AMD, and non-diabetic retinal vascular disease. Prior to joining the department, Dr. Eliott was Professor of Ophthalmology, Director of Clinical Affairs and Director of the Vitreoretinal Fellowship Program at the USC Keck School of Medicine's Doheny Eye Institute in Los Angeles. Dr. Eliott has been awarded a Heed fellowship, an American Academy of Ophthalmology 2004 Achievement Award, and the Vitreous Society's 2003 Honor Award.

FOCUS:

CLINICAL INNOVATIONS

Drug delivery: envisioning alternatives to eye drops

Approximately 90 percent of ocular medications are delivered to the eye topically—often in the form of eye drops. Because drops are administered periodically, they do not provide sustained drug levels. Drops are also inefficient because reflexive blinking washes away much of the medication; typically, the eye absorbs less than 10 percent of each dose, and the rest may be absorbed by other tissues and result in unwanted side effects. Moreover, studies show that many patients often don't follow their medication schedules. This is of particular concern as the population ages and the frequency of age-related ocular disorders continues to rise.

Drug delivery is thus an increasingly intense focus of translational ophthalmology research—particularly for conditions that require repeated, long-term pharmacologic intervention. Two new methods of drug delivery, currently in development in the HMS Department of Ophthalmology, may overcome many of the limitations of eye drops.

Drug-eluting contact lenses

Some research innovations have multiple therapeutic applications that may directly benefit a wide range of patients. This may very well be the case with a novel drug-eluting contact lens—developed in a collaboration between Children's Hospital Boston and MIT—that directly releases medications into the eye. Inspired in part by the needs of keratoprosthesis (KPro) patients, Drs. Joseph Ciolino, Daniel Kohane (MIT and Children's Hospital Boston), Claes Dohlman, and colleagues published a paper describing the development of a drug-eluting contact lens, which can potentially improve surgical outcomes by both protecting the ocular surface of the eye and by preventing post-operative infections. The prototype lens consists of a thin polymer film (containing the pharmaceutical agents) that is encapsulated within a hydrogel material that is used in standard contact lenses. The lens was characterized using scanning electron microscopy and drug-release studies, and showed a steady release rate of an antibiotic (ciprofloxacin) that effectively inhibited bacterial growth for more than four weeks. The design and characterization of the drug-eluting contact lens was reported in July 2009 in Investigative Ophthalmology and Visual Science. Although the contact lens could benefit KPro patients, this technology may potentially also benefit a wide range of ophthalmic conditions. It also lays the groundwork for developing additional sustained ocular drug delivery systems.

Drug-eluting contact lens

Implants for intraocular drug delivery

More than three million people in the United States undergo cataract extraction each year. This procedure involves replacing a clouded lens with an artificial lens, and is the most common type of intraocular surgery. Patients usually require eye drops containing anti-inflammatory and antibiotic medications for at least one month after cataract surgery; however, inadequate dosing and patient compliance are regular concerns. Moreover, in some cataract surgery patients, an opaque membrane forms on the rear surface of the artificial lens—which often requires laser surgery as a follow-up intervention to optimize vision. To address these post-surgical issues, Dr. Joseph Rizzo, III has designed an implantable intraocular lens that may allow targeted, noninvasive, and controlled drug delivery to prevent inflammation and infection after surgery. The patented lens design may also be engineered to dispense anti-fibroblastic growth factors to prevent opaque membrane development, which may in turn reduce the number of follow-up laser surgeries. Other key benefits may include fewer complications post-surgery, reducing or eliminating the need for vision rehabilitation, and decreasing the need for medicated eye drops.

New screening method identifies infants at risk for ROP

Every year, according to the National Eye Institute, about 15,000 thousand infants in the United States are born prematurely. About 10 percent of these infants will develop retinopathy of prematurity (ROP), which, if left untreated, can lead to blindness. Traditionally, ophthalmologists have tracked the progress of at-risk infants (primarily those born before 31 weeks gestation) by conducting exams to check for signs of developing retinopathy. However, a new screening algorithm may offer a more accurate, efficient and less costly alternative to traditional screening methods.

Drs. Lois Smith of Children's Hospital Boston and Ann Hellström, a collaborator in Sweden, have developed an algorithm currently in trial called WINROP (Weight IGF-1 Neonatal ROP) that can predict ROP nine weeks before development of the disease based on postnatal weight gain indicative of postnatal IGF-1 (protein) levels. In prior research, Drs. Smith and Hellström identified IGF-1 levels as a key predictor of whether or not an infant would develop ROP. This simple surveillance model can eliminate the need for costly and stressful eye exams in infants by as much as 75 percent. Identifying children at-risk for the disease early on also can lead to more timely interventions, and possibly prevent loss of vision.

Detecting strabismus the easy way

Dr. David Hunter has developed a Pediatric Vision Scanner that detects amblyopia and strabismus in children. The device is a quick 2.5 second test that can identify these eye conditions at their earliest stages when they are most amenable to treatment. The Pediatric Vision Scanner also has the potential to identify children with medical eye disease, including cataract and retinoblastoma. This means that the device will someday be used not just in the United States for detecting amblyopia, but also to improve medical care in developing nations by identifying most vision and life threatening eye conditions—instantly.

Strabismus treatments benefit children and adults

"It's hard enough to convince adult strabismus patients to get corrective surgery, because doctors may have told them it's too late," says Dr. David Hunter, Ophthalmologist-in-Chief at Children's Hospital Boston. "So imagine how hard it is to convince grown-ups to come to a hospital for kids!" he laughs.

Commonly known as "lazy eye" or "crossed eyes," strabismus occurs when a person's eyes are misaligned because the muscles or the nerves that control them are weak or don't function properly. Some people are born with strabismus, while others can develop the condition in adulthood as a result of illness or injury. People who develop strabismus as adults may also suffer from double vision, which can be severe enough to cause functional disability. Even so, many adults are hesitant to get corrective surgery for strabismus.

Children's Hospital Boston and Mass. Eye and Ear Infirmary are home to a group of surgeons who specialize in evaluating, diagnosing, and treating all forms of adult strabismus, including Dr. Linda Dagi, Director of Adult Strabismus at Children's. The group's highly-skilled pediatric ophthalmologists perform delicate eye muscle surgery in patients of all ages, routinely handling difficult cases and correcting the condition in patients who have experienced failed surgeries elsewhere. Dr. Dean Cestari, Neuro-ophthalmologist and adult strabismus surgeon at Mass. Eye and Ear, notes that there are many causes of the disorder, including very subtle medical or neurological disease. "Some people are under the false impression that strabismus correction is a vanity procedure," he said. "However, strabismus isn't just a cosmetic issue—it's a genuine medical condition that sometimes requires reconstructive surgery." Drs. Hunter, Cestari, and Gena Heidary, Children's Hospital's dedicated pediatric neuro-ophthalmologist, are currently preparing a case-based textbook on strabismus, which is slated for publication in early 2012.

With recent advancements like adjustable sutures and non-surgical alternatives, strabismus correction can be far less invasive and have greater long-term success than traditional procedures. Dr. Hunter has led efforts to improve the utility and surgical success of adjustable sutures. He developed an adjustable

PEDRAM HAMRAH, MD

suture procedure called the "short tag noose," which allows physicians to wait up to one week after initial surgery to make final suture adjustments in the office if needed; prior to this, corrections were required within 24 hours of surgery. The short-tag noose procedure widens considerably the window of opportunity to ensure exact and proper positioning of the eye muscle(s) and, often times, eliminates the need for subsequent surgeries.

For some patients, Botox injections offer a viable, permanent, and non-surgical solution for treating strabismus. Physicians at Children's Hospital Boston and Mass. Eye and Ear use Botox to successfully treat a variety of complex strabismus cases. Dr. Hunter and colleagues also have used Botox to correct residual strabismus in adults for whom previous multiple incisional surgeries have failed, as well as strabismus in children with cerebral palsy or developmental delays.

Going live: new imaging techniques are patient-friendly

In routine ophthalmic practice, many standard diagnostic procedures are invasive, slow, and yield only limited insight into the pathology of corneal diseases. To better understand the underlying mechanisms of corneal physiology and pathology, Dr. Pedram Hamrah has applied live corneal imaging techniques that may be used to examine nerves, vessels, and immune cells of the ocular surface. As director of the newly formed Ocular Imaging Center, Dr. Hamrah aims to standardize the use of in vivo confocal microscopy (IVCM) in clinical practice. IVCM is far less invasive than traditional biopsy tests, and may facilitate earlier detection and treatment for patients with corneal diseases—ultimately benefiting the quality of care given to patients and imposing less of a burden on the health care system. IVCM may also help shorten the treatment periods with medications (some of which can have harmful side effects), enable more targeted medical treatment, decrease the need for surgery, and delay disease progression—resulting in an overall improvement in visual acuity.

Recently, Dr. Hamrah, in collaboration with Drs. Deborah Langston and Reza Dana, used IVCM to measure corneal innervation, in patients with herpes simplex keratitis (HSK). Corneal innervation is a marker of disease severity in HSK and other corneal conditions, including dry eye syndrome and keratoconus. This study, and more recent studies, not only demonstrated that corneal innervation (as measured by IVCM) correlated with corneal sensation, but has also demonstrated that both corneal innervation and immune cells are altered bilaterally in unilateral corneal diseases. Prior to this study, clinicians could only measure corneal sensation using subjective and invasive methods. These prospective studies, the first of which was published September 2010 in the journal Ophthalmology, presents a rapid, noninvasive, qualitative, and reproducible method for measuring corneal innervation and inflammation, and assessing disease progression in clinical practice.

Surgical advances benefit glaucoma patients

Glaucoma is the second leading cause of irreversible blindness in the United States,—affecting an estimated three million Americans—and the principal cause of blindness for people of African and Latino descent. This "silent thief of sight" progresses slowly and painlessly, leaving half the people affected by the disease unaware of it. Left untreated, glaucoma's signature risk factor of high fluid pressure within the eye—known as intraocular eye pressure (IOP)—can eventually destroy the optic nerve, robbing people of their sight. There is no cure and early detection is critical; glaucoma can be controlled with eye drops, laser therapy, and surgery, but any vision lost to the disease is lost forever.

Illustration by Laurel Cook Lhowe

Personalized glaucoma surgery saves sight

"With a number of surgical procedures available under one roof, we can offer glaucoma patients options for the best, most individualized care, and ultimately, the best outcomes," says Dr. Rhee.

PATIENT PROFILE

Fran Hall is one of the most active octogenarians you'll ever meet. At 82, she still works professionally as a psychotherapist, skis in the winter, and plays tennis year-round. She also finds time to sing in a chorus, restore furniture, and participate in a book club. Amazingly, Fran maintains this lifestyle 15 years after she was first diagnosed with glaucoma, and just two and a half years after sight-saving surgery at Mass. Eye and Ear.

For ten years, Fran successfully controlled her glaucoma pressure with medicated eye drops and laser treatments. Over time, however, the pressure in both of Fran's eyes continued to rise, and the treatments gradually became less effective. Fran sought the advice of glaucoma specialist Dr. Douglas Rhee at Mass. Eye and Ear. They discussed her busy lifestyle, and Dr. Rhee suggested they forego traditional trabeculectomy surgery in favor of a newer, less invasive procedure—trabectome surgery—that offers patients shorter recovery times and a lowered risk of complications.

Trabectome surgery works by treating the eyes' primary "drain," called the trabecular meshwork, which helps to remove fluid from the eye. The procedure is appropriate for patients with open-angle glaucoma, the most common form of the disease in the United States. Dr. Rhee was the first physician in New England to perform the trabectome procedure, and is currently one of the most experienced physicians in the world performing the procedure.

Dr. Rhee performed the surgery on both of Fran's eyes. As expected, Fran's recovery time was short and the pressure in both eyes is now under control. Aside from regular check-ups at the hospital's Glaucoma Service, Fran is back to an active lifestyle, swinging her tennis racket and spending time with her grandchildren.

Besides trabectome surgery, Mass. Eye and Ear is also the first academic medical center in New England to offer canaloplasty—another new and innovative surgical option for pediatric and adult glaucoma patients. While the trabectome procedure utilizes an internal approach and removes part of the trabecular meshwork, canaloplasty utilizes an external approach without accessing the interior of the eye. During canaloplasty, surgeons dilate the canal behind the trabecular meshwork and place a suture to keep the canal open. As with trabectome surgery, canaloplasty helps to provide better drainage in the eye. It also speeds recovery time and lowers the risk of complications compared to traditional surgical interventions. "With a number of surgical procedures available under one roof, we can offer glaucoma patients options for the best, most individualized care, and ultimately, the best outcomes," said Dr. Rhee. Fran agrees. "I'm one happy camper," she says.

Years after having glaucoma surgery, Fran Hall is doing well. To celebrate her 80th birthday in 2007, Fran jumped from a wharf in Nahant, MA, with her three sons (left to right) David, Gordy, and Max.

FOCUS:

KERATOPROSTHESIS

Boston KPro offers a second chance at sight

There are an estimated eight million people in the world—including 1.5 million children—who are blind from corneal disease. In many severe cases of corneal disease, cornea transplants are the only hope for restoring vision. However, because transplantation facilities and suitable donor corneas are not always accessible, only a fraction of patients who need corneal transplants actually receive them. Moreover, standard corneal transplants are not successful in many corneal conditions—such as such as recurrent graft failure, congenital corneal dystrophies, ocular burns, or autoimmune diseases.

The Boston Keratoprosthesis (KPro), an artificial cornea developed at Mass. Eye and Ear, is an economically sustainable option for many cases that cannot be treated with classic donor-tissue corneal transplants. First conceptualized by Dr. Claes Dohlman in the 1960s, the Boston KPro received FDA clearance in 1992, and is now the most successful artificial cornea in the world with over 5,000 implantations to date. Dr. Dohlman, now working with Dr. James Chodosh and a number of research fellows, continues to lead advancements in Boston KPro design and postoperative management, and the device continues to grow in clinical success and worldwide demand.

The Boston KPro is made of medical grade poly(methyl methacrylate) or PMMA, a clear plastic with excellent tissue tolerance and optical properties. The three parts of the device form a collar-button shape when fully assembled. The device is inserted into a corneal graft and sutured into the patient's cornea using similar techniques as a standard corneal transplant.

Design innovations have greatly improved patient outcomes with the Boston KPro. Holes in the back plate now allow the donor corneal graft tissue to access nutrients from the aqueous humor, thus reducing complications such as stromal necrosis and corneal melt. Newer devices also incorporate a titanium locking ring, which prevents loosening of the device after implantation. Further updates include a threadless stem, which reduces the risk of damage to donor graft tissue during device assembly; this also reduces manufacturing costs, making the KPro more economically accessible. Mass. Eye and Ear researchers, including Drs. James Chodosh and Roberto Pineda II, are conducting ongoing studies of the Boston KPro in developing countries.

Improved postoperative care has been central to the clinical success of the Boston KPro. Common complications such as inflammation and infection are becoming more rare with new prophylactic drug regimens. Innovative devices also have significantly improved postoperative management of KPro. Soft contact lenses are now worn continuously to improve graft retention and prevent irritation and evaporative damage; with the current efforts of Dr. Joseph Ciolino, and colleagues at MIT and Mass. Eye and Ear, contact lenses may soon be used for drug delivery as well. Dr. Dohlman, with the help of Drs. Cynthia Grosskreutz, Teresa Chen, and Louis Pasquale, recently developed shunts that direct aqueous humor away from the anterior chamber to an epithelialized cavity (sinus, etc); these have been shown to reduce IOP after KPro surgery, and may effectively prevent glaucoma. Dr. Samir Melki is spearheading the development of a technique to insert a pressure transducer into the eye, which allows the intraocular pressure to be read from the outside via radio wave telemetry.

The Boston KPro is now the primary therapeutic option for a growing number of conditions. Studies using combined immunomodulatory therapy with the Boston KPro II, led by Drs. Chodosh, Stephen Foster, and George Papaliodis, may continue to improve the outcome in autoimmune disease in cases where the disease makes corneal allograft failure inevitable. A series of case reports by Drs. Dohlman and Deborah Langston demonstrated the Boston KPro's effectiveness in treating corneal damage caused by herpetic keratitis. At Mass. Eye and Ear, Dr. Kathryn Colby pioneered the use of the Boston KPro to treat corneal conditions in pediatric patients. Use of the Boston KPro has grown rapidly—from only 46 procedures in 2002 to 1,200 procedures worldwide in 2010—as corneal surgeons become increasingly aware of the device's numerous advantages.

The Boston KPro continues to evolve. A large number of research fellows are working with Dr. Dohlman to improve the device and its postoperative care. Ongoing research in collaboration with Dr. Eli Peli at Schepens Eye Research Institute is examining the optics in various Boston KPro models. Dr. Lucy Young and colleagues are studying ways to prevent postoperative retinal detachment, and Dr. Ilene Gipson is leading an effort to inhibit enzymes that can cause tissue melt and perforation around the Boston KPro. Dr. Irmgard Behlau and colleagues are examining antibacterial coatings for the device while, at the Kohane lab at MIT, Dr. Daniel Kohane is directing a large-scale effort in biointegration. Continued improvements will lead the Boston KPro ever closer to the goal of providing safe, economical, and effective treatments for corneal blindness.

FOCUS:

VISION REHABILITATION

Technology and tools shaping the future of vision—today

Despite many breakthrough treatments for eye disorders, millions of Americans suffer from irreversible vision loss that restricts their productivity, independence, and quality of life. By 2020, there will be an estimated 53 million Americans aged 65 and over who will suffer some form of visual impairment—a number that will rise as America ages. One of the goals of the HMS Department of Ophthalmology is to develop and implement new tools and technologies that can help patients make the best use of their remaining eyesight.

Maximum impact

It's 1968. Imagine that you've been diagnosed with advanced age-related macular degeneration (AMD) or diabetic retinopathy; a time when there are few vision-saving tools, technologies, and therapies to prevent you from going blind or slowing the progress of your disease. Medical options exhausted and facing an uncertain future, you're told by your doctor, "There's nothing more I can do." Fortunately, not all physicians—including Dr. Joel Kraut, a pioneer in Vision Rehabilitation at Mass. Eye and Ear—subscribed to this pessimistic but widely accepted mantra of the day. Instead, beginning in the 1960s, Dr. Kraut collaborated with social worker Dagmar Friedman and a dedicated group of trustees headed by Robert P. Storer. Together, they developed one of the nation's first comprehensive hospital-based Vision Rehabilitation Services at Mass. Eye and Ear.

Fast-forward fifty years. Much as Dr. Kraut envisioned, vision rehabilitation services have emerged as a separate subspecialty, and an integral and vital component in the ophthalmologic continuum of care. Today, the Vision Rehabilitation Center (VRC) at Mass. Eye and Ear, under the direction of Dr. Mary Lou Jackson, utilizes leading diagnostic tools and therapies to evaluate remaining vision, and to provide comprehensive and sophisticated vision rehabilitation care for hundreds of patients every year. The center assists patients with a wide range of eye diseases and disorders, with the ultimate goal of teaching patients how to maximize their remaining vision and enhance their mobility, independence, and quality of life.

Expert staff members in ophthalmology, optometry, occupational therapy, and social work provide a patient-centric approach that aims to improve reading, activities of daily living, patient safety, community participation, and psychosocial well-being. During the last two years, the VRC has experienced significant growth in patient referrals, underscoring the value of the patient-centric nature of the program and highlighting the increasing demand and need for services as the population ages.

Vision snapshot: This perimetry obtained with the Scanning Laser Ophthalmoscope provides a "map" of the patient's field of vision to assess, in this case, reading ability. Here, the word Mississippi was projected on to the central retina. The patient was unable to see several of the central letters (SSIS) because they fell into a scotomatous (degenerative) area of the patient's retina.

Through a variety of tests, patients receive an in-depth clinical evaluation that enables VRC staff to determine which areas of the retina are affected by vision loss. The VRC houses one of New England's only scanning laser ophthalmoscope (SLO) with macular perimeters. Far more sensitive and accurate than the Amsler Grid, this unique tool produces a real-time, high-resolution map of the functioning areas of the patient's retina. VRC staff can instantly evaluate a patient's visual function, and develop appropriate interventions such as teaching the patient how areas of macular degeneration are affecting their reading.

Determination and Diligence Mark the Career of HMS Ophthalmology Legend:

Claes Henrik Dohlman, MD, PhD

Claes Henrik Dohlman, MD, PhD, Emeritus Professor of Ophthalmology at Harvard Medical School, was born in 1922 in Uppsala, Sweden. Dr. Dohlman earned his MD and a Doctorate of Medical Research (biochemistry) from the University of Lund in Sweden, and completed his residency in ophthalmology in the Eye Clinic of the University of Lund. In 1958, he was recruited to work at The Retina Institute of Boston by former mentor and world-renowned retina surgeon, Dr. Charles Schepens, founder of the Institute (now Schepens Eye Research Institute). He was also asked by Dr. Edwin Dunphy, then Chief of Staff at Mass. Eye and Ear, to establish a Cornea Service at the Infirmary. In 1974, the same year he achieved HMS professorial status, Dr. Dohlman was appointed Chairman of the Department of Ophthalmology of Harvard Medical School, Director of the Howe Laboratory of Ophthalmology, and Chief of Ophthalmology at Mass. Eye and Ear.

In a career that now spans six decades, Dr. Dohlman stands as one of the most highly honored ophthalmologists in the world. Recognized as the founder of modern corneal science, his work is considered "classic" literature on understanding corneal biology. His investigations of corneal physiology laid the groundwork for modern clinical practice in dry eye disease, management of corneal burns, wound healing, corneal transplantation, and keratoprosthesis.

His career reflects a remarkable number of firsts: Dr. Dohlman was first in the world to create an organized cornea subspecialty (Mass. Eye and Ear), first to create a formal structured cornea fellowship program (Mass. Eye and Ear and Schepens), first to recruit full-time cornea fellows to HMS, and first to pioneer surgical innovations in keratoplasty and keratoprosthesis. His most notable achievement is the Boston Keratoprosthesis (KPro), an artificial cornea he first conceptualized in the 1960s and is now the most successful artificial cornea in the world with over 5,000 implantations to date. During his career, Dr. Dohlman has trained first-hand over 200 cornea specialists—more than any other ophthalmologist in the world. His "real" contributions to ophthalmic education are incalculable considering the hundreds of second- and third-generation cornea specialists who have trained under his protégées, and the thousands more who have benefitted from his prolific contributions to corneal literature and science.

In 2007, the American Academy of Ophthalmology named Dr. Dohlman recipient of the Laureate Award—the highest honor possible to bestow by the Academy—in recognition of his contributions spanning 50+ years of continuous service to the profession The following year, he was again honored for his lifetime accomplishments in a named Harvard Professorship whose first incumbent is Dr. Reza Dana, famed for his pioneering science in corneal immunology and transplantation biology.

"Dr. Dohlman's opus of research and clinical work set the stage for a world-class cornea center of excellence at Harvard," remarked chief and chair Joan W. Miller. "His work has benefitted millions of people around the world, and his legacy of knowledge thrives today in the hundreds of fellows, students and colleagues he has trained and mentored over the years. Harvard Medical School—and indeed, the whole world—is a far better place today because of his remarkable talent, contributions, and character."

Dr. Dohlman retired from formal administrative roles in 1989. Today, at the age of 88, he continues to advise and mentor students and colleagues, run a specialized KPro patient clinic, and pursue multi-disciplinary research to enhance clinical KPro outcomes. Despite a lifetime of achievement, Dr. Dohlman is remarkably self-effacing. While he acknowledges his numerous accomplishments, he prefers not to focus on what he has achieved, but rather what still needs to be accomplished—particularly in the area of KPro development. He continues to shape and set new standards for the field, and remains an inspiration to everyone in the Harvard community—and beyond.

An interview with Dr. Claes Dohlman begins on page 160.

"Dr. Dohlman's work has benefitted millions of people around the world and his legacy of knowledge thrives today in the hundreds of fellows, students and colleagues he has trained and mentored over the years. Harvard Medical School—indeed the world—is a far better place today because of his remarkable talent, contributions and character."
— Joan W. Miller, MD

Mary Louise Jackson, MD

Assistant Professor of Ophthalmology, Harvard Medical School

Director, Vision Rehabilitation Center, Massachusetts Eye and Ear Infirmary

Dr. Mary Louise Jackson is a vision rehabilitation expert, committed to helping patients with impaired vision make the best use of their remaining eyesight. As Director of the Vision Rehabilitation Center (VRC) at Mass. Eye and Ear, Dr. Jackson aims to provide optimal treatment through rehabilitation techniques and visual aids. A graduate of York University in Toronto, Dr. Jackson completed her MD and internship at McMaster University in Hamilton, Ontario. She completed a residency in ophthalmology at the University of Toronto, and practiced in Victoria, British Columbia prior to joining the HMS Department of Ophthalmology in 2006.

One of Dr. Jackson's research interests is Charles Bonnet hallucinations, which are recurrent visual hallucinations seen by otherwise healthy individuals with significant vision loss. She is examining patients referred to the VRC to determine the frequency of these hallucinations, why patients experience them, and how they affect quality of life. She is involved with national research collaborations, and is currently conducting a trial of the impact of using a video magnifier on reading performance.

Dr. Jackson's focus is clinical practice and resident education. At Mass. Eye and Ear, she has restructured the multi-disciplinary VRC to follow a patient-centered model of rehabilitation. Under her direction, the VRC has seen significant growth in patient referrals, and is rapidly emerging as a national leader in the field. Dr. Jackson is the Secretary on the Executive Committee of the International Society for Low Vision Research and Rehabilitation. She serves on the American Academy of Ophthalmology's Vision Rehabilitation Committee; as Chair, she leads the development of a national vision rehabilitation residency curriculum and a web-based vision rehabilitation course for ophthalmology residents.

Tiny telescope restores vision to some AMD patients

Jo Ann Preece has a spring in her step and a sparkle in her eye despite living with end-stage age-related macular degeneration (AMD). The vibrant 84-year-old had a miniature telescope implanted in her eye in 2003 during a clinical trial at Mass. Eye and Ear. At a recent check up, JoAnn peered out of a sixth floor window and saw the cars driving by below. Before the surgery, these cars—and everything else—would have appeared blurry. "It's like you're in a fog," JoAnn explains. "I stopped driving and reading."

The CentraSight® Implantable Miniature Telescope (IMT), a new option for some AMD patients, gave JoAnn a new outlook on life—literally—by restoring central vision to one of her eyes. This innovative device is surgically implanted in one eye, where it magnifies and projects central images onto a healthy portion of the retina. This enables patients to see objects in fine detail, and perform "near" activities like reading, watching TV and recognizing faces. The non-implanted eye is then used for peripheral vision.

Post-surgery rehabilitation helps patients develop the skills needed to make their eyes work together to achieve the best possible vision.

Dr. Kathryn Colby has played a key role in optimizing methods for implanting the miniature telescope in AMD patients, and described the surgical procedure in the August 2007 issue of *Archives of Ophthalmology*. Dr. Colby was also an investigator in a multicenter clinical trial that showed the IMT significantly improved vision in most patients who received the implant. She describes the pea-sized technology as a true "breakthrough" for millions of patients with end-stage AMD, whose treatment options, until now, have been limited. But she also cautions that the telescope, approved by the FDA in July 2010, will not work for everyone, and is geared specifically for patients 75 years and older with blind spots (bilateral central scotomas) associated with end stage AMD. For many of these patients, however, the device is life-changing. "Over 90 percent of patients in the clinical trial improved two lines in vision as measured in the doctor's office, but what really matters is how this technology impacts quality of life," Dr. Colby said. "Can you write out a check? Watch TV? See your grandson's face? That's significant improvement."

Restoring peripheral visual function with prisms

Peripheral vision loss makes it extremely difficult for patients to navigate safely around objects and other people. This occurs in retinitis pigmentosa, which causes gradual loss of eyesight starting from the outside edges of the visual field. Another condition that affects peripheral vision is homonymous hemianopia, which causes loss of half of the visual field on one side in both eyes—not due to a problem with the eyes themselves, but rather due to brain injury. Stroke, trauma, brain tumors, and surgery are common causes of this condition, which affects over one million people in the United States. Hemianopia can severely impact activities of daily living, such as driving or even walking.

Dr. Eli Peli, Co-Director of Research at Schepens Eye Research Institute and Professor of Ophthalmology at HMS, has devised a solution using prism lenses. Mounted on eyeglasses, the prisms redirect images from a blind side and project them onto functional parts of the visual field. This causes objects from the blind side to appear as "ghost images" in the remaining visual field. People wearing these special prism glasses can then be aware of objects in their blind side, and make adjustments to either examine them further or move to avoid collision. So far, the prism lenses have been tested in two multi-center clinical trials directed by Dr. Peli, who is also an optometrist and Director of the Vision Rehabilitation Service at the New England Eye Center. In the first trial, published in the May 2008 issue of Archives of Ophthalmology, 43 patients with hemianopia reported that the prism glasses were "very helpful" in navigating around obstacles. These results were confirmed in a later randomized control study of 61 patients, presented at ARVO 2010. At around $600 for glasses with permanently mounted prisms—and even less for temporary stick-on prisms—these lenses represent an affordable breakthrough for people with hemianopia and other conditions that cause peripheral vision loss.

Eliezer (Eli) Peli, MSc, OD

Professor of Ophthalmology, Harvard Medical School

Senior Scientist, Co-Director of Research, and Moakley Scholar in Aging Eye Research, Schepens Eye Research Institute

Director Vision Rehabilitation Service, New England Eye Center

Dr. Eli Peli, trained as an engineer and optometrist, is a worldwide authority in low vision. Born in Tel-Aviv, Israel, Dr. Peli earned his BSc and MSc degrees in electrical engineering from the Technion-Israel Institute of Technology. Since 1983, when he received his DO degree from the New England College of Optometry, Dr. Peli has specialized in vision rehabilitation care. He has developed innovative clinical techniques and a variety of low vision aids, and continues to provide specialized patient care as Director of the Vision Rehabilitation Service at New England Medical Center Hospital in Boston. At Schepens, where he is Senior Scientist and Moakley Scholar in Aging Eye Research, Dr. Peli leads the Vision Rehabilitation Laboratory and the Mobility Enhancement Center; additionally, he serves as Co-Director of Research.

Drawing upon his multidisciplinary expertise, Dr. Peli consults for the National Institutes of Health, NASA Aviation Operations Systems, National Highway Safety Administration, Federal Motor Carrier Safety Administration, Natural Sciences and Engineering Research Council of Canada, and numerous high-tech and ophthalmic corporations. He holds various editorial board positions and co-founded TaperVision Inc., a manufacturer of fiber-optics-based magnifiers for the visually impaired, and Visya, Inc., a manufacturer of adjustable spectacle lenses for presbyopia. He serves as Professor of Ophthalmology at HMS and Adjunct Professor at both New England College of Optometry and Tufts University School of Medicine.

Dr. Peli's work reflects his multifaceted background in engineering, optometry, and vision research. With over 150 scientific publications, two books, and nine patents, he has made significant contributions to the areas of eye movement analysis, image processing, image communications, and optics. In the last decade, Dr. Peli's work has concentrated on issues of mobility with impaired vision, including pedestrian mobility and driving. The Peli Lens, which Dr. Peli developed for a form of vision loss known as hemianopia ("half blindness"), represents a clinical breakthrough for individuals with peripheral vision loss.

During his career as a clinician scientist, Dr. Peli has received several notable and prestigious awards. These include the Pisart Vision Award from Lighthouse International, a worldwide organization dedicated to vision research, rehabilitation, and advocacy. Dr. Peli was co-recipient of the 2004 Alfred W. Bressler Prize in Vision Science (along with Robert Massof, PhD, of Johns Hopkins University) and received the 2009 Alcon Research Institute award. In 2009, Dr. Peli was also honored by the American Academy of Optometry with the William Feinbloom Award, which is given annually to individuals who have made distinguished and significant contributions to the advancement of visual and optometric service. More recently, he was awarded the 2010 Otto Schade Prize from the Society for Information Display and the 2010 Edwin H Land Medal by the Optical Society of America.

PROSE treatment: for some people, simply a miracle

Astonishing. Miraculous. Life altering. This is how some patients have described the powerful and life-transforming impact of a small, plastic prosthetic device. More than two million people in the United States suffer from complex corneal disease, making their lives a painful, daily struggle. Dr. Perry Rosenthal, HMS Assistant Clinical Professor of Ophthalmology, is a pioneer and innovator in the field of contact lens and the treatment of eye disease. As Founding President and Vice Chairman of Boston Foundation for Sight, Dr. Rosenthal has spent the last two decades developing and refining this life-changing treatment, which has restored sight to thousands of people blinded or impaired by corneal disease, helping them to reclaim their lives.

The concept behind this treatment is simple but groundbreaking: prosthetic replacement of the ocular surface ecosystem (PROSE) uses a piece of gas-permeable plastic, about the size of a nickel, to replace or support the functions of the ocular surface system. Unlike contact lenses, which touch the cornea, PROSE devices are designed to "vault" over the cornea and rest on the sclera, the sturdy white of the eye.

PERRY ROSENTHAL, MD

The device is filled with sterile saline at the time of insertion. Once inserted, the device protects the cornea and conjunctiva from the environment and blink trauma, while creating a reservoir of fluid that continuously bathes the ocular surface with oxygenated artificial tears. A PROSE device creates a transparent, smooth optical surface over a damaged or irregular cornea, masking imperfections, and improving vision by transmitting a sharp image to the back of the eye.

PROSE devices are made using a proprietary CAD/CAM software system linked to a manufacturing lathe via the internet. The system uses mathematical functions, called splines, which allow physicians at Boston Foundation for Sight and its partner clinics to design and fit prosthetic devices to each eye to exacting specifications that maximize ocular surface system function. For patients with complex corneal disease—many of whom have suffered from blinding and painful ocular conditions for years—the devices are immediately transforming, capable of restoring vision and mitigating symptoms, including pain and light sensitivity.

Although this technology was initially developed for patients with irregular astigmatism from keratoconus, trauma, or cornea transplantation, the benefits became apparent for patients with ocular surface disease, including Stevens-Johnson syndrome, chronic ocular graft-versus-host disease (GVHD), Sjogren's syndrome, and neurotrophic keratitis. Continuous technological and clinical innovations have yielded a treatment approach

Boston Foundation for Sight: restoring sight, reclaiming lives

Today, PROSE treatments for the majority of patients are covered by health insurance, although this was not always the case. Based on the principle that "sight should not be a gift—it should be a birthright," Dr. Rosenthal founded Boston Foundation for Sight (BFS) in 1994 as a nonprofit eye health care organization. The organization is dedicated to restoring vision and improving the quality of life for patients and their families, regardless of their ability to pay. Since its inception, the Foundation has provided free care to approximately 20 percent of its patients.

Under Dr. Rosenthal's stewardship, BFS has evolved into a renowned and innovative corneal research, education, and treatment facility. PROSE has become an invaluable, front-line tool for helping patients manage the debilitating effects of complex corneal disease—combining patient-centered medical care, advanced clinical research, professional education, and community outreach. To broaden its availability, the Foundation recently established PROSE clinics in partnership with top-ranked academic medical centers in the United States and abroad, including the University of Southern California's Doheny Eye Institute in Los Angeles, and Weill Cornell Eye Associates at Weill Cornell Medical College in New York. Dr. Deborah Jacobs, Assistant Clinical Professor of Ophthalmology and Director of the Core Medicine Clerkship at Mass. Eye and Ear, joined Boston Foundation for Sight in 2006 as Medical Director. "Boston Foundation for Sight plays a unique role in the rehabilitation of patients with complex corneal disease," she says. "My goal as Medical Director is to increase awareness, appreciation, and availability of our treatment and approach to patient care, which together produce life-changing results."

Twice monthly at Mass. Eye and Ear, Dr. Jacobs sees patients referred by other physicians for consideration of PROSE treatment. If needed, candidates for treatment are referred to BFS headquarters in Needham, MA. Additionally, Mass. Eye and Ear cornea fellows come to Boston Foundation for Sight for a rotation under Dr. Jacobs' supervision, where they learn about all facets of the BFS treatment model and collaborative, patient-centered approach to care. The fellows also participate in clinical research projects that have led to presentation at scientific meetings and publication.

with demonstrated clinical benefits and cost-effectiveness, as highlighted recently in publication in the *American Journal of Ophthalmology*. A recent study published in *Seminars in Ophthalmology* details the case reports of five patients who have a history of significant corneal disease and glaucoma surgery who benefited from this innovative approach to visual rehabilitation.

Improving peripheral vision in AMD patients

For some, even the best available medicines for AMD can only delay the gradual loss of vision; for others, the treatments may not help at all. As a result, some people with AMD may be left with only peripheral vision—which makes it extremely difficult to read or to see complex images. Dr. Peter Bex, an Associate Scientist at Schepens Eye Research Institute, uses computational models to understand how the brain processes peripheral vision, and uses this information to explain why it is so difficult to see details in the peripheral field. Dr. Bex is studying a phenomenon known as crowding, an effect that makes magnified peripheral images very difficult to distinguish. Because people with AMD often use magnifying lenses to read, these studies may lead to new rehabilitation techniques to improve peripheral vision. Dr. Bex and colleagues also showed that when people try to read with their peripheral vision, the size or shape of the letters may not be as important as how stable the images are. These results suggest that vision therapy with fixation training may help people to stabilize images in their peripheral fields to best utilize their remaining vision.

Emerging retinal prosthesis technology aims to restore sight to the blind

A state-of-the-art retinal prosthesis, designed to help some people blinded by retinal disease to regain a portion of their vision, may soon be within reach. In many retinal disorders, such as retinitis pigmentosa and age-related macular degeneration (AMD), the image-sensing photoreceptors (rods and cones) eventually die—resulting in vision loss. However, even in patients who become legally blind, cells in the optic nerve—which connects the retina to the brain—may still be alive and functional.

Hoping to take advantage of the surviving nerve cells, Dr. Joseph Rizzo III and scientists of the Boston Retinal Implant Project are developing an implantable microelectronic prosthesis that will deliver visual information to the brain through the remaining retinal circuits. This highly sophisticated "bionic eye" will consist of internal electronic components that will be implanted around and behind the eyeball. Users wear a small camera, mounted to eyeglasses, that captures visual scenes and converts them into electrical impulses. The impulses are transmitted wirelessly to the prosthesis which stimulates the healthy nerve cells. The nerve cells, in turn, carry the visual impulses to the brain for image processing—helping patients with macular degeneration or retinitis pigmentosa regain some vision. Special innovations to the prosthesis include an ultra-low power design and a geometric architecture that minimizes that amount of hardware that is placed into the eye. The team has also developed a minimally invasive surgical method of implantation.

The retinal implant may not work for all blind patients—particularly those with significant optic nerve damage, or those who were born blind because the visual centers in the brain have not developed. Furthermore, it's still too early to tell exactly how much vision can be restored by the retinal prosthesis. Nonetheless, many blind patients maintain that even the smallest improvements to their eyesight can dramatically improve their quality of life. This technology represents a major milestone toward restoring some vision in many patients blinded by retinal disease.

Dr. Rizzo, Director of the Center for Innovative Visual Rehabilitation at the Boston Veterans Administration and Director of the Neuro-Ophthalmology Service at Mass. Eye and Ear, founded the Boston Retinal Implant Project in the late 1980s. This collaborative effort of Mass. Eye and Ear Infirmary, Massachusetts Institute of Technology, U.S. Department of Veterans Affairs, Schepens Eye Research Institute, Boston University Medical Center, and the University of Alabama brings together experts with diverse backgrounds. This multi-disciplinary team hopes to treat many forms of blindness by overcoming both the biological and engineering challenges of creating an advanced retinal prosthesis. Drs. Rizzo and John Loewenstein performed the first surgery to insert microelectronic components onto the retina of a human eye in 1998, and have since performed successful short-term electrical stimulation studies in humans. Soon, Dr. Rizzo's team will perform longer-term studies with the retinal implants, which could last longer than 10 years in the eye.

Joseph Rizzo III, MD

Professor of Ophthalmology, Harvard Medical School

Director, Neuro-Ophthalmology Service, Massachusetts Eye and Ear Infirmary

Director, Center of Innovative Visual Rehabilitation, Department of Veterans Affairs, Boston, MA

Founder and Co-Director, Boston Retinal Implant Project

Dr. Joseph Rizzo III is a clinician scientist dedicated to understanding the mechanisms of vision loss, and his decades-long mission has focused on improving the diagnostic and treatment methods for blinding diseases. A native of New Orleans, Dr. Rizzo received his undergraduate and medical training at Louisiana State University. Following an internship in adult medicine at UCLA Medical Center, Dr. Rizzo completed both a neurology residency at Tufts University/New England Medical Center and an ophthalmology residency at Boston University. He completed a clinical fellowship in neuro-ophthalmology at Mass. Eye and Ear before joining the faculty of the HMS Department of Ophthalmology.

As a clinician, Dr. Rizzo specializes in visual disorders that result from damage to the eye or brain. He is Director of the Neuro-Ophthalmology Service at Mass. Eye and Ear, which houses three of only a handful of dually trained neuro-ophthalmologists worldwide. Dr. Rizzo evaluates roughly 40 percent of all patients referred to the service, and collaborates closely with neurologists at MGH to deliver high-quality care for patients with visual disorders. As Professor of Ophthalmology at HMS, Dr. Rizzo is directly responsible for training clinical fellows, residents, and medical students in neuro-ophthalmology. He regularly delivers lectures on diverse ophthalmic issues, and directs the neuro-ophthalmology section of the Lancaster Course, which is the oldest and largest training course for ophthalmologists.

Dr. Rizzo devotes a major portion of his professional focus to developing new therapeutic options for vision disorders. He is Director of the Center of Innovative Visual Rehabilitation at Boston Veteran's Administration Hospital and Co-Director of the Boston Retinal Implant Project (BRIP), an initiative he founded in 1988 to develop a retinal prosthesis for patients with acquired blindness. This multidisciplinary and international research collaboration now includes scientists and clinicians from over 20 institutions worldwide. For his significant contributions to visual science, Dr. Rizzo was presented with the Senior Achievement Award by the American Academy of Ophthalmology in 2007.

"Developing a retinal prosthesis is an enormous challenge, but if you never dive in you'll never have an option for treatment."
-Joseph Rizzo III, MD, Co-Founder of the Boston Retinal Implant Project (BRIP)

It takes vision...
to get vision, which is remarkably complex. Developing a retinal prosthesis requires sophisticated engineering technology aimed at stimulating electrodes on the retina while protecting the delicate prosthesis. Equally tasking is the physical challenge of implanting the device in and around the eye without harming the retina. The advent of micro-fabrication technology 15 years ago has enabled Dr. Rizzo and his team to embed wires and electrodes onto an ultra thin plastic "membrane" many times thinner than a human hair. This membrane is the only component of the prosthesis that comes in contact with the delicate retina.

It takes a deep fund of knowledge...
and an understanding of how the brain interprets data coming from the retina to develop a functional and useful prosthesis. The BRIP is now focusing considerable effort to unravel some of these mysteries. "Despite the challenges," said Dr. Rizzo, "we've made considerable progress on many fronts and I believe solutions are within reach."

It takes a village...
of collaborators with multidisciplinary talents to move a research project of this magnitude forward, and the BRIP enlists experts from a diverse array of fields. Today, the 36-member team is comprised of retinal surgeons, physiologists, biologists, rehabilitation specialists, material engineers, chip designers, wireless communication specialists, and metallurgists.

It takes resources...
Now in its third decade of development, the bionic prosthesis has required continuing and substantial resources. Initially funded by private industry and some federal monies, the project received a financial boost in 2001 with a grant from the U.S. Department of Veterans Affairs.

To find out more visit:
www. bostonretinalimplant.org

RESEARCH &

"Imagination is truly the key to any discovery, and science to cure blindness is no exception.It is the constant reexamination of the facts along with creative leaps of thought that give birth to innovation in every field."

— Michael Young, PhD, Associate Scientist, Schepens Eye Research Institute

DISCOVERY

This Research & Discovery section highlights some of the many scientific contributions made in recent years by the dedicated scientists in the HMS Department of Ophthalmology, whose investigations have resulted in major advancements in medical science and ophthalmic practice. Discoveries made in various fields—including genetics, immunology and ocular biology—have reshaped the foundations of ophthalmology and formed many new paradigms for the repair, regeneration, and rehabilitation of countless disorders.

Today, using a uniquely synergistic approach that combines both laboratory research and applied medicine, this pioneering team continues to advance clinical care for the eye. Fields under intensive study span several areas: physiology, ocular inflammation and immunology, neoangiogenesis optic neuropathies; ocular prostheses; new approaches to drug delivery; laser surgery, and; ocular therapeutics and surgery. Investigations have also expanded to include the specialty fields of genomics, proteomics, gene-gene and gene-environment interactions, gene therapies, and stem cell therapy.

HMS investigators also conduct preclinical investigations using a variety of disease models, and carry out small-scale clinical trials to establish a foundation for "first proof in man." In recent years, this work has led to revolutionary treatments for macular degeneration, including the development of photodynamic therapy as well as a number of anti-angiogenesis agents. Current work focuses on the development of novel pharmaceutical, biological, and gene-therapy approaches for the treatment of blinding diseases.

With ample collaborative dialogue between talented researchers and clinicians, scientific advances are being rapidly transformed into cutting-edge clinical practice.

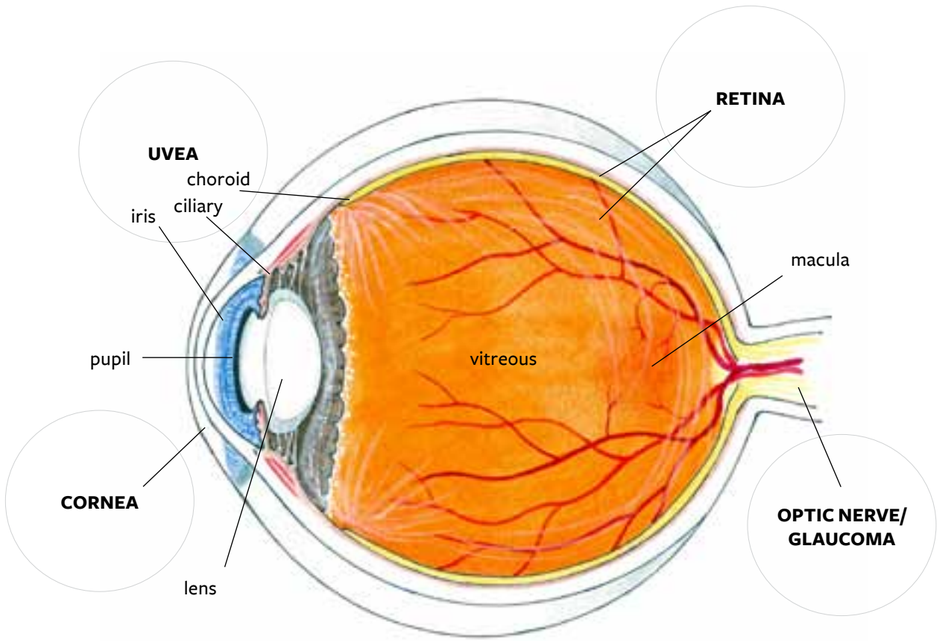
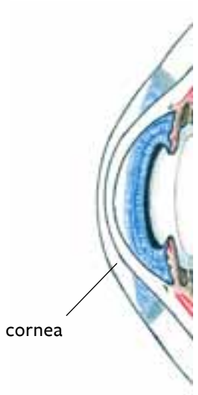


Illustration by Laurel Cook Lhowe

CORNEA

As the eye's most powerful focusing structure, the cornea is essential for acute vision. Injuries, infections, and genetic disorders can rob vision by disrupting normal corneal function. The HMS Department of Ophthalmology houses the world's largest and most esteemed group of scientists and physicians —nearly 80 MDs and PhDs in all—committed not only to understanding corneal biology, but also to treating or preventing corneal disease. With a potent arsenal of tools, technologies, and knowledge, the department is continually applying laboratory discoveries to clinical practice. With increasing success, we're treating or averting the potentially devastating effects of corneal disease, infections and injury.



CORNEAL INFECTIONS

The cornea protects the rest of the eye from injuries and microbial pathogens, such as bacteria, fungi, or viruses; however, because it is constantly exposed, the cornea itself is susceptible to infections that may cause keratitis, or corneal inflammation. Besides causing irritation, pain, and blurry vision, keratitis can damage or scar the cornea, and may lead to permanent vision loss. Several scientists in the HMS Department of Ophthalmology are conducting research and improving treatments for this potentially blinding condition.

Inflammatory responses in epidemic eye infections

Keratoconjunctivitis (commonly known as "pink eye") refers to inflammation of the mucous membranes covering the surface of the eye, including the cornea and conjunctiva. There are many causes of keratoconjunctivitis, including allergens, microbes, and chemicals; however, adenoviral keratoconjunctivitis is particularly contagious, and spreads so rapidly that it commonly causes epidemic keratoconjunctivitis (EKC). Although EKC infections generally resolve on their own, the inflammatory immune responses in the cornea may lead to corneal clouding that may linger for several weeks, months, or even years in severe cases.

James Chodosh, MD, MPH and his team generated the first mouse model of adenoviral keratitis, as well as the first whole genome sequences of EKC-causing adenoviruses. Bioinformatic analyses performed by his group provided evidence for new emergent adenoviral serotypes in EKC. His laboratory also studies how cells called keratocytes in the cornea respond to adenoviral infections, and how signals produced by these cells lead to inflammation. Because the inflammatory response is a well-conserved host defense mechanism against injury or infection, these studies are relevant to various insults to the eye beyond EKC, and may lead to novel, rationally designed therapies for numerous causes of corneal inflammation.

Treating herpes keratopathy with the Boston KPro

Varicella zoster, the virus that causes the common childhood disease known chickenpox, remains dormant in the nerves of most infected individuals. However, the virus may later reactivate and cause a painful skin rash known as herpes zoster or shingles. If the rash affects any part of the eye, it is known as herpes zoster ophthalmicus (HZO). About 10-20 percent of shingles patients develop HZO, which can cause severe corneal damage (keratopathy) and blindness. With approximately 200,000 new cases each year in the United States—and the overall number of herpes zoster cases expected to increase—HZO poses a serious public health concern.

Deborah Langston, MD, FACS, an expert in viral eye disease, recently described a patient who developed corneal ulceration and secondary bacterial and fungal infections due to HZO. Because a standard corneal transplant would have likely failed in this case, the patient received a Boston Keratoprosthesis (KPro), developed by Claes Dohlman, MD, PhD, to successfully replace the severely damaged cornea. Inflammation subsided within a week of surgery, and vision gradually improved over the next four months. This report, published in the February 2008 issue of the journal *Ophthalmology* with Dr. Dohlman as co-author, demonstrates that Boston KPro may restore vision to a great number of patients with otherwise inoperable corneal damage.

The changing landscape of atypical keratitis

Fungi and Acanthamoeba (a genus of protozoa) are relatively uncommon causes of corneal infections, yet both are difficult to treat and can be visually devastating when they occur. Kathryn Colby, MD, PhD, in collaboration with other colleagues within HMS and nationwide, has examined the changing landscape of these atypical pathogens, both at Mass. Eye and Ear, and throughout the United States. These studies demonstrated an increase in both fungal (Jurkunas, Behlau and Colby, June 2009 issue of the journal *Cornea*), and Acanthamoeba (Tanhehco and Colby, *Cornea*, September 2010) infections at Mass. Eye and Ear in recent years, paralleling nationwide trends. In addition, filamentous fungi were found to have replaced yeasts as the predominant pathogens in fungal keratitis at Mass. Eye and Ear. Soft contact lens wear was a major risk factor for developing either infection. By pinpointing the major pathogens and risk factors involved in atypical keratitis, this work may lead to improved prevention and treatment strategies for these potentially blinding infections.

CORNEAL CLARITY

The focusing power of the cornea relies on its clarity. Many conditions—from injuries to infections to dietary or genetic deficiencies—can cause the cornea to lose transparency, and thus its ability to properly refract light. Inflammatory responses to infections, injury, or even corrective surgery can also cause the cornea to become cloudy; moreover, inflammation can induce corneal neovascularization which can also impair vision. Understanding the factors that promote corneal clarity is a major area of study in the HMS Department of Ophthalmology, where scientists have defined many of the molecular and physiological mechanisms that maintain corneal transparency, as well as the pathological processes that cause corneal clouding.

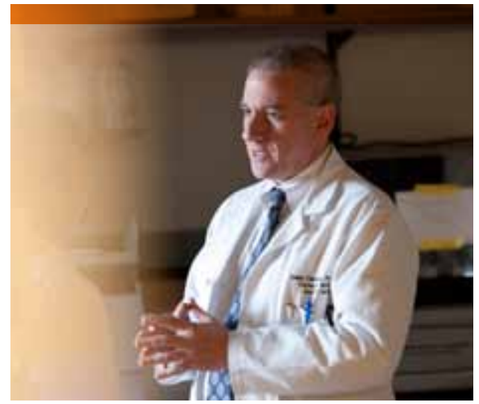
Laying the cornerstone of corneal clarity research

How the corneal matrix maintains its clarity is one of the fundamental questions in ophthalmology, and much of the current understanding of corneal clarity began with the early work of Claes Dohlman, MD, PhD. Using basic science approaches to analyze clinical samples, Dr. Dohlman helped to define the molecular and physiological mechanisms of corneal swelling and edema—major pathological processes that contribute to corneal clouding. These discoveries form the basis of many techniques currently used to restore corneal clarity and visual acuity in patients.

Investigating the mechanisms of corneal clarity

For decades, it was unclear how the cornea maintains its avascular state. To retain clarity, it must prevent the development of blood vessels. In the July 25, 2006 issue of *Proceedings of the National Academy of Sciences* (*PNAS*), a team of researchers led by Reza Dana, MD, MSc, MPH revealed a novel role for vascular endothelial growth factor receptor 3 (VEGFR3) in maintaining corneal avascularity. Prior to this study, scientists believed that only lymphatic vessels and proliferating blood vessels expressed VEGFR3; however, Dr. Dana and colleagues showed that VEGFR3 is also strongly expressed "ectopically" by normal epithelial cells in the cornea, where it acts as a "sink" for factors that induce blood vessel growth in response to inflammation. These findings presented an effective and novel mechanism for suppressing inflammation-induced CNV.

Dr. Dana is also examining the



James Chodosh, MD, MPH

Professor of Ophthalmology, Harvard Medical School

Fellowship Director, Cornea Service, Massachusetts Eye and Ear Infirmary

Dr. James Chodosh, HMS Professor of Ophthalmology and an investigator in the Howe Laboratory Viral Pathogenesis Unit, is internationally known and respected for his work on molecular virology, viral genomics, and viral epidemiology. His laboratory leads the field of ocular adenoviral pathogenesis and epidemic keratoconjunctivitis (EKC), and has contributed greatly to the prevention and treatment of vision loss due to infection, corneal inflammation, and scarring. Dr. Chodosh is also committed to promoting the use of the Boston Keratoprosthesis (KPro) worldwide, and has performed and assisted with artificial cornea implantation surgery in India, Italy, England, and Israel. Recently, he began a project to develop a $50 KPro for use in underprivileged nations. In collaboration with Claes Dohlman, MD, PhD, Dr. Chodosh is studying how to improve keratoprosthesis surgery outcomes by regulating immune responses.

Dr. Chodosh is a committed teacher and mentor, and is Fellowship Director for Mass. Eye and Ear's Cornea Service. He has authored over 110 articles and book chapters, and is a three-time recipient of awards from Research to Prevent Blindness. Having served as Chair for the Anterior Eye Disease NIH Study Section and the Department of Defense's Peer Reviewed Medical Research Program on Eye & Vision, Dr. Chodosh presently serves as a Member of the NIH National Advisory Eye Council.

Deborah P. Langston, MD, FACS

Professor of Ophthalmology, Harvard Medical School

Director of Virology Service, Massachusetts Eye and Ear Infirmary

Dr. Deborah Langston was the first woman to complete ophthalmology residency training at Harvard, and the first female fellow in Dr. Claes Dohlman's corneal fellowship program. She was also among the first to study the efficacy and toxicity profiles of antivirals in animal models, later translating these findings successfully to humans. Her expertise is sought quite prominently in national and international health policy for the treatment of ophthalmic disease, including issues of viral latency, diagnosis, public health and clinical treatment. Dr. Langston is now principally a clinician-educator, focusing on patient care, clinical research, committee work and teaching appointments. Former Chair of the FDA Ophthalmic Drug Advisory Committee, she now serves on the President's Commission on Bioterrorism Preparedness and Response Committee at the Center for Disease Control and Prevention. Dr. Langston's single-authored text, *The Manual of Ocular Diagnosis and Therapy*, comprises six editions and has been published in seven languages.

use of drugs that block blood vessel growth, such as bevacizumab (Avastin), for treating corneal neovascularization. Promising results were obtained in a recent prospective, open-label, noncomparative study using eye drops for the topical delivery of bevacizumab to treat CNV in 10 patients. This study was published in the April 2009 issue of *Archives of Ophthalmology*, with Dr. Dana as senior author. Co-authors included HMS faculty colleagues Pedram Hamrah, MD; Ula Jurkunas, MD; Roberto Pineda II, MD; and Deborah Langston, MD, FACS.

CORNEAL DYSTROPHIES

Corneal dystrophies form a diverse group of conditions that involve gradual deterioration of the cornea. Diseased corneas may become cloudy or abnormally curved, which results in impaired vision. Most corneal dystrophies are inherited; many have no symptoms for decades, and vision loss may vary widely from mild to severe. Researchers in the HMS Department of Ophthalmology are advancing therapeutic strategies for corneal dystrophies by understanding their genetic causes and developing improved treatment and surgical interventions.

Finding molecular clues in Fuchs Endothelial Corneal Dystrophy

In Fuchs' endothelial corneal dystrophy (FECD), the endothelial layer of the cornea deteriorates and eventually leads to corneal swelling and loss of vision. FECD accounts for over 10,000 corneal transplants (roughly one-third of all corneal transplantations) each year in the United States. Corneal transplantation is currently the only modality to treat FECD because the exact cause of endothelial cell degeneration is unknown. Even though FECD is an inherited condition, the genetic defects underlying this common and age-related condition have not been clearly identified.

HMS Assistant Professor Ula Jurkunas, MD, a full-time member of the Cornea Service at Mass. Eye and Ear, is spearheading efforts to understand the complex interaction between the environmental stressors and the genetic factors that, in turn, cause the development of FECD. Dr. Jurkunas is leading a laboratory effort at Schepens Eye Research Institute to evaluate the role of oxidative damage to endothelial cells as an underlying cause of FECD. They found that that reactive oxygen species are involved in the development and progression of FECD, and these novel findings were published November 2010 in the *American Journal of Pathology*. This discovery is significant because understanding the key regulators of oxidative stress-induced cellular damage may facilitate development of pharmacologic treatments for FECD patients.

Collagen cross-linking for keratoconus

The most common corneal dystrophy in the United States is keratoconus, which affects one in every 2,000 people. In keratoconus, corneal thinning causes the cornea to bulge and become uneven, which results in nearsightedness and astigmatism. Vision problems in mild or moderate keratoconus can usually be corrected with hard contact lenses, but patients with advanced keratoconus often need corneal transplantation surgery. Kathryn Colby, MD, PhD, is currently a principal investigator for a clinical trial evaluating the safety and efficacy of collagen cross-linking for preventing the progression of keratoconus. Roberto Pineda II, MD is a co-investigator for the study. This procedure aims to strengthen the cornea by applying riboflavin and ultraviolet light to the corneal surface, which introduces cross-links between the structural collagen strands. Cross-linking therapy is currently being used for the treatment of keratoconus in Europe, and the current studies at Mass. Eye and Ear are conducted in collaboration with the SUNY-Buffalo School of Medicine and the Verdier Eye Center in Grand Rapids, Michigan.

Stem cell therapy for corneal disease

In Fuchs' endothelial corneal dystrophy (FECD), the endothelial layer of the cornea deteriorates and eventually leads to corneal swelling and loss of vision. FECD accounts for over 10,000 corneal transplants (roughly one-third of all corneal transplantations) each year in the United States. Corneal transplantation is currently the only modality to treat FECD because the exact cause of endothelial cell degeneration is unknown. Even though FECD is an inherited condition, the genetic defects underlying this common and age-related condition have not been clearly identified.

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Dr. Jurkunas has received approval from PACT (Production Assistance for Cellular Therapies) for support in the manufacture of cultivated corneal and oral epithelial stem cells for corneal transplantation. Drs. Jurkunas and Dana are collaborating with researchers from Harvard's Immune Disease Institute and the Dana Farber Cancer Institute.

ULA V. JURKUNAS, MD

DRY EYE DISEASE

The triple-layered tear film, which covers the ocular surface, is a critical component of the eye and visual system; any component of the tear film may be disrupted in dry eye disease. Although it rarely leads to severe vision loss or blindness, dry eye disease can lead to extreme discomfort and significant disability. Tens of millions of people have persistent or severe dry eye disease in the United States—making it a major public health concern. In the HMS Department of Ophthalmology, the efforts of several researchers have contributed to the development of new therapies for this widespread and potentially debilitating condition.

Inflammation, immunity, and dry eye disease

For the past decade, the pathology of dry eye disease has been known to involve inflammation and immunity; however, until recently, these disease mechanisms have been

(*continues on page 80*)

Kathryn A. Colby, MD, PhD

Assistant Professor of Ophthalmology, Harvard Medical School

Dr. Kathryn Colby is HMS Assistant Professor of Ophthalmology and a corneal specialist at Mass. Eye and Ear and Children's Hospital, Boston. Dr. Colby's research and clinical interests involve advancing new surgical techniques for various corneal diseases. Dr. Colby was one of the first surgeons in Boston to perform selective endothelial transplantation, which replaces only the diseased endothelial cells of the cornea in conditions such as Fuchs' corneal dystrophy; she has been performing different forms of this surgery since 2002. She was the first surgeon in the area to implant the Boston Keratoprosthesis (KPro) in children, and she is currently examining novel therapies for keratoconus. Dr. Colby has been pivotal in optimizing the surgical technique for the implantable miniature telescope for restoring vision in patients with end-stage age-related macular degeneration (AMD). She has the largest ocular surface tumor practice in the New England region, and is currently evaluating the biology of conjunctival melanoma, one of the few ophthalmic conditions capable of causing death.

SPOTLIGHT:

Bridging the Gap Between Research and Clinical Application

AN INTERVIEW WITH

Reza Dana, MD, MPH, MSc

Dr. Reza Dana studies how the immune, lymphatic, and vascular systems interact during ocular inflammatory responses, and how inflammation contributes to transplant rejection, corneal neovascularization (CNV), and other pathological processes in the eye. At HMS, Dr. Dana is Professor of Ophthalmology and holds the Claes H. Dohlman Chair in Ophthalmology. He also serves as Associate Chief of Ophthalmology and Vice Chair for Academic Programs, Senior Scientist and Co-Director of Research at Schepens Eye Research Institute, Principal Investigator for the Harvard Vision Clinical Scientist Development program (K12), and Director of the Cornea and Refractive Surgery Service at Mass. Eye and Ear. With numerous ongoing projects in his laboratory and multiple collaborations with other researchers, Dr. Dana has made substantial contributions to the bodies of knowledge in both basic science and clinical research.

You are Principal Investigator of the Department's Harvard Vision Clinical Scientist Development Program, a federally funded K12 program. Explain what the K12 program is, and how it's contributing to Harvard's translational research in ophthalmology.

RD: We've made a huge effort to recruit clinician scientists to the HMS Department of Ophthalmology K12 program, which is a mentored learning and career-development program funded by the National Eye Institute (NEI) of the National Institutes of Health. It awards 4-year career development grants that provide exceptional junior faculty with financial support, mentorship and 75 percent protected research time to pursue and build independent research careers. The program has numerous benefits: it bridges the translational gap between research and clinical activities, helps us attract and retain the best and brightest talent, and enriches our clinical, teaching and research programs. For trainees, it provides an unparalleled learning and research experience not typically nurtured in an academic research institution. Straight from training, the program helps jumpstart their careers as independent, leading clinician scientists in an amazingly supportive environment.

Our K12 "alumni" have included Pedram Hamrah, Ula Jurkunas and Joseph Ciolino in cornea research, and Lucia Sobrin in retina and uveitis. Our first K12 recipient, Jennifer Sun, is conducting diabetic eye research with Lloyd P. Aiello at the Beetham Eye Institute at Joslin. This program has allowed enormous growth in our translational science program. I'm pleased to say that NEI has approved the Harvard Department of Ophthalmology's five-year grant renewal.

What is "translational research" and how is it carried out among the Harvard Department of Ophthalmology's cornea specialists?

RD: Translational research helps move a basic scientific discovery or idea from the lab to the clinic so patients benefit directly. There's a clinical side and a preclinical side, and both avenues of investigation are carried out by our HMS Ophthalmology affiliates; much of this work is complemented by the extensive preclinical laboratory work at Schepens. Combined, our prodigious team of nearly 80 HMS principal investigators and research fellows represent the world's largest group of scientists dedicated to corneal research, and they are working beyond "collaboration" in the usual sense. We've also maintained longstanding and fruitful collaborations with many of our HMS faculty who maintain private practices in the community—including Dr. Marc Abelson at Ora, Inc., and Drs. Perry Rosenthal and Deborah Jacobs at the Boston Foundation for Sight. Their work has contributed significantly to corneal translational research.

What are some of the latest developments in Cornea's infrastructure at Mass. Eye and Ear Infirmary?

RD: In the last four years, we've doubled the cornea faculty at Mass. Eye and Ear, all of whom are clinician scientists with active research programs. We've developed a corneal research infrastructure with five full-time coordinating managers and research technicians. We've also established a Cornea and Ocular Surface Imaging Center that utilizes an incredible collection of hardware and software geared toward corneal imaging, making it the leading front-of-the-eye imaging center anywhere. We're using these new technologies in cutting-edge clinical care, as well as in clinical and translational research. At the moment, corneal research at Mass. Eye and Ear involves more than 20 investigator-sponsored translational and clinical studies—a growth of more than 400 percent compared to just a handful of years ago.

What are some examples of your most novel translational Cornea research programs and initiatives?

RD: There are several active programs to highlight, including regenerative and stem cell medicine, corneal angiogenesis, corneal inflammation and dry eye, corneal transplantation, corneal imaging, drug delivery and corneal infections, and a large keratoprosthesis program.

For example, we're among the few programs that have applied for several investigational new drug applications (INDs) to the FDA to develop novel therapeutic agents. Corneal angiogenesis and inflammation are major causes of blindness worldwide, so we're looking at new ways of suppressing growth of blood vessels in cornea using topical therapies. We have active and ongoing trials related to this, and some of our findings are now published.

"We study the fundamental biological processes in the lab and define potential therapeutic targets, bringing these findings to the clinic for testing and proof of concept—it's very much a circle."
—Dr. Reza Dana

We've also made great advances in the field of imaging as well. Eight or nine years ago, using preclinical models, we identified a new class of immune cells that are present in the cornea. Now we've taken our research to the clinic. We're currently using precise high-powered confocal imaging instruments to look at the corneas of live patients. This gives us a better sense of the degree of neuropathy and immune cell activation in the cornea. The experience we gained in our earlier lab work has proven invaluable to our understanding of the clinically relevant metrics of imaging.

Another interesting development is in the field of drug delivery. Along with colleagues at MIT, we've developed an innovative design for contact lenses that elute or release drugs, representing a novel venue for sustained drug delivery. This addresses a big problem in ophthalmology, since many people can't use eye drops. Right now, we're looking at preclinical models, and the next stage will be to apply it to clinical practice.

As Director of the Cornea and Refractive Surgery Service at Mass. Eye and Ear, and Co-Director of Research at Schepens, what are your goals for the translational research program?

RD: I've tried to develop a seamless process between the two institutions—lab to clinic and clinic to lab—to understand at a cellular and molecular level what is happening to patients. We study the fundamental biological processes in the lab and define potential therapeutic targets, bringing these findings to the clinic for testing and proof of concept. In many cases, we also procure information from the clinic (for example, cells in fluid such as tears) and analyze these in the lab, so it's very much a circle. We've made significant inroads to bridge the gap between research and clinical application.

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poorly defined. In the past few years, studies led by HMS Professor Reza Dana, MD, MPH, MSc showed that autoimmune processes in dry eye result from dysregulation of certain immune cells, including regulatory T cells (Tregs) and pathogenic effector T cells. Dr. Dana and colleagues recently identified a previously unknown pathogenic T cell subset, Th17, which is associated specifically with Treg dysfunction in dry eye disease. Th17 thus represents a new therapeutic target for dry eye disease. Recent studies led by Dr. Dana have further elucidated the mechanisms underlying corneal inflammation in dry eye disease, and have identified novel therapies and dosing regimens, such as high-frequency topical cyclosporine, a blockade of specific pro-inflammatory cytokines, for this extremely prevalent condition.

Sex, steroids, and dry eye disease

David Sullivan, PhD is one of the leading ocular surface scientists in the world. Dr. Sullivan discovered that gender and sex steroid hormones are critical factors in the regulation of ocular surface tissues, as well as in the pathogenesis of dry eye disease. This disorder, which occurs predominantly in women, afflicts an estimated 30 million people in the United States alone. Dr. Sullivan has also discovered that androgens may suppress aqueous-deficient and/or evaporative dry eye, whereas that estrogens may promote the conditions. These discoveries were termed in a Castroviejo Lecture as "the most exciting development in recent years" in dry eye research. Most recently, Dr. Sullivan and colleagues have discovered boundary lubrication at the ocular surface, which may be a critical factor protecting the cornea against damaging shear forces in dry eye. Dr. Sullivan's unique and novel research findings have led to the development of various topical therapies, which may potentially treat both aqueous-deficient and evaporative dry eye disease.


DAVID A. SULLIVAN, PHD

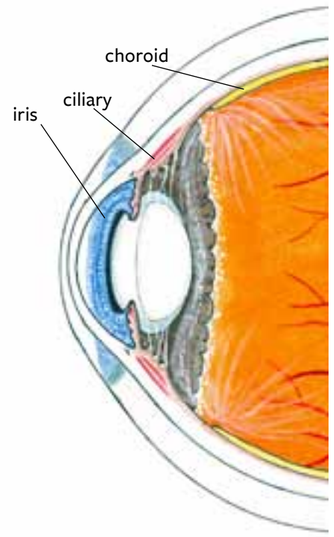

ILENE K. GIPSON, PHD

The multiple roles of mucin molecules

The ocular surface contains two types of mucins, which help protect and lubricate the cornea by holding the tear film in place. These hydrophilic molecules are either secreted into the tear film by the conjunctival goblet cells, or emanate from the membranes of the cornea and conjunctival epithelium, forming a lawn-like protective barrier on the corneal/ocular surface. In 2004, Ilene Gipson, PhD, demonstrated that membrane-tethered mucins are disrupted in both Sjögren's (autoimmune) and non-Sjögren's forms of dry eye disease. Using ocular-surface epithelial cell-culture systems that she developed, Dr. Gipson is currently identifying additional factors that regulate mucin expression, and is elucidating their roles in ocular surface biology, infectious disease, and human reproduction. Recently, researchers in Dr. Gipson's laboratory showed that pro-inflammatory molecules, particularly interferon-gamma, can alter mucin expression at the gene and protein levels, thus providing a link between inflammation and mucin behavior in dry eye syndrome. These findings were reported March 2010 in the journal *Experimental Eye Research*.

Mucins not only help keep the cornea moist, but may also form a protective barrier against bacterial infections at the ocular surface. In collaboration with Michael Gilmore, PhD, Dr. Gipson showed that MUC16 prevents the bacterium *Staphylococcus aureus* from binding corneal cells. MUC16 suppression resulted in loss of barrier function, thus allowing bacteria to bind more efficiently. These findings were reported October 2007 in the journal *Investigative Ophthalmology and Visual Science*. In a subsequent study published in the November 2008 issue of *Infection and Immunity*, Schepens Assistant Scientist Pablo Argüeso, PhD, in collaboration with Dr. Gilmore, showed that the barrier function of MUC16 was dependent on chains of carbohydrate molecules called O-glycans. These findings suggest that new strategies for preventing bacterial infections could center on improving mucin function.

UVEA



The uvea refers to the structures (iris, ciliary body and choroid) that form the middle, pigmented layer of the eye. Because uveal tissues contain many blood vessels, they are susceptible to inflammation and other immune responses from a variety of eye disorders. Inflammation of the uvea, or uveitis, can be caused by many conditions, including injuries, infections, autoimmune disorders, and systemic inflammatory diseases. If left untreated, uveitis can lead to other conditions—such as glaucoma, macular edema, and cataract—that may result in profound vision loss.

The HMS Department of Ophthalmology offers a unique combination of scientific and clinical expertise in ocular inflammatory disorders like uveitis. Multiple clinics within Mass. Eye and Ear and Massachusetts General Hospital (MGH) form the Ocular Immunology and Uveitis Service, which is one of the busiest uveitis services in the country. Outfitted with state-of-the-art diagnostic and examination equipment, the Ocular Immunology and Uveitis Service is establishing a patient information database that will allow case series, epidemiologic studies, genetic analyses, and assessments of treatment efficacy and clinical outcomes for uveitis. These combined efforts have optimized existing treatments for uveitis, and have yielded potential novel therapeutic strategies for protecting eyesight in ocular inflammatory disorders.

Expanding treatment options for ocular inflammation

Uveitis is usually treated with corticosteroids, which themselves can have serious side effects (including cataract and glaucoma). Immune-suppressing drugs, such as cyclosporine and mycophenolate mofetil, may also be used to treat some forms of uveitis; however, vision loss can still occur despite treatment with standard immunosuppressants. Thus, Dr. Sobrin and other clinician-scientists in the HMS Department of Ophthalmology are working to expand the therapeutic options for uveitis. Daclizumab and infliximab, which are immune-modulating drugs that specifically target inflammatory cytokines, have been used to effectively treat some forms of uveitis that were resistant to traditional immunosuppressant therapies. Bevacizumab (Avastin®), a prominent anti-angiogenic drug, has shown success in treating cystoid macular edema (CME) caused by posterior uveitis. Intravitreal injections of clindamycin represent a novel use of this antibiotic for treating uveitis caused by toxoplasmosis infections. Case studies conducted by Dr. Sobrin and colleagues serve as evidence-based decision support tools for uveitis, particularly in cases that are resistant to standard therapies.

A novel non-invasive treatment for anterior uveitis

Anterior uveitis, which affects the front of the eye, can cause swelling of the iris (iritis), and the painful condition known as "redeye." Like other forms of uveitis, anterior uveitis is usually treated with corticosteroids via eye drops, local injections, or systemic delivery. A potential non-invasive treatment option is the ActiPatch® device, which is based on pulsed electromagnetic field (PEMF) technology.

By emitting a low-frequency electromagnetic field, the ActiPatch® device is thought to restore the tight junctions between endothelial cells, which may in turn minimize inflammation within the eye. In an ongoing randomized, double blinded, placebo-controlled trial led by George Papaliodis, MD, patients with anterior uveitis will wear the ActiPatch® (or a placebo device) over the affected eye for eight hours per day. Inflammation, redness, and pain will then be assessed after a one-week course of treatment. This prospective trial is expected to be complete by December 2011, and may lead to larger clinical trials of PEMF therapy for uveitis. The PEMF device has great potential to reduce the dose or duration of corticosteroid treatment—thus representing a safer adjunct or alternative to standard drug therapy.

Keratoprosthesis and autoimmune disease

The Boston Keratoprosthesis (KPro) artificial cornea, developed by Claes Dohlman, MD, PhD at Mass. Eye and Ear, is highly successful in most patients—even those with failed corneal allografts. However, in patients with autoimmune disorders, current surgical treatments—including the Boston KPro—remain marred by complications and prosthetic failure. In this subset of patients, ocular inflammation and neovascularization are common concerns; the tissues adjacent to the prosthesis may also break down, which can lead to prosthetic failure.

At Mass. Eye and Ear, these issues in keratoprothesis implantation were highlighted by two recent cases of corneal blindness secondary to autoimmune disease. The team of C. Stephen Foster, MD; Jessica Ciralsky, MD; George Papaliodis, MD; Claes Dohlman, MD, PhD; and James Chodosh, MD, MPH, reviewed these cases to better understand the underlying mechanisms of keratoprosthesis failure in autoimmune patients. Because prosthetic dental and orthopedic implants have been successful in autoimmune patients, this team of clinician scientists looked to previous reports of prosthetic complications to find unifying mechanisms of prosthetic failure.

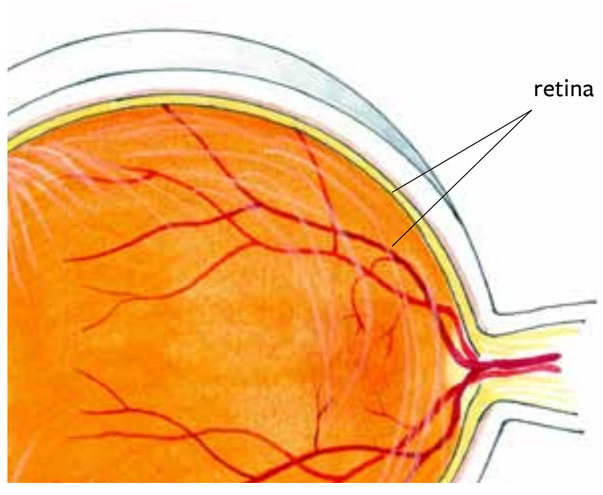
Upon systematically reviewing the published literature, the team found that prosthetic failure is clearly linked to inflammation and immune activation in autoimmune patients. Keratoprosthetic materials, such as polymethylmethacrylate (PMMA) and titanium, generally have low potential for inducing immune responses; however, the available literature suggested that in autoimmune patients, these materials themselves might stimulate inflammatory cascades that may damage recipient tissues. These findings called for further study of keratoprosthesis materials and the underlying mechanisms of autoimmunity and inflammation. Because more and more treatment options are becoming available for autoimmune diseases, ongoing efforts in the HMS Department of Ophthalmology will produce new, targeted approaches to restoring vision in autoimmune patients.

GEORGE N. PAPALIODIS, MD

RETINA

The retina, which lines the inside of the back of the eye, contains highly specialized cells that convert visual images into electrical signals. The retina then transmits the signals to the brain via the optic nerve. Genes, lifestyle, and age-related factors can all affect the retina, which is susceptible to numerous disorders. In the United States, the leading causes of adult blindness—age-related macular degeneration (AMD) and diabetic retinopathy—are diseases of the retina.

For patients with retinal disease, vision loss may be slowed or even reversed with therapies pioneered by the members of the HMS Department of Ophthalmology. Today, translational research across the HMS campus continues at an intense pace. As scientific discovery is continuously translated into clinical practice, innovative sight-saving treatments are breaking ground in vision care.



BACTERIAL INFECTIONS

Ending retinal damage in bacterial endophthalmitis

Endophthalmitis is a form of uveitis that affects much of the eye. It can rapidly damage the retina and cause loss of vision—or even loss of the entire eye. Despite advances in antibiotic therapy and ophthalmic care, infectious endophthalmitis—often caused by bacteria—remains a serious complication of eye surgeries or injuries. Although bacterial toxins cause much of the damage in this condition, the host immune responses that clear the pathogens may inadvertently damage normal host tissues.

Michael Gilmore, PhD, pioneered studies on why some causes of infectious endophthalmitis do not respond to antibiotic treatment. His lab found that if a bacterium causing endophthalmitis is producing a specific toxin, killing the bacteria with antibiotics and treating the inflammation does not limit the damage to the retina. However, if the bacteria were rendered incapable of producing the toxin, antibiotics and anti-inflammatory agents prevented this damage. His laboratory is using this scientific knowledge, as well as studies of the bacterial genome, to design new treatments to spare the retina. His studies are also identifying host components that are important for immune protection as well as damage in these infections. Unexpectedly, his lab found that a component called Fas ligand is important for activating immune cells and protecting the eye, whereas another factor in the complement system (part of the innate immune system) had little effect. Recently, he and collaborators Bruce Ksander, PhD, and Meredith Gregory-Ksander, PhD, found that the retinal protein alphaB-crystallin protects against retina cell death while the immune system clears bacteria.

Michael S. Gilmore, PhD

Sir William Osler Professor of Ophthalmology, Harvard Medical School

Member, Biological and Biomedical Sciences Program, Harvard Medical School

Member, Microbial Sciences Initiative, Harvard University

Dr. Michael Gilmore, former President and Director of Research at Schepens Eye Research Institute,and first incumbent of the Sir William Osler Professor of Ophthalmology at HMS, , joined the Howe Laboratory at Mass. Eye and Ear in July 2010 to further the development of new treatments for bacterial infection. Eye infections are potentially blinding complications of injury and surgery, and many of the causes are resistant to antibiotics. As Principal Investigator of the NIH-sponsored interdisciplinary Harvard-wide Program on Antibiotic Resistance, Dr. Gilmore is promoting collaborations between HMS, affiliate hospitals, the Broad Institute, and the pharmaceutical industry. This collaboration is identifying and validating new compounds for treating multidrug resistant staphylococcal infection, and studies of bacterial genomes are identifying new therapeutic targets.

Dr. Gilmore received his PhD in biochemistry and molecular biology, as the Colin MacLeod Fellow, from the University of Oklahoma Health Sciences Center (OUHSC). After postdoctoral training at the University of Wuerzburg in Germany and at the University of Michigan, he returned to the OUHSC to join the faculty in 1984. There he rose through the ranks in the Department of Microbiology and Immunology, and the Department of Ophthalmology, to hold the titles of George Lynn Cross Research Professor in the College of Medicine, and MG McCool Professor of Ophthalmology. From 2000–2004 he also served as OUHSC Vice President for Research. At HMS, Dr. Gilmore is an affiliate of the HMS department of Microbiology and Molecular Genetics, and is a member of the Biological and Biomedical Sciences Program. He serves on the steering committees of the Harvard Microbial Sciences Initiative, and the Broad Institute of MIT and Harvard Infectious Disease Initiative. His numerous honors include a Fogarty Senior International Fellowship at Cambridge University, an Alexander von Humboldt Fellowship, a VH Honeymon Distinguished Lecturership, and the OUHSC Regents Award for Distinguished Research.

Continuing his studies on dangerous multidrug-resistant infections that plague patients following surgery or associated with injuries, Dr. Gilmore and his former trainees Janet Manson, PhD, and Lynn Hancock, PhD, discovered a mechanism used by harmless gastrointestinal microorganisms to acquire multidrug resistance. They found that plasmids—circular pieces of DNA that replicate independently of the bacteria's chromosomal DNA—facilitated the transfer of virulence and antibiotic-resistance genes from one bacterium to another. Infections from multidrug-resistant Enterococcus are leading complications of surgeries, ranging from cataract extractions to knee replacements. Understanding the origins of these strains will help guide the judicious and effective use of antibiotics, and the development of new treatments. This groundbreaking article, published in the *Proceedings of the National Academy of Science* in 2010, was rated by Faculty of 1000 as being in the top 2% of published articles in biology and medicine.

BIOLOGY

The retinal atlas project

Specialized neurons called rods and cones are the primary light-sensing cells in the retina. These photoreceptors trigger a cascade of reactions through a complex cellular network, which recodes images into electrical impulses. Major research efforts are focused on defining the cellular events that process visual images.

Richard H. Masland, PhD, Director of the Howe Laboratory at Mass. Eye and Ear, has devoted his research career to mapping the retinal atlas, which involves identifying the cell types in the retina's complex neuronal network. The goal of this effort is to understand the fundamental mechanisms of vision, which may reveal new strategies for preventing or reversing vision loss. With contributions from several research groups worldwide, the retinal atlas is now virtually complete. This endeavor has identified approximately 60 distinct retinal cell types that are capable of an even greater number of intracellular connections.

Besides deciphering the fundamental biology of vision, the retinal atlas project may also reveal the underlying mechanisms of degenerative retinal disorders. This work, according to Dr. Masland, "extends beyond our studies in the retina, and underpins our efforts in the Howe Laboratory to treat various diseases of the eye." Now, with the detailed map of cellular architecture of the retina in hand, Dr. Masland and other Howe Laboratory researchers anticipate novel treatment strategies like directed gene and stem cell therapies. In the Howe Laboratory, researchers are currently refining preclinical discoveries for clinical evaluation. The primary goal of this ongoing translational research is to restore vision in degenerative retinal disease. "Curing blindness," says Dr. Masland, "would be the ultimate payoff for our years of research in fundamental cell biology."

Retinal patterning

Cellular diversity is not the only hallmark of retinal complexity; the cells of the retina are also arranged in defined patterns that are critical for vision. Interestingly, though retinal cell types may differ widely, many are derived from the same progenitor cells. Through various genetic, molecular, environmental, and hormonal events, the retinal progenitors produce specific cell types in specific positions in the retinal landscape.

Connie Cepko, PhD, has uncovered many mechanisms that determine the ultimate fate of retinal progenitor cells. Her laboratory has developed various lineage marking techniques, which demonstrated how progenitor cells in the retina can give rise to different cell types (such as neuronal and glial cells). These studies helped decipher the complex mechanisms of retinal cell fate determination.

Dr. Cepko's team has also uncovered many genetic factors that control various features of eye development. Her laboratory has identified many gene expression patterns within the developing eye which direct the organization of the retina and other eye structures. Using techniques to introduce gene reporters into cells (such as viral vectors and electroporation) and expression profiling techniques (such as microarrays), Dr. Cepko's laboratory is working to decipher the formation of the retinal cell types, as well as their complex circuits. They have also identified chemical factors (such as retinoic acid) and hormonal factors (such as thyroid hormone) that may help determine the spatial layout of the retina, including the formation of the macula. These studies, combined with new advances in gene therapy and stem cell technology, may lead to novel strategies for treating retinal degenerative diseases.

Rescuing photoreceptors in retinal degenerative disorders

Because genes that control development are often disrupted in disease, Dr. Cepko's research in retinal development has contributed greatly to the understanding of retinal degenerative disorders. Her laboratory mapped developmental gene expression patterns that are now used to model the molecular events that cause retinal degeneration. Having discovered several genetic factors that contribute to photoreceptor cell death, Dr. Cepko is now using gene delivery methods to help "rescue" dying rods and cones in retinal degenerative disorders. In a January 2009 report in the journal *Science*, Dr. Cepko and postdoc-

Richard H. Masland, PhD

David Glendenning Cogan Professor of Ophthalmology and Professor of Neurobiology, Harvard Medical School

Director of the Howe Laboratory of Ophthalmology and Associate Chief of Ophthalmology Research, Massachusetts Eye and Ear Infirmary

Dr. Richard Masland is an accomplished scientist in basic and translational research in the retina. He completed his undergraduate studies at Harvard College, received his PhD from McGill University, and conducted postdoctoral work at Stanford University and Harvard Medical School. Dr. Masland was an Investigator of the Howard Hughes Medical Institute from 1993–2006, and joined Mass. Eye and Ear in 2009 as Associate Chief for Ophthalmology Research and the Director of the Howe Laboratory, which houses much of the research in eye development and disease at Mass. Eye and Ear.

Dr. Masland's laboratory focuses on the neuronal diversity of the retina, its cellular interactions, and the complex photoreceptor microcircuitry that recodes visual input. Because the retina is a readily assessable extension of the central nervous system, the findings of Dr. Masland and colleagues are applicable to other neuronal processes. His ambitious and collaborative retinal atlas project is fundamental to the understanding of retinal disease, and has opened up new avenues of investigation and potential therapies for a host of degenerative retinal disorders.

For his outstanding contributions to the field of ophthalmology, Dr. Masland received the 2010 Proctor Medal, which is the highest honor bestowed by the Association for Research in Vision and Ophthalmology (ARVO). A former Howard Hughes investigator, Dr. Masland has also received Brian Boycott Prize for his retinal research. His honors for excellence in teaching include the Hoopes Prize and the Irving M. London award.

Constance L. Cepko, PhD

Professor of Genetics and Ophthalmology, Harvard Medical School

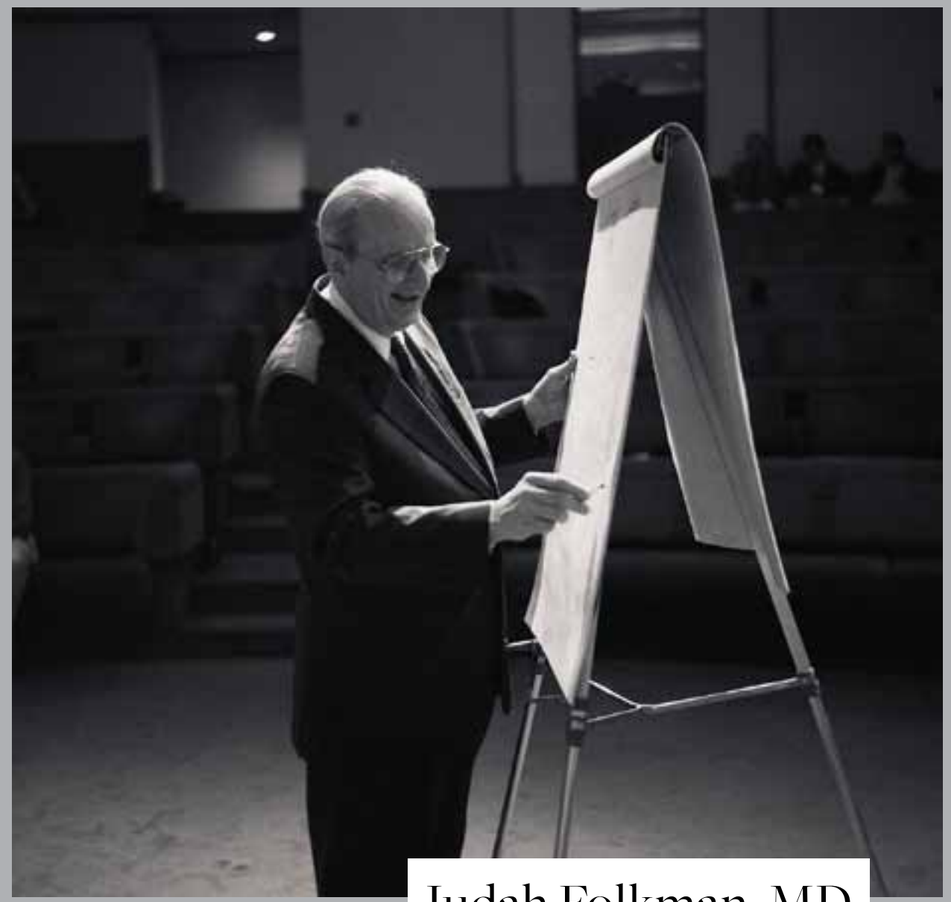
Investigator, Howard Hughes Medical Institute

Dr. Constance Cepko's scientific career began with a seventh-grade science fair project in microbiology; this led to a weekend research internship that continued through high school, followed by baccalaureate studies in biochemistry and microbiology at the University of Maryland. At MIT, under the direction of Phillip Sharp, PhD, Dr. Cepko conducted her doctoral research on adenoviral proteins. As a postdoctoral fellow in the laboratory of Richard Mulligan at MIT, Dr. Cepko helped pioneer the use of retroviruses to express transgenes in cells.

Recognizing the utility of retroviral vectors in developmental biology, Dr. Cepko used them to study retinal development when she became an independent investigator at HMS in 1985. Besides significantly advancing the basic science underlying retinal development, Dr. Cepko has applied the tools of genetics and molecular cell biology to understanding the basis of retinal disease.

Dr. Cepko has received numerous honors for vision research, including the David Cogan Outstanding Young Investigator Award in Vision Research, the Alcon Institute Research Award for Vision, and the Bressler Prize for Vision from the Jewish Guild for the Blind. Dr. Cepko has been an Investigator of the Howard Hughes Medical Institute since 1994; she was inducted into the American Academy of Arts and Sciences in 1999 and the National Academy of Sciences in 2002. She is a member of the Society for Neuroscience and the Association for Research in Vision and Ophthalmology.

toral fellow Bo Chen, PharmD, PhD, showed that histone deacetylase 4 (HDAC4), a nuclear co-repressor that regulates bone and muscle development, also regulates survival of rod photoreceptors. Because rods are the primary cells that are lost in retinitis pigmentosa, a progressive retinal degenerative disorder, this discovery is highly relevant to retinal disease. In a mouse model of retinitis pigmentosa, Drs. Cepko and Chen used electroporation to deliver HDAC4 DNA into the retina. They found that high HDAC4 expression in the mouse retina could rescue dying rod photoreceptors. This effect was due in part to the activity of hypoxia-inducible factor 1alpha (HIF1), an oxygen-sensitive transcription factor that regulates many genes involved in cell survival and function. Dr. Cepko's laboratory is currently studying how HDAC4 promotes rod survival, and is now developing gene delivery techniques that may someday be used to treat retinal degenerative disorders in humans.



Judah Folkman, MD

February 24, 1933 – January 14, 2008

The Father of Angiogenesis

As a young navy doctor in 1961, Dr. Judah Folkman noticed that tumors needed blood vessels to grow. Ten years later, Folkman published a controversial theory that is now widely accepted: targeting angiogenesis may potentially arrest cancer. Although others described tumor angiogenesis as early as 1945, Dr. Folkman's paramount achievements formed the foundation of antiangiogenic therapy, and he is unequivocally considered the "Father of Angiogenesis." By the time Dr. Folkman passed away, an estimated 1.2 million people had received antiangiogenic treatments. His scientific legacy endures through the HMSARG scientists who were mentored or otherwise influenced by this visionary of translational research.

ANGIOGENESIS

Because blood vessels play important roles in many human diseases (including cancer), they have become a major focus of translational research and drug development. Realizing that blood vessels are central to many blinding retinal diseases, scientists and clinicians of the Harvard Medical School Angiogenesis Research Group (HMSARG)[1] have focused intense scrutiny on the underlying mechanisms of blood vessel development. HMSARG researchers have individually and collaboratively discovered many mechanistic features of vascular biology, thus forming new paradigms for diseases that involve neovascularization (the abnormal formation of new blood vessels) or angiogenesis (the growth of existing vessels). Efforts of the HMSARG have translated groundbreaking scientific discoveries into innovative treatments for millions of patients with vascular disease.

Vascular endothelial growth factor (VEGF)

Antiangiogenic therapy, first advocated by Judah Folkman, MD, in 1971, targets factors in the body that regulate blood vessel growth. One molecule, first discovered in 1983, was named vascular permeability factor (VPF) for its ability to make blood vessels leaky. In 1989, researchers realized that VPF could also make blood vessels grow. Unlike other angiogenic factors that stimulate the growth of many cell types, VPF's potent effects were very specific for vascular endothelial cells. Moreover, VPF can be secreted into the bloodstream; thus, it can have effects distant from the cells of origin. Because of its specific and far-reaching effects on blood vessels, VPF was renamed vascular endothelial growth factor (VEGF), and is the primary target of current antiangiogenic therapies.

PATRICIA A. D'AMORE, PHD, MBA

The genetics of angiogenesis

An individual's genetic makeup can greatly affect many biological processes, including angiogenesis. Prompted by the fact that African-Americans rarely develop neovascular AMD or hemangiomas (benign tumors composed of endothelial cells), Robert D'Amato, MD, PhD, set out to identify genetic factors that modify the angiogenic response. In 2000, he demonstrated that genetic variations among different strains of mice may lead to differences in angiogenic response. In 2004, Dr. D'Amato mapped genetic regions that control the angiogenic response to basic fibroblast growth factor (bFGF) in mice. More recently, Dr. D'Amato's team mapped genetic regions that control the degree of choroidal neovascularization induced by laser injury. This study, reported in the July 2009 issue of *The FASEB Journal*, identified several candidate genes that may regulate angiogenesis, which presents new targets for antiangiogenic therapies. These findings may also lead to new screening tests that determine disease risk, as well as methods to predict a patient's response to specific treatments.

The benevolent side of VEGF

With the advent of antiangiogenic therapies for cancer and other vascular disorders, VEGF is often viewed in an unfavorable light. However, VEGF also has numerous important physiological roles that HMS scientists have helped to define. For example, in 1999, Ivana Kim, MD, and colleagues demonstrated that the genes for VEGF and two VEGF receptors were constantly expressed in normal eyes, indicating that these genes play active roles in normal eye physiology. While working as an investigator with Patricia D'Amore, PhD, MBA, Magali Saint-Geniez, PhD, showed that the normal adult retinal pigment epithelium (RPE) expresses VEGF abundantly. This suggested that VEGF is a survival factor for non-proliferating choroidal vessels. Dr. Saint-Geniez subsequently showed that endogenous VEGF is critical for lens development, and may even have neuroprotective effects on photoreceptors. Dr. Saint-Geniez demonstrated that abnormal VEGF expression in the RPE resulted in degeneration of the choroidal vessels, Bruch's membrane, and the RPE itself. This study was published November 2009 in *Proceedings of the National Academy of Sciences*, and was featured in the February 2010 issue of *EyeNet*, the electronic journal of the American Academy of Ophthalmology. These studies highlight the importance of endogenous VEGF in normal eye health, and emphasize the need for strategies that selectively target pathological VEGF activity without disrupting normal VEGF function when using antiangiogenic therapies.

MAGALI SAINT-GENIEZ, PHD

[1] Original group of nine HMS angiogenesis researchers who conducted pioneering bench and translational research to elucidate the role of angiogenesis in blinding ocular diseases, and subsequently developed revolutionary clinical treatments. Much of their work was initiated under the mentorship of Judah Folkman, MD. HMSARG researchers include: Anthony Adamis, MD; Lloyd P. Aiello, MD, PhD; Robert D'Amato, MD; Patricia D'Amore, PhD, MBA; Evangelos Gragoudas, MD; George King, MD, Joan Miller, MD; David Shima, PhD, and Lois Smith, MD, PhD.

Robert J. D'Amato, MD, PhD

Professor of Ophthalmology, Harvard Medical School

Judah Folkman Chair in Surgery, Children's Hospital Boston

Director, Center for Macular Degeneration Research, Children's Hospital Boston

As one of Judah Folkman's scientific trainees, Dr. Robert D'Amato has made many notable contributions to the field of angiogenesis. In 1994, as a postdoctoral fellow in the Folkman laboratory, Dr. D'Amato demonstrated the potent antiangiogenic properties of thalidomide, a sedative drug that was withdrawn in 1961 due to its devastating side effects. This discovery explained the drug's toxicity and potential to cause birth defects, and led to its current FDA-approved use in treating multiple myeloma. Dr. D'Amato completed a residency in Ophthalmology at Mass. Eye and Ear before joining Dr. Folkman's laboratory at Children's Hospital Boston, where he has been an independent investigator since 1994. He has since characterized lenalidomide (Revlimid®), an analog of thalidomide, which was approved in 2006 for treating myeloma; he also identified another potent analog Actimid®, which is currently in Phase II clinical trials.

Dr. D'Amato currently serves as Director of the Center for Macular Degeneration Research at Children's Hospital Boston, holds the Judah Folkman Chair in Surgery, and is Professor of Ophthalmology at HMS. He has studied VEGF regulation and ocular angiogenesis both independently and in collaboration with other HMSARG investigators. With a continued interest in developing new therapies for vascular disorders, Dr. D'Amato has characterized several antiangiogenic compounds in recent years. These include polymeric TNP-470 (a derivative of a fungal compound), 2-methoxyestradiol, various non-steroidal anti-inflammatory drugs (NSAIDs), and a modified form of the anthrax toxin. His recent studies demonstrated a potentially broader-spectrum antiangiogenic role for a TNP-470 polymer, Lodamin, in animal models where treatment resulted in regression of established choroidal neovascularization (CNV) lesions and a reduction of inflammatory cytokines. Dr. D'Amato envisions broader-spectrum agents such as Lodamin to have the potential to suppress a greater number of pathological disease processes, including those in AMD and cancer. Dr. D'Amato's current research focuses on the genetic factors that control angiogenesis as well as continuing work on antiangiogenic agents.

HMS ANGIOGENESIS RESEARCH Fuels a Revolution in Retinal Care

1971

Judah Folkman and colleagues at Children's Hospital and Harvard Medical School describe the isolation of a "tumor angiogenesis factor" (TAF) in the February issue of *Journal of Experimental Medicine.*

Dr. Folkman later publishes his seminal theory of tumor angiogenesis in the November issue of *New England Journal of Medicine.*

1989

George King demonstrates how protein kinase C, activated by elevated glucose levels, contributes to retinopathy and other vascular complications in diabetes. This mechanistic model of diabetic retinopathy is published in the July issue of *Proceeding of the National Academy of Sciences.*

1995

Based on the work of Joan Miller and Evangelos Gragoudas, the first AMD patient in the world is treated with Visudyne®.

1995–1997

Work from the HMSARG intensifies, and several studies led by Lloyd P. Aiello, George King, Lois Smith, Evangelos Gragoudas, Robert D'Amato, Patricia D'Amore, and Joan Miller further implicate VEGF and other angiogenic factors in vascular eye disorders. The investigators help define the role of hypoxia in regulating VEGF, and show how angiogenic inhibitors may block ocular neovascularization. These studies provide the scientific foundation for using anti-angiogenic therapies for vascular disorders of the eye.

1998

A phase IA clinical trial for pegatanib (Macugen®), a VEGF inhibitor, begins in AMD patients .

1999

Photodynamic therapy (PDT) with verteporfin (Visudyne®) shows efficacy in treating wet AMD in Phase I/II clinical studies. Joan Miller and Evangelos Gragoudas are lead investigators of these studies.

2002

The phase IA clinical trial for Macugen® shows promise for treating AMD. The results of this study are reported in the April issue of the journal *Retina.*

In studies led by Evangelos Gragoudas and Joan Miller using primate animal models, choroidal neovascularization is prevented by intravitreal injection of an anti-VEGF antibody fragment. The lead author, Magdalena G. Krzystolik, publishes the study in the *Archives of Opthalmology.*

2005–2006

In a series of studies, Evangelos Gragoudas and Joan Miller examine the safety and efficacy of combination therapies of Lucentis® and Visudyne® in preclinical models.

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1983

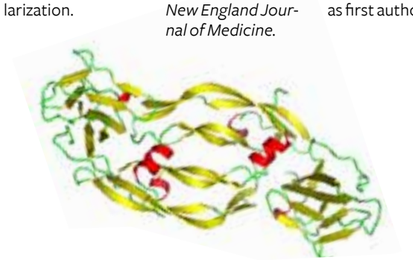
Vascular permeability factor (VPF) is discovered in the laboratory of Harold Dvorak at Harvard Medical School, and described in the journal *Science.* Dvorak's group demonstrated that this factor is 34-42,000 daltons in size and is secreted by a variety of tumors. VPF later becomes known as vascular endothelial growth factor (VEGF).

1984

The first "tumor angiogenesis factor" is isolated and identified as basic fibroblast growth factor (bFGF) by the laboratory of Michael Klagsbrun at Harvard Medical School. Judah Folkman is a co-author on the report, published in the February issue of the journal *Science.*

1994

In the journal *American Journal of Pathology*, Joan Miller, Patricia D'Amore, Judah Folkman, and colleagues correlate VEGF with ocular angiogenesis in primates. This is the first *in vivo* demonstration of VEGF's role in ocular neovascularization.



Beetham Eye Institute researchers Lloyd P. Aiello and George King also associate elevated levels of VEGF in eye fluids of patients with diabetic retinopathy and other ischemic retinal diseases. This work is published in the December issue of *New England Journal of Medicine.*

A group including Anthony Adamis, Joan Miller and Judah Folkman finds increased VEGF levels in ocular fluid of diabetic retinopathy patients; this is reported in the October issue of *American Journal of Ophthalmology,* with Tony Adamis as first author.

In the most-cited article in the journal *Investigative Ophthalmology and Visual Science,* Lois Smith and Patricia D'Amore describe a mouse model of retinopathy of prematurity (ROP) and other oxygen-induced retinal disorders.

In the July issue of *Proceeding of the National Academy of Sciences,* Robert D'Amato, working with Judah Folkman, describes how the toxicity of thalidomide is primarily due to its antiangiogenic effects. This drug is now used to treat multiple myeloma.

1997

Judah Folkman's laboratory identifies endostatin, an endogenous inhibitor of angiogenesis, and shows that it inhibits tumor growth. These findings are published in the January issue of the journal *Cell.*

1998–2004

The HMSARG maintains its dramatic pace of research, and further elucidates the molecular and genetic mechanisms of angiogenic ocular diseases. These studies serve as the foundation for further development of anti-angiogenic therapies for ocular disorders.

2000

On April 13, 2000, PDT with Visudyne® becomes the first FDA-approved drug treatment for wet AMD.

Lucentis®, a fragment of the anti-VEGF antibody bevacizumab, enters clinical testing for AMD.

2004

On December 17, Macugen® becomes the first FDA-approved anti-VEGF therapy for neovascular (wet) AMD. The approval is based on a large multi-center clinical trial published December 30 in *New England Journal of Medicine. E*vangelos Gragoudas is an investigator in this study.

2006

On June 20, Lucentis® receives FDA approval for the treatment of AMD.

2010

A landmark clinical trial shows that intraocular Lucentis® injections remarkably improve the results of standard laser photocoagulation for diabetic macular edema. Lloyd P. Aiello and Jennifer Sun are investigators of this collaborative study, conducted at 52 clinical sites within the Diabetic Retinopathy Clinical Research Network and published in the June issue of the journal *Ophthalmology.*

In July, the FDA approved Lucentis® for the treatment of diabetic macular edema following retinal vein occlusion.


JENNIFER K. SUN, MD

AGE-RELATED MACULAR DEGENERATION (AMD)

At the center of the retina is a photoreceptor-rich region known as the macula, which processes images in the middle of the visual field. The macula has a high density of cones, which are the photoreceptors that distinguish color and fine detail in bright light. The fovea, which lies at the center of the macula, is made entirely of cones, and thus provides the most acute vision. As people age, their maculas may begin to degenerate, causing progressive loss of central vision. This condition is known as age-related macular degeneration (AMD). Some AMD patients retain enough peripheral vision to continue many activities of daily life; however, as the disease progresses, it can have devastating effects on quality of life as patients lose the ability to drive, recognize faces, or read. In the United States, AMD is the leading cause of blindness in people over the age of 50.

Photodynamic therapy: a breakthrough treatment for AMD

Studies initiated in the early 1990's by Joan Miller, MD, and Evangelos Gragoudas, MD, produced a breakthrough for patients with wet AMD: photodynamic therapy (PDT) with verteporfin (Visudyne®). In this procedure, verteporfin (a light-sensitive dye) is injected systemically.; acool laser is then directed at the eye, which activates the drug specifically in the choroidal vessels. This blocks the leakiness of the immature vessels and prevents further growth. This therapy allows targeted and non-invasive treatment for patients with CNV under the fovea, which is the cone-rich central portion of the macula. Approved by the FDA for treating neovascular AMD on April 13, 2000, Visudyne® was the first pharmacologic therapy for AMD and has also been used to treat CNV caused by other ocular conditions. Photodynamic therapy also laid the foundation for a new class of vascular-targeting therapies for AMD, altering the landscape of ophthalmic care.


JOAN W. MILLER, MD

Drs. Miller and Gragoudas are actively pursuing ways to improve standard PDT. Although this therapy slows disease progression in most patients who receive it — and may even improve vision in some — PDT itself can damage the retina by causing retinal cells to undergo apoptosis (cell suicide), which is the primary cause of vision loss in both dry and wet AMD. In 2007, to better understand the mechanisms of PDT-induced photoreceptor apoptosis, Drs. Miller and Gragoudas used animal models of CNV to identify the factors that control apoptosis in photoreceptors. In 2008, using the same models, they also showed several promising ways to prevent photoreceptor apoptosis after PDT, such as injections of dexamethasone (a potent steroid) or L-NAME (a nitric oxide synthase inhibitor). These studies are helping to optimize current PDT protocols for treating CNV secondary to AMD.

Inspiring the development of VEGF inhibitors for AMD

Beginning in the early 1990s, HMSARG scientists began to reveal the role of VEGF in ocular neovascularization. In 1993, Patricia D'Amore, PhD, MBA, David Shima, PhD, Tony Adamis, MD, Judah Folkman, MD, and colleagues showed that the human retina synthesizes VEGF, and in 1995 they found that VEGF expression is induced in low-oxygen (hypoxic) conditions. Using preclinical models, Drs. Miller, Adamis and D'Amore showed that VEGF expression was virtually undetectable in healthy eyes, but dramatically increased with severity of retinal ischemia (lack of blood flow in the retina) and iris neovascularization. This 1994 discovery was the first time VEGF was implicated in ocular neovascularization. In a series of studies published between 1995 and 1996, several HMSARG members (including D'Amore, Gragoudas, Miller, Adamis, Lloyd P. Aiello, MD, PhD, George King, MD, and Lois Smith, MD, PhD) showed that VEGF inhibitors could block ocular neovascularization in preclinical models. In 1994, Drs. Adamis, Miller and Folkman showed increased VEGF in the vitreous of patients with proliferative diabetic retinopathy. This study, published October 1994 in *American Journal of Ophthalmology*, directly linked VEGF with disease. These findings were replicated in a study led by Dr. Aiello, which was published December 1994 in *the New England Journal of Medicine*. This cumulative work of the HMSARG inspired the development of anti-VEGF therapies, which have since replaced PDT as first-line treatments for wet AMD.

Macugen®

Pegaptanib (Macugen®), which consists of aptamers (short pieces of RNA) that target VEGF, was the first anti-VEGF therapy approved for treating AMD. In 2004, the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial demonstrated efficacy for pegaptanib for neovascular age-related macular degeneration, and was published in the December 30th issue of the *New England Journal of Medicine*. FDA approval of Macugen®, granted on December 17, 2004, was based on this study, and opened a new era of treatment for AMD and other retinal diseases.

Lucentis®

Ranibizumab (Lucentis®), approved on June 20, 2006 for the treatment of wet AMD, was a revolutionary advance because it could improve vision in about one-third of patients treated. Ranibizumab is an anti-VEGF fragment related to bevacizumab (Avastin®), a full-length anti-VEGF antibody and the first-ever antiangiogenic drug (FDA-approved for treating colon cancer in 2004). Ranibizumab and bevacizumab were both based on the scientific principles established by Dr. Judah Folkman, and members of the HMSARG contributed to pivotal preclinical studies that laid the foundation for further development of the drug. Drs. Adamis, Shima, Gragoudas, D'Amore, Miller, and Folkman collaborated with Napoleone Ferrara, MD, of Genentech to show that an anti-VEGF antibody fragment could prevent neovascularization in a primate model. They also showed that injection of VEGF alone into the eye was sufficient to produce neovascularization, again in a primate model.

Moving from preclinical studies to clinical trials, Drs. Gragoudas and Miller led clinical safety studies of ranibizumab in 2005, and along with Ivana Kim, MD, tested its effectiveness in combination with Visudyne® PDT. Recent and ongoing studies conducted by the HMSARG are expanding the list of ocular diseases that may be treated with ranibizumab or other antiangiogenic therapies. Dr. Kim contributed to a Phase I clinical trial reported January 2011 in the journal *Ophthalmology*, demonstrating the effectiveness of ranibizumab for CNV caused by conditions other than AMD. Dr. Aiello and Jennifer Sun, MD, have also studied ranibizumab as a potential therapy for diabetic macular edema, and are participating in an ongoing, multi-center clinical trial sponsored by the Diabetic Retinopathy Clinical Research Network. Preliminary results from the trial demonstrated that anti-VEGF therapies may reduce diabetes-associated swelling in the retina. Dr. Aiello was a lead author for the study. (see profile, page 154).

Dry AMD: the unmet challenge

Dry AMD involves the degeneration of the retinal pigment epithelium (RPE), which is a thin layer of supportive cells beneath the macula. An early finding of dry AMD is the accumulation of cellular deposits under the retina. These deposits, called drusen, are associated with atrophy of the macular photoreceptors and loss of central vision. Dry AMD is the most common form of this disease; 90 percent of all AMD cases represent this subtype, and nearly one million patients per year progress from dry AMD to geographic atrophy (GA), which results in severe vision loss. Dry AMD also increases the risk of developing wet (neovascular) AMD, the more serious form of the disease, which typically progresses more rapidly and leads to profound vision loss.

HMS Ophthalmology researchers are aggressively pursuing new therapies for the dry form of AMD, which still has no FDA-approved treatments. The first step involves defining the mechanisms that underlie dry AMD and its progression to GA. Ivana Kim, MD, and Demetrios Vavvas, MD, PhD, are exploring animal models of dry AMD to better understand its pathophysiology. Currently funded efforts support the establishment and characterization of a primate model of dry AMD. In this model, experimentally induced autoimmunity is expected to induce the accumulation of drusen, a hallmark of dry AMD, as well as the neural atrophy that is typical in GA.


IVANA K. KIM, MD

By establishing preclinical models and delineating key mechanisms of vision loss in dry AMD, researchers can test novel interventions for this widespread condition.

Genes, smoking, and genetic smoking guns in AMD

AMD is a complex disease that often involves a combination of multiple genetic and environmental risk factors. Researchers in the Mass. Eye and Ear Ocular Molecular Genetics Institute seek to identify genes that contribute to AMD, and to understand how the interactions between genes and the environment may alter an individual's risk of developing AMD. By studying pairs of siblings in which one had AMD and the other did not, Margaret DeAngelis, PhD, Thaddeus Dryja, MD, and Dr. Miller identified cigarette smoking as a risk factor for wet AMD. In 2005, multiple groups identified complement factor H (CFH), a protein involved in immune responses, as a susceptibility locus for AMD. This study showed that the Y402H variant of CFH accounted for over 40 percent of AMD risk in older adults. In a 2007 study that addressed both genetic and environmental factors, Drs. DeAngelis, Dryja, Miller and Kim showed that specific variants of the CFH gene, combined with


DEMETRIOS G. VAVVAS, MD, PHD


LLOYD M. AIELLO, MD

cigarette smoking, increased AMD risk 144-fold. Using powerful genetic studies combined with gene expression microarrays and proteomic techniques, ongoing studies have identified several novel gene variants and gene-gene interactions that affect AMD risk.

Based on the genetic findings implicating the complement pathway in AMD pathogenesis, several complement-directed therapies are currently under clinical investigation. The Mass. Eye and Ear Retina Service is participating in a Phase I/II study, sponsored by Genentech, of an anti-complement factor D antibody for the treatment of advanced dry AMD or GA.

In March 2010, Alexandra Silveira, PhD, and colleagues, working with Drs. Miller, Kim and DeAngelis, also identified variants in the retinoic acid receptor-related orphan receptor alpha (*RORA*) gene that substantially contribute to an individual's risk of AMD. Because the *RORA* gene codes for a receptor that binds cholesterol and other hormones, this finding links new biological pathways to AMD, suggesting new ways to prevent or potentially treat AMD and other retinal disorders.

DIABETIC RETINOPATHY

Prior to the 1920s, type 1 diabetes was often fatal within a few years after diagnosis, usually due to ketoacidosis, kidney failure, and other life-threatening complications of uncontrolled hyperglycemia. The discovery of insulin in 1921 allowed people with this type of diabetes to live longer lives; however, the increased life expectancies also revealed long-term vascular complications of chronic hyperglycemia, such as diabetic retinopathy. By the 1950s, diabetic retinopathy had become the leading cause of blindness in the United States. Many patients with diabetes are now able to avoid blindness thanks to laser photocoagulation, a therapy developed in 1967 by researchers Lloyd M. Aiello, MD, PhD, and William P. Beetham, MD, at the Joslin Diabetes Center Despite this revolutionary treatment, diabetic retinopathy remains a major public health concern as the leading cause of blindness among working-age Americans. Researchers at the Beetham Eye Institute (BEI) at Joslin are continually advancing available treatments for diabetic retinopathy, and have also contributed greatly to the development of antiangiogenic therapy for vascular eye disorders.

Picking PKC as a target of diabetic retinopathy treatments

George King, MD, HMS Professor of Medicine at HMS and Director of Research at Joslin Diabetes Center, first detailed some of the cellular signaling pathways that underlie diabetic retinopathy over two decades ago. In his landmark report, published in July 1989 in *Proceedings of the National Academy of Sciences,* Dr. King proposed that elevated glucose levels activate protein kinase C (PKC), which in turn leads to vascular complications in diabetic retinopathy. Dr. King and his collaborator, Lloyd P. Aiello, MD, PhD, have continued to define the role of PKC in diabetic retinopathy. A report in the November 2009 issue of *Nature Medicine* showed how PKC-delta activation by hyperglycemia causes blood vessel cells to die—resulting in vascular complications in the early stages of diabetic retinopathy.

The cumulative findings of Drs. King and Aiello led to the development of ruboxistaurin (Arxxant®), a PKC-beta inhibitor, which was demonstrated to inhibit vascular disorders in preclinical models of diabetes. Results of a Phase 3 clinical trial of ruboxistaurin were reported in 2006; compared to placebo, ruboxistaurin reduced risk of sustained moderate vision loss by 40 percent in patients with moderate to severe non-proliferative diabetic retinopathy. There are still ongoing clinical trials to further test the safety and efficacy of this PKC inhibitor. Although endpoints to prevent the progression of diabetic retinopathy were not achieved in recently completed clinical trials, the secondary endpoints from these studies suggest that ruboxistaurin may still have some potential in preventing vision loss from diabetic retinopathy. More importantly, these studies have advanced the understanding of the disease processes in diabetic retinopathy, and help to guide new approaches for developing potential therapies.

VEGF as a villain of diabetic retinopathy

Since diabetic retinopathy involves leaky blood vessels and pathological neovascularization in advanced stages, it is not surprising that it involves VEGF; in fact, some of the earliest studies implicating VEGF in neovascular eye disorders were conducted in patients with diabetes. In 1994, researchers at Mass. Eye and Ear (including Drs. Miller and Adamis) and at BEI (including Drs. Aiello and King) found increased VEGF levels in the eyes of patients with diabetic retinopathy. In November of 1995, Drs. Aiello, King, and Lois Smith, MD, PhD, published the first report that VEGF inhibitors could suppress retinal neovascularization. In January of 1996, a team that included Drs. Adamis, Shima, Gragoudas, Folkman, D'Amore and Miller used a primate model to show that VEGF inhibition with a monoclonal antibody could prevent neovascularization. These studies were instrumental in the development of ranibizumab (Lucentis®), which is a fragment of a VEGF-specific antibody, for the treatment of AMD.

Although laser photocoagulation therapy, which was developed at BEI, continues to be the gold standard for treating diabetic macular edema (DME), new studies suggest that ranibizumab therapy may improve the visual outcomes of standard laser therapy for complications of diabetic retinopathy. In a multicenter clinical trial of 854 eyes in 691 patients with DME, laser combined with ranibizumab was more effective at slowing or reversing vision loss than using laser alone. At a two-year follow-up, vision was still dramatically improved in patients who received the combination treatment. This study was conducted by the Diabetic Retinopathy Clinical Research Network and published June 2010 in *Ophthalmology*. Expanded two-year results were published April 2011 in *Ophthalmology*, and confirmed the results of the previous report. Drs. Aiello and Sun were among the lead investigators of this study, which gives promising evidence that antiangiogenic therapy can greatly benefit patients with diabetic retinopathy.


GEORGE L. KING, MD

The Joslin 50-Year Medalists: holding the keys to escaping diabetic retinopathy

Because chronic hyperglycemia can have ravaging effects on blood vessels, the vast majority of people with diabetes—especially those who depend on insulin injections to control blood sugar—will eventually develop retinopathy and other vascular problems. However, some patients live with type 1 (insulin-dependent) diabetes for 50 years or longer without apparent complications. The Joslin Diabetes Center recognizes these unique individuals through its 50-Year Medalist program, and many Medalists are participating in a long-term study that aims to determine how they manage to avoid vascular complications.

Led by Dr. King, Joslin scientists discovered that only 50 percent of Medalists reported retinopathy after surviving diabetes for 50-60 years. Surprisingly, even fewer (44 percent) of the 60-year to 70-year Medalists reported retinopathy, and those who survived diabetes for over 70 years reported the lowest rates of all—only 27 percent. In contrast, over 90 percent of all patients with type 1 diabetes develop serious vascular complications. These initial findings of the 50-Year Medalist Study, which were published in the August 2007 issue of the journal Diabetes Care, suggest that certain traits make some individuals resistant to hyperglycemia-induced complications, including retinopathy. Recently, Drs. King and Aiello, along with Jennifer Sun, MD, MPH, showed that only 50 percent of Medalists have advanced retinopathy in either eye. Drs. King, Sun and Aiello are now examining these patients more closely in hopes of identifying genetic or biochemical factors that can protect people with diabetes from neovascular diseases. Results from these studies, published April 2011 in *Diabetes Care,* may lead to new strategies for improving the quality and duration of life for people with diabetes.

Genetics of diabetic retinopathy and the Jackson Heart Study

In the United States, African Americans have an increased risk of cardiovascular disease and related conditions, including diabetes. For reasons that are not entirely clear, diabetic retinopathy is not only more common in African Americans compared to other groups, but the disease also tends to progress more quickly. Because this disparity cannot be explained by differences in blood sugar control alone, researchers suspect that other reasons exist.

Lucia Sobrin, MD, MPH, believes that genetics may explain why African Americans are especially prone to diabetic retinopathy. Through a collaboration between Mass. Eye and Ear, the University of Mississippi Medical Center, and the Jackson Heart Study group, Dr. Sobrin hopes to uncover genes that may alter an individual's risk of diabetic retinopathy.

The Jackson Heart Study follows African Americans living in the greater Jackson, Mississippi area, and is the largest study in history to examine the genetics of cardiovascular disease and related conditions in African Americans. Researchers have collected DNA samples from consenting participants, and are looking for genetic clues as to why certain people are more prone than


LUCIA L. SOBRIN, MD, MPH

others to certain conditions.

Dr. Sobrin has carefully examined the clinical signs and genetic maps of over 500 participants thus far, and will continue to enroll participants through 2012. Genetic mapping is being done at the Broad Institute in Cambridge, Massachusetts, where Dr. Sobrin has been working with David Altshuler, MD, PhD, and Mark Daly, PhD. By identifying genes that may affect retinopathy risk and rate of progression, Dr. Sobrin hopes to improve monitoring, counseling, and therapeutic strategies for patients that may suffer vision loss from diabetic complications.

RETINAL DEGENERATIONS

Retinal degenerations are diverse genetic conditions that progressively destroy the light-sensing photoreceptors of the retina. Those that are hereditary are known collectively as retinitis pigmentosa and allied diseases, and affect approximately 100,000 people in the United States and 2 million people worldwide. Most people afflicted by this condition become night blind in adolescence, lose side vision in young adulthood, develop tunnel vision, and become blind by age 60; if untreated, some individuals become virtually blind by age 30. Though vision loss in retinitis pigmentosa is irreversible, treatment regimens developed in the HMS Department of Ophthalmology may slow the course of disease, and postpone blindness for up to 20 years. Research is ongoing with the ultimate goal of restoring vision among those with early stages of this group of diseases.

ELIOT L. BERSON, MD

Treating hereditary retinal degenerations and deciphering their genetic origins

Eliot L. Berson, MD, the William F. Chatlos Professor of Ophthalmology at HMS, has been at the forefront of research on retinal degenerations for more than four decades. In the 1960s, Dr. Berson discovered that electroretinography (ERG) could detect photoreceptor dysfunction years to a decade before vision starts to deteriorate in retinitis pigmentosa; since then, ERG has been used routinely to diagnose this condition and to estimate visual prognoses. Dr. Berson and colleagues, working in the Berman-Gund Laboratory for the Study of Retinal Degenerations, developed the first treatment regimens for retinitis pigmentosa: supplementation with vitamin A palmitate and an omega-3 rich fish diet (of which docosahexaenoic acid, or DHA is a major constituent). They have recently shown that lutein supplementation slows midperipheral visual field loss (*Archives of Ophthalmology*, 2010).

In the early 1990s, Dr. Berson and his colleague Thaddeus Dryja, MD, discovered the first gene defects associated with retinitis pigmentosa: point mutations in the rhodopsin gene, which encodes a light-sensitive pigment in photoreceptor cells. Drs. Berson and Dryja have since pinpointed identified approximately 20 genes associated with retinitis pigmentosa—revealing numerous biochemical pathways that are altered in this heterogeneous group of diseases. More recently Dr. Berson has collaborated with Carlo Rivolta, PhD, a former fellow of Dr. Dryja, to define further the mutation spectrum in these disorders. In the July 2010 issue of the journal *Human Gene Therapy*, Dr. Berson, Michael Sandberg, PhD, Basil Pawlyk and coworkers reported successful gene therapy of both rod and cone photoreceptors in an animal model of a severe form of retinitis pigmentosa (Leber congenital amaurosis) caused by with loss of the RPGRIP1 gene. These genetic studies form the foundations for new disease models and developing targeted therapies for these other forms of these debilitating disorders.

TERESA C. CHEN, MD, FACS

Deciphering the genetic origins of retinitis pigmentosa

The X chromosome also contains a gene that is often associated with retinitis pigmentosa; it codes for a protein called retinitis pigmentosa GTPase regulator (RPGR), which is missing or nonfunctional in about 10 percent of all cases of the degenerative retinal disease. Studies conducted in the Berman-Gund Laboratory of Retinal Degenerations have significantly advanced the understanding of how RPGR functions in the retina, and have led to promising new therapies for retinitis pigmentosa.

In the early 2000s, Dr. Tiansen Li, PhD, used a mouse model of X-linked retinitis pigmentosa to study RPGR function in photoreceptors. He showed that RPGR helps maintain proper distribution of light-sensitive opsin proteins in the cilium, a thin structure that connects the cell body with the outer segment. Dr. Li and colleagues discovered that in order for RPGR to function, it requires a cilium-specific protein called RPGR-interacting protein (RPGRIP), which anchors RPGR in the photoreceptor cilium. Moreover, they found that the gene encoding RPGRIP, located on human chromosome 14, is mutated in some patients with Leber congenital amaurosis (LCA). In this severe form of retinitis pigmentosa, lack of RPGRIP in the cilium essentially abolishes RPGR function, causing progressive vision loss that begins in early childhood.

These findings led Dr. Li's team to develop gene replacement strategies for RPGR and RPGRIP defects and for the first time utilized gene therapy delivery to photoreceptors. In a study reported in September 2005 in the journal *Investigative Ophthalmology and Visual Science*, Dr. Li and colleagues used adeno-associated virus (AAV) to express RPGRIP in a mouse model of LCA. This gene therapy approach preserved photoreceptor function as confirmed by electroretinography (ERG). In a subsequent preclinical study, reported August 2010 in the journal *Human Gene Therapy*, Drs. Li, Berson, and colleagues used a similar strategy to restore photoreceptor function in LCA mice—this time using the human RPGRIP gene. This provided proof-of-concept that gene replacement therapy is feasible for the human form of LCA, and called for clinical testing in patients with RPGRIP deficiencies. This study also suggested that gene replacement could work for other retinal degenerations caused by ciliary defects. Ongoing studies are testing AAV-mediated RPGR replacement therapy for X-linked retinitis pigmentosa.

Optical coherence tomography (OCT): a revolutionary technique in evaluating retinal disease

Optical coherence tomography (OCT) is a non-invasive technique that uses light to produce high-resolution, three-dimensional images of fine ocular structures. OCT was developed in the early 1990s at Mass. Eye and Ear in collaboration with Massachusetts Institute of Technology and Massachusetts General Hospital. OCT is now used worldwide in routine clinical practice to diagnose and monitor numerous ocular conditions. In the retina, OCT was first used to characterize morphology in the macula, and the technique expanded quickly into a role in the management of neovascular (wet) AMD.

In a case series reported June 2006 in *American Journal of Ophthalmology*, researchers at Mass. Eye and Ear (including Teresa Chen, MD, Joan Miller, MD, and Evangelos Gragoudas, MD) demonstrated for the first time that histological changes in dry AMD can be detected in time domain OCT (TD-OCT) scans of the retina. OCT is now rapidly becoming the "gold standard" for diagnosing and monitoring both wet and dry forms of AMD, and HMS researchers are continually optimizing techniques for measuring retinal changes in this increasingly prevalent condition.

TD detection is the classic and probably most widely used OCT technology. A newer form, based on spectral domain (SD) detection, has greatly improved the image quality for retinal morphology. SD-OCT has had a major impact in the diagnosis and management of patients with retinal conditions. Clinician scientists in the HMS Department of Ophthalmology continue to improve OCT techniques. Ongoing studies are using OCT to better understand the pathology of retinal disease, and to determine the effectiveness of novel therapeutic regimens.

As SD-OCT has become an integral part of AMD management, so has the need to better understand the implications of OCT findings and how they relate to other clinical findings. Andrea Giani, MD, Daniel Esmaili, MD, and Dr. Miller of Mass. Eye and Ear, in collaboration with Giovanni Staurenghi, MD, and colleagues at the University of Milan, recently evaluated patients with classic CNV using SD-OCT, and correlated the findings with vessel leakage as determined by flourescein angiography (FA). The researchers found that the absolute difference between CNV material and retinal pigment epithelial reflectivity (REF), as determined by SD-OCT, was higher in untreated CNV than in previously treated (but still leaky) CNV. Moreover, the difference between CNV material and REF was higher in leaky lesions than in those without leakage. This study, slated for 2011 publication in the journal *Retina*, demonstrates that SD-OCT findings may provide important information regarding vessel leakage measurements by FA. In a related study, published August 2001 in the journal *Investigative Ophthalmology and Visual Science*, Drs. Giani, Esmaili, Miller, Staurenghi, and colleagues tested whether SD-OCT may be used to predict FA leakage in CNV. Indeed, the researchers found that SD-OCT findings were significantly correlated with FA leakage in CNV with fluid presence and with certain patterns of fluid presentation. These cumulative findings will establish the clinical relevance of OCT imaging and its use in manag-

ing AMD patients.

OCT has also proven to be useful for evaluating diabetic retinal complications and treatment regimens. In a study reported May 2010 in the journal *Ophthalmology*, Joslin researchers led by Lloyd P. Aiello, MD, PhD, used OCT to measure retinal volume in a multicenter, randomized, controlled clinical trial of focal/grid photocoagulation therapy for diabetic macular edema (DME). The researchers showed that higher baseline measurements of retinal volume were associated with worsening visual acuity two years after treatment. Overall, the study supported the use of focal/grid photocoagulation as the standard therapy for DME, and showed OCT to be a clinically useful tool in evaluating and predicting visual acuity after treatment.

For retinal degenerative disorders like as retinitis pigmentosa, OCT has proven to be extremely valuable for measuring retinal thickness and detecting complications, such as cystoid macular edema (CME) and macular cysts. In a 2005 study led by Drs. Sandberg and Berson, and published in the journal *Investigative Ophthalmology and Visual Science*, researchers showed that both retinal thinning (due to cell loss) and retinal thickening (due to presumed edema) determined by TD-OCT measurements

KIP CONNOR, PHD

ANNE B. FULTON, MD

were associated with lower acuity. More recently, in a 2010 *Investigative Ophthalmology and Visual Science* report, Dr. Sandberg and colleagues showed that macular pigment optical density (MPOD), a measure of carotenoid concentration in the fovea, was lower in eyes with higher degrees of CME as measured by TD-OCT. OCT testing is now being used by Drs. Sandberg and Berson to help identify nutritional factors that may be associated with the development of CME in patients with retinitis pigmentosa.

Research in OCT technology continues. In the October 2008 issue of *Investigative Ophthalmology and Visual Science*, HMS researchers (including Drs. Chen, John Loewenstein, MD, and Johannes de Boer, PhD) assessed the utility of optical frequency domain imaging (OFDI), a high-speed OCT system developed at Massachusetts General Hospital. The researchers used OFDI with a center wavelength of 1050 nm, previously shown to improve the imaging of deeper retinal structures (such as the choroidal vessels). OFDI was used to acquire various measures of CNV (including CNV volume, retinal thickness, subretinal fluid volume, and magnitude of photoreceptor detachment) before and after treatment with ranibizumab (Lucentis®). This study demonstrated that high-speed, three-dimensional OFDI at 1050 nm may have advantages over standard TD-OCT and current state-of-the-art SD-OCT at 850 nm for imaging neovascular (wet) AMD.

RETINOPATHY OF PREMATURITY

If a baby is born too early, the retinal vessels—which grow outward from the center of the retina—may stop growing before they reach full length. This may lead to retinopathy of prematurity (ROP), and can deprive the developing peripheral retina of oxygen and nutrients. This early stage of ROP affects about 15,000 premature infants each year in the United States; while most recover without treatment, about 10 percent of ROP cases progress to a neovascular stage that can severely damage the retina and cause vision loss. VEGF plays a major role in both stages of ROP, and its regulation by oxygen is central to the disease process. VEGF is induced by low oxygen (hypoxia) but repressed by high oxygen (hyperoxia), so when a baby is exposed to the oxygen-rich environment outside of the womb, the relative hyperoxia may halt normal retinal vessel growth by suppressing VEGF. As a result, the blood-starved peripheral retina becomes hypoxic, and produces VEGF and other angiogenic factors to induce neovascularization.

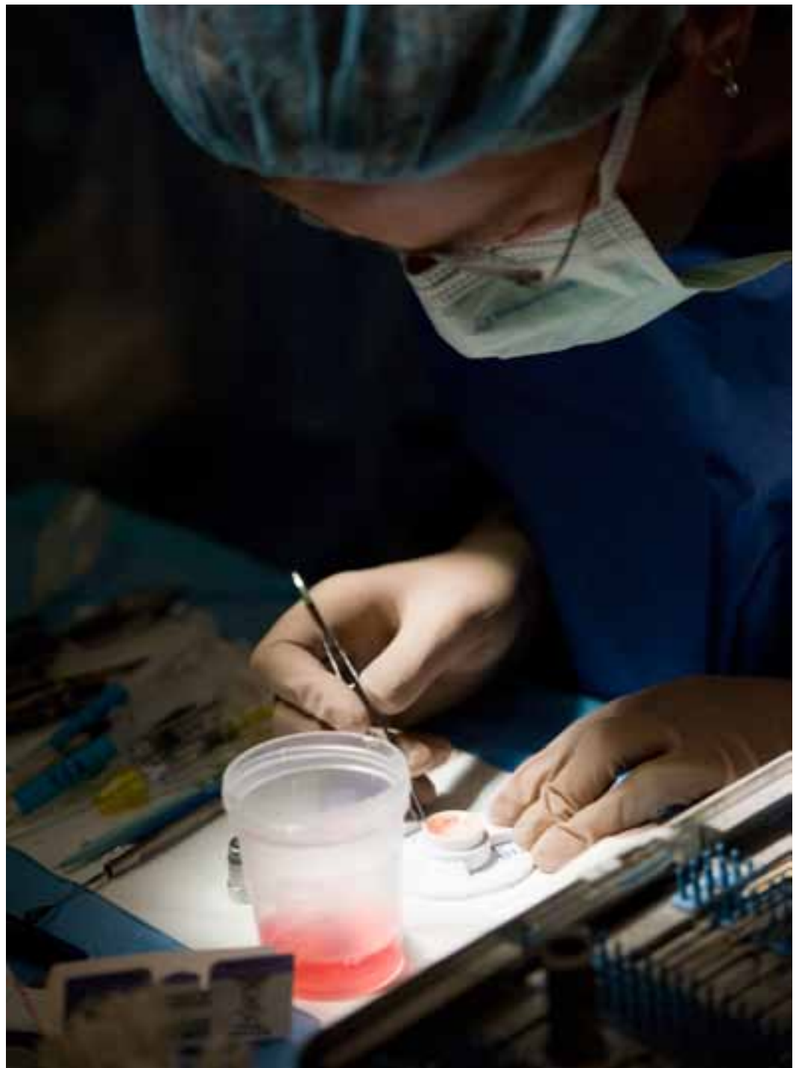
The interplay between neural and vascular networks in the developing retina

In babies with ROP, the disease starts to appear at approximately 32 weeks of gestation, or about eight weeks short of full term. This happens to be the time when the photoreceptors (the rod cells in particular) undergo rapid maturation. Because nerves and blood vessels often grow side by side, the interplay between the neural and vascular networks in the retina may be important in ROP. This neurovascular interaction is the focus of Anne Fulton, MD, HMS Professor of Ophthalmology and Senior Associate in Medicine at Children's Hospital Boston. Dr. Fulton's recent studies have explored the possibility that the rapidly maturing photoreceptors, with their increased metabolic demands, create a hypoxic environment that promotes neovascularization; thus, photoreceptor function may actually occur before vascular abnormalities appear. Using non-invasive assessment techniques such as electroretinography (ERG) in babies with or without ROP, Dr. Fulton showed that rod sensitivity could predict vascular outcome at a later age. These observations were confirmed in animal models of ROP, and suggest that rod dysfunction may have a causative role in the vascular problems of ROP. These studies establish the immature photoreceptors as potential pharmacological targets, and offer promise of very early intervention in the treatment of ROP.

Understanding unique aspects of angiogenesis in the eyes of children

By studying ROP, Lois Smith, MD, PhD, has made several notable contributions to the field of angiogenesis research. In the 1990s, Dr. Smith worked with Patricia D'Amore, PhD, MBA, and Robert D'Amato, MD, PhD, to develop a mouse model of ROP that is widely used to study VEGF regulation and oxygen-induced retinopathies. In collaboration with George King, MD and Lloyd P. Aiello, MD, PhD, Dr. Smith was among the first to implicate VEGF in retinopathy and to suppress ocular neovascularization using VEGF inhibitors. Dr. Smith has since shifted her focus to other factors that are also important in the development of ROP, and has defined novel strategies for treating and preventing this disease.

In 2007, Dr. Smith, with John Paul San Giovanni, ScD, Jing Chen, PhD, and Kip Connor, PhD, showed that omega-3 fatty acids promote normal vessel growth in the retina while reducing abnormal neovascularization. This suggested that prenatal supplementation with omega-3 fatty acids may help prevent retinopathy in newborns. In a series of studies published in the past few years, Drs. Smith and Chen demonstrated that erythropoietin (EPO) and insulin-like growth factor I (IGF-I) are both deficient in the early stages of ROP when retinal vessels are insufficient—yet both contribute to the pathological angiogenesis that occurs during neovascular ROP. These studies not only present new pharmacological targets, but also demonstrate that timing is critical for preventing and treating ROP.



RESCUING THE VISION OF NEWBORNS

As a pediatric ophthalmologist, Lois Smith, MD, PhD, has cared for many extremely premature babies—some weighing less than one pound. Not only do these vulnerable infants have life-threatening health problems, but many also suffer from retinopathy of prematurity (ROP). A number of years ago, Smith decided that she needed to find a way to help these babies preserve their vision.

Dr. Smith's quest began by looking at the first ROP risk factor: oxygen delivery. She worked with newborn mice, which, like premature babies, have only partially developed retinas. When the mice were given supplemental oxygen at high levels, their retinal blood vessels stopped growing or disappeared. Moreover, retinal levels of VEGF plummeted. But when the mice were brought back into normal room air, VEGF levels surged and blood vessels resumed growth—sometimes abnormally.

Many years of follow-up experiments revealed that VEGF is actually involved in two biochemical pathways. Targeting one pathway could enhance the normal, "good" vessel growth in the first phase of ROP without affecting the abnormal second-phase vessel growth.

To discover other critical factors acting in these pathways, Dr. Smith began to investigate growth hormone (GH), which is produced by the pituitary gland and implicated in diabetic retinopathy. Her work gradually led her to another hormone known as insulin-like growth factor I (IGF-I), which works in concert with GH and is important for growth and development of the brain, lungs, intestines and other organs. Dr. Smith conducted a series of experiments in mice that could not produce IGF-I. "We found out that IGF-I was really important for normal vessel growth," Dr. Smith says. "If IGF-I is low, vessels don't grow." The research quickly moved into humans. Dr. Smith's group found that in the third trimester of pregnancy, IGF-I levels in the fetus rise markedly because they get the factor from the mother in the womb. In very premature babies, however, this supply is cut off, and their levels of IGF-I begin to decline.

In children, retinopathy of prematurity (ROP) is a major cause of vision loss in the U.S. Each year, about 1,500 premature infants develop ROP severe enough to require medical treatment; approximately 500 children each year become legally blind from ROP.
(*National Eye Institute*)

This finding prompted Dr. Smith and Ann Hellström, MD, PhD, a collaborator in Sweden, to assess IGF-I levels in 80 babies born at 24 to 32 weeks of gestation. They found that IGF-I levels at the gestational age of 30 to 33 weeks were the most important predictor of whether a preterm baby would develop ROP. In babies who developed ROP, IGF-I levels never rose to the level they would have achieved at 30 to 33 weeks *in utero*. In contrast, premature babies who did not develop ROP managed to make enough IGF-I soon enough after birth to prevent disease.

Drs. Smith and Hellström next conducted a Phase I clinical trial in Sweden to see if supplementing IGF-I in premature newborns would prevent ROP. Starting at birth, the babies received small amounts of IGF-I intravenously until they were able to make sufficient levels of the growth factor on their own. Successful results from this trial have led to an expanded, multi-center Phase II trial in Sweden. "In science, you have to look at one thing at a time," says Dr. Smith. "You try to find pathways that you can alter to make a difference, and you just keep on pushing."

Excerpted from the Spring 2004 issue of *Dream: The Magazine of Possibilities*, a publication of Children's Hospital Boston. Original story by Nancy Fliesler. Content has been adapted and updated for this report.

FRONTIERS IN RETINAL RESEARCH: PRESERVING & RESTORING VISION

Preserving vision: new agents for neuroprotection

Though blinding retinal diseases have many different origins, they often converge on pathways that trigger the death of photoreceptors (the light-sensing neurons of the retina), resulting in vision loss. Two well-characterized biological pathways, apoptosis (cell suicide) and necrosis (cell death caused by stress and other external factors), are controlled routes of cellular destruction. Therapeutic interventions that prevent photoreceptor death by both apoptotic and necrotic pathways may potentially preserve vision for a myriad of retinal diseases. Thus, neuroprotection is an avid area of current research in the HMS Department of Ophthalmology.

In 2003, a collaboration between Cynthia Grosskreutz, MD, PhD, and Joan Miller, MD, demonstrated that apoptotic photoreceptor cell death and caspase activation occurred in an experimental model of retinal detachment. In 2008, a group led by Dr. Miller showed that a class of anti-AIDS drugs known as protease inhibitors could protect against photoreceptor death in laboratory models. In 2010, in an article published in the Proceedings of the National Academy of Science, Dr. Miller and Demetrios Vavvas, MD, PhD, reported findings that, although the caspase pathway was activated and apoptosis occurred in the model, cell death also occurs through another pathway triggered by receptor interacting protein (RIP). In this study, they demonstrated that blockage of both pathways, with a caspase inhibitor and necrostatin-1 (a RIP kinase inhibitor), was required to effectively prevent apoptosis, necrosis, and oxidative stress. Similarly, deficiency of Rip3 (a key activator of RIP1 kinase) prevented the necrotic changes. Thus, two pathways to cell death were triggered by retinal detachment in animal models, indicating that combination therapy to prevent both capase-dependent apoptosis and RIP-mediated necrosis may help preserve vision.

Retinal research at the zenith: restoring vision

The convergence of research progress in many areas has created an unrivaled opportunity in vision research. The retina, which is more accessible (and has a simpler neuronal structure) than the brain, is likely to yield the first successful neuroregenerative treatments using gene-targeting and stem cell therapies. Moreover, the retinal atlas project provides investigators with the complete cellular architecture of the retina, which complements new advances in gene therapy and stem cell research. Under current study are three distinct approaches to restoring vision: persuade healthy retinal cells to acquire photoreceptor functions, targeted gene therapies, and stem cell engraftment into the retina. These approaches are designed as revolutionary treatments for patients with vision loss, and can be applied to a multitude of ocular diseases that cause blindness.

Gene therapy with help from retinal ganglion cells

Retinal ganglion cells relay visual information, in the form of electrical impulses, from the photoreceptors to the brain. Some ganglion cells express the light-sensitive pigment melanopsin, which allows them to act as photoreceptors as well. Melanopsin is also known to impart photoreceptor-like qualities to cells that do not normally express it; thus, Richard Masland, PhD, wondered whether retinal ganglion cells, induced to express melanopsin using gene therapy techniques, could substitute for photoreceptors in eyes with retinal degeneration. In a mouse model of hereditary retinal degeneration, a team led by Dr. Masland used viral vectors to deliver the melanopsin gene to a large number of retinal ganglion cells. This treatment restored an appreciable degree of vision in mice that lacked rod and cone photoreceptors. This study, published in the October 2009 issue of *Proceedings of the National Academy of Sciences*, established melanopsin as a candidate gene therapy for retinal degenerations. More importantly, this work provides proof-of-principle that photoreceptor substitution is a viable approach for treating retinitis pigmentosa and other retinal degenerative disorders. Dr. Masland's group is currently refining this technique for potential use in patients blinded by retinal disease.

Making stem cell therapy a reality for retinal disease

Tissue and stem cell therapies hold enormous promise for repairing the retina in diseases that cause photoreceptor destruction. This is the focus of Michael Young, PhD, Associate Professor of Ophthalmology at HMS, and Director of the Minda de Gunzburg Center for Ocular Regeneration at Schepens Eye Research Institute. Studies led by Dr. Young during the past five years have significantly advanced the understanding of tissue and stem cell transplantation in the retina—particularly in terms of graft survival and the formation of functional neural connections after transplantation. Dr. Young's laboratory has developed biomaterials that can be used for delivering neuroprotective agents or stem cells to the retina; the engineered biomaterials have also been shown to promote survival and functional growth of neurons after transplantation.

In 2007, Dr. Young established a novel role for matrix metallo-

MICHAEL J. YOUNG, PHD

proteinases (MMPs) in promoting neural regrowth. Using a mouse model of retinal degeneration, Dr. Young showed that MMPs support the growth of transplanted neural progenitor cells in the retina. Subsequent studies showed that increased MMP levels create a permissive environment for neural regeneration. Recently, Dr. Young's laboratory engineered a cell delivery system consisting of a biodegradable/biocompatible polymer that provides a steady release of MMP2 to promote neural regeneration at sites of retinal injury. This technology represents a significant step toward making stem cell therapy a reality in the treatment of retinal disease.

A pharmacological approach to regenerating the retina

Another possible way to treat blinding retinal disorders is to induce the growth of new photoreceptors. So far, this strategy has remained elusive; however, in a breakthrough study published March 2008 in the journal *Investigative Ophthalmology and Visual Science*, Dong Feng Chen, MD, PhD, demonstrated a potential way to simulate photoreceptor regrowth. Dr. Chen, HMS Associate Professor of Ophthalmology and Schepens Associate Scientist, showed that non-neuronal Müller cells could become photoreceptors when stimulated with either glutamate or its analogue alpha-aminoadipate, which are both naturally occurring chemicals. Moreover, alpha-aminoadipate, which has fewer toxic effects than glutamate, also caused the newly transformed photoreceptors to migrate to appropriate places in the retina. These studies were performed in cell culture and in healthy mice; if the same approach restores visual function in preclinical models of retinal degenerations, clinical testing could soon follow. Because this pharmacological strategy targets cells that already exist in the adult retina, it could be a viable alternative to stem cell transplantation for treating hereditary retinal degenerations or vascular retinal disorders, such as age-related macular degeneration (AMD) and diabetic retinopathy.

DONG FENG CHEN, MD, PhD

From mouse to man and from man to mouse: a vision-saving discovery [3]

For the past ten years, reversing vision loss in RP has been the mission of Michael Young, PhD, an Associate Scientist who heads the Minda de Gunzburg Center for Ocular Regeneration at Schepens Eye Research Institute. Today, he is on the verge of using stem cells in clinical trials to repair human retinas damaged by this sight-robbing disease; however, his journey began far from the clinic.

Young's insight came in the form of encouragement and inspiration from one of his mentors, Fred "Rusty" Gage, PhD, who believed that the retina might be a place where stem cells could flourish and integrate to repair damaged tissue.

"We were skeptical," says Young, "that is until we witnessed it for ourselves." Young put his mentor's theory to the test almost immediately. His first subjects were rats. Dr. Young injected brain stem cells into their eyes, watched in awe as the neural stem cells transformed into retina-like cells.

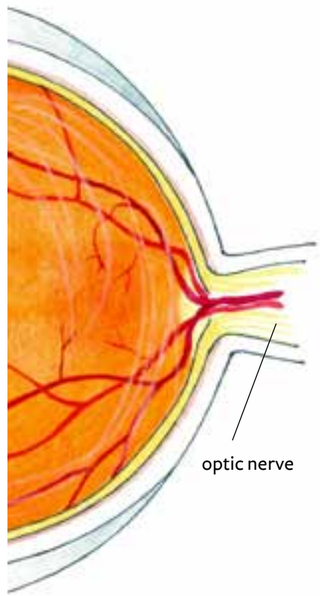
Further proof came when he transplanted retinal stem cells, which not only morphed into retinal cells in mouse eyes, but also wired themselves into the optic nerve and appeared to make the mice more light sensitive. Next, Young and his team performed the same kinds of studies in pigs who have larger, more human-like eyes, and had similar results.

Nearly a decade after these discoveries, Dr. Young is now preparing for clinical trials. To facilitate this critical step, he has enlisted the help of two new collaborators. The first is Reneuron, a company in England that can develop "immortalized" stem cells — genetically altered stem cells that reproduce indefinitely. "With just a few cells, we can produce sufficient tissue for thousands of patients," says Dr. Young.

The second new partner is the Harvard Center for Human Cell Therapy (CHCT), which will grow and store the human retinal stem cell tissue for clinical trials. The CHCT helps scientists within the Harvard community to more rapidly translate stem cell therapy to the clinic. The CHCT selects promising discoveries from many applicants, and then provides assistance from the technical level to the submission of Clinical Protocols and Investigational New Drug (IMD) applications.

Over the next three years, Dr. Young and his research team will refine their animal studies and make certain that the therapy will be safe for human beings. "We are not expecting miracles in these first trials," he says. "Our initial goal will be to regrow some of the rods in the retinas of patients with RP to increase their light perception. Our hope is that the potential of this kind of therapy will improve as we continue to refine our techniques."

[3]Excerpted with permission from the Autumn 2009 issue of *Sightings*, a publication of Schepens Eye Research Institute. The article has been adapted for this report.



OPTIC NERVE/GLAUCOMA

After photoreceptors in the retina convert visual images into electrical impulses, retinal ganglion cells transmit the impulses to the brain for processing. These neuronal cells have characteristically long axons that extend from the retina to the brain and form a cable of nerve fibers known collectively as the optic nerve. Damage to the optic nerve, or optic neuropathy, is a major cause of irreversible vision loss because it can be very difficult to diagnose or treat.

Early intervention is important for virtually any eye disorder; for optic neuropathies, it is absolutely critical because damaged optic nerve cells cannot heal or regenerate. Much effort in the HMS Department of Ophthalmology is devoted to understanding the underlying mechanisms of optic neuropathies, and developing more effective prognostic and diagnostic tools so optic nerve conditions can be treated as soon as possible.

In some optic neuropathies, both genetic and environmental triggers are likely at play; thus, research in the HMS Department of Ophthalmology aims to identify genes that modify disease risk, and to further study how these genes interact with the environment. Scientists are also developing new strategies for preventing and treating optic neuropathies—and even pursuing ways of coaxing the optic nerve to regenerate.

Preventing primary and secondary optic neuropathy

For many optic neuropathies, the lack of suitable preclinical models has hindered efforts to improve existing treatments and develop novel neuroprotective strategies. Dean Cestari, MD, a specialist in neuro-ophthalmology, is developing animal models of hereditary optic nerve disorders with the goal of preventing disease progression. Dr. Cestari also studies conditions that lead to secondary optic neuropathy, including giant cell arteritis and neurofibromatosis type I. He is particularly interested in the inflammatory and pro-angiogenic factors that mediate cell death and visual loss during ischemia (lack of blood flow) in the optic nerve. With the knowledge gained from his studies, Dr. Cestari hopes to develop novel therapies for many optic nerve conditions.

GLAUCOMA

Glaucoma encompasses several conditions that cause optic neuropathy, and affects an estimated 60 million people worldwide. Primary open-angle glaucoma (POAG) is the most common form; it is associated with increased intraocular pressure (IOP), also known as ocular hypertension, which may in turn lead to retinal ganglion cell death and optic neuropathy. Secondary glaucoma occurs as a complication of eye surgeries, injuries, or other ophthalmic conditions. Glaucoma may even occur without increased IOP in normal tension glaucoma. Many kinds of glaucoma have strong genetic and/or environmental risk factors, and any form of the disease can cause irreversible blindness if left untreated.

GENETIC SCREENING AND PROGNOSIS

The most common forms of glaucoma have complex inheritance patterns that seem to involve multiple genetic and environmental factors. By identifying genes associated with glaucoma, scientists hope to develop screening tests that allow rapid risk

LOUIS R. PASQUALE, MD

assessment and targeted treatment. The emerging importance of environmental cues may also lead to new strategies for preventing or averting this potentially blinding disease.

Nature, nurture, and glaucoma

For diseases that do not have straightforward inheritance patterns, finding a genetic basis is very much like searching for a needle in a haystack; thus, identifying glaucoma-causing genes in the human genome requires significant collaboration and the ability to search multiple genomes at once. One major collaborative project, now in its third year, is the NEIGHBOR Consortium—a multicenter cohort study organized by Janey Wiggs, MD, PhD, and Louis Pasquale, MD. This study includes case samples and controls from the Massachusetts Eye and Ear Infirmary, the Nurses' Health Study (NHS), the Health Professionals Follow-up Study (HPFS), and thousands of additional subjects from 22 other investigators at eight different institution[1], for a total of 8,000 glaucoma cases and controls.

This large, collaborative effort not only taps into the intellect and resources of multiple institutions, but also provides the large and statistically robust sample sizes needed to identify major genes that contribute to glaucoma. "Collaboration is essential for this type of study because no single hospital or glaucoma service can produce this many samples," notes Dr. Pasquale. "It's an incredibly exciting effort, and my expectation is that we'll find some major genes that contribute to glaucoma."

The NEIGHBOR Consortium and other related studies form the basis of several genetic and epidemiological projects led by Drs. Pasquale and Wiggs. The highly anticipated results of these studies may ultimately allow at-risk patients to be identified through genetic screening tests.

- A genetic epidemiology study, published in early 2010 in the journal of *Investigative Ophthalmology and Visual Science*, identified potential interactions between endothelial nitric oxide synthase 3 (eNOS3) gene variants and hormone replacement therapy in POAG. This study shows that the association between NOS3 gene variants and POAG is modified by postmenopausal hormone use. Drs. Pasquale and Wiggs are currently collaborating with researchers at MGH and Schepens to validate a mouse model of POAG that may, in turn, be used to validate these epidemiological findings.

- Genomic studies have also identified candidate genes for pseudoexfoliation syndrome, a major risk factor for glaucoma. In pseudoexfoliation, a fibrous buildup on the inner surfaces of the anterior chamber (including the lens) may exfoliate, or flake off, and block drainage of the aqueous humor. Pseudoexfoliation has been associated with LOXL1 gene variations in patients from Scandinavian countries, where the condition was first described. In 2008, researchers at Mass. Eye and Ear associated the same LOXL1 variants with pseudoexfoliation in ethnically diverse patients in the United States. This study, published in the journal *BMC Medical Genetics,* suggested that certain variations in LOXL1 confer significant risk for adult-onset glaucoma worldwide.

- The LOXL1 gene encodes an enzyme that helps build elastic fibers in numerous tissue types, and Mass. Eye and Ear researchers showed that the mutations potentially reduce LOXL1 gene expression. This study, slated for 2011 publication in *Investigative Ophthalmology and Visual Science,* increases the understanding of the pathology of exfoliation glaucoma, and reveals potential therapeutic targets for this widespread condition.

- Data from over 100,000 subjects in the NHS and HPFS cohorts revealed interesting trends for exfoliation glucoma: the disease is more common in higher geographical latitudes; risk increases with distance from the equator. When exfoliation glaucoma affects only one eye, it even appears to vary according to which side people sleep on. These results suggest that temperature and radiation exposure (such as to UV light) are factors in exfoliation glaucoma. Though not yet published, these results highlight the importance of gene-environment interactions in various forms of glaucoma.

- An NIH-funded study in India seeks to identify other genes and measurable traits (such as optic nerve size) that may affect glaucoma risk. This study focuses on certain large families with closely inter-related members, participant characteristics that often yield a wealth of genetic information. Data from these ongoing studies are currently being analyzed, and may yield new diagnostic tests for glaucoma.

CLINICAL EXAMINATION & DIAGNOSIS

Existing diagnostic tests for glaucoma often are unreliable or may catch the disease too late. For instance, IOP measurement is not a definitive test because ocular hypertension does not necessarily cause glaucoma, nor does it occur in all forms of the disease. Other diagnostic techniques, such as standard visual field testing or direct examination of the optic nerve, can only detect abnormal optic nerve function after significant numbers of retinal ganglion cells have already died. Tests that can detect optic nerve dysfunction before retinal ganglion cell death are thus urgently needed.

Improved imaging of the optic nerve

One of the most exciting areas of glaucoma research involves developing imaging techniques that allow early diagnosis and real-time monitoring of glaucomatous optic nerve damage. Although the major glaucoma imaging technologies used today include optical coherence tomography (OCT), confocal scanning laser ophthalmoscopy, and scanning laser polarimetry, only spectral domain OCT allows for ultra-high resolution, three-dimensional video imaging of the optic nerve. Because of its unprecedented ultra-high resolution and ultra-high acquisition speeds, spectral domain OCT holds the most potential for non-invasive imaging and detection of pathological changes in the optic nerve. Spectral domain OCT can also detect retinal nerve fiber layer (RNFL) thinning, which can occur before clinically-detectable, irreversible vision loss in glaucoma.

Teresa Chen, MD, FACS, Associate Professor of Ophthalmology, specializes in spectral domain OCT and was the principal clinical collaborator on the research team that first developed ultra-high resolution video-rate spectral domain OCT. Dr. Chen recently published a study which was the first comprehensive description of the full range of qualitative and quantitative changes of the optic nerve and RNFL in glaucoma. This paper also depicted the first spectral domain OCT images of an eye with glaucoma. This study was published December 2009 in the journal*Transactions of the American Ophthalmological Society.* In a subsequent study, slated for publication in a 2011 issue of Journal of Glaucoma, Dr. Chen and colleagues used spectral domain OCT to examine the eyes of 45 healthy subjects and 33 glaucoma patients. This study is the first to show that a spectral domain OCT machine with tracker has the best ability for reproducible RNFL thickness measurements. These studies provide a basis for further developing and optimizing this imaging technique in larger-scale clinical trials.

Diagnosing glaucoma using psychophysics

Peter Bex, PhD, Assistant Professor of Ophthalmology and Associate Scientist at Schepens Eye Research

PETER J. BEX, PHD

Janey L. Wiggs, MD, PhD

Associate Professor of Ophthalmology, Harvard Medical School

Associate Director of the Howe Laboratory and Associate Chief for Clinical Research, Massachusetts Eye and Ear Infirmary

Director, Genetic Diagnostics Section, Ocular Genomics Institute, Massachusetts Eye and Ear Infirmary

Dr. Janey Wiggs is an accomplished clinician scientist specializing in the genetics of glaucoma. Using a uniquely collaborative and multidisciplinary approach, Dr. Wiggs' overall research goal is to identify genetic factors that underlie various forms of glaucoma, including adult onset primary open angle glaucoma, pseudoexfoliation glaucoma, juvenile open angle glaucoma, and others. Her research, which has been continuously funded by the National Eye Institute for over 15 years, has provided critical information regarding the biology of the disease. Ongoing studies may greatly improve current methods of diagnosis, and lead to more effective and specific therapies.

Dr. Wiggs is the Associate Director of the Howe Laboratory, Associate Chief for Clinical Research, and co-directs the Glaucoma Center of Excellence with Louis Pasquale, MD. Together, Drs. Wiggs and Pasquale, and Howe Laboratory Director Richard Masland, PhD, have led successful efforts to cultivate interdepartmental collaboration within HMS, as well as multicenter partnerships with other universities and hospitals in the U.S. and abroad. Dr. Wiggs is also co-chair of the US INDO Joint Working Group, an international vision research partnership initiated in 2005 between the National Eye Institute and the Indian government's Department of Biotechnology. The goal of the group is to advance vision science through collaboration of ideas, expertise, and resources. In 2011, Dr. Wiggs was also tapped to lead the Genetic Diagnostics Section of the department's new Ocular Genomics Institute. In this role, she will closely collaborate with Dr. Eric Pierce, who has been recruited as Director, to develop the institute into a premier Center of Excellence for leading genomics-based advances in patient care.

Dr. Wiggs lectures nationally and internationally and is the recipient of numerous awards including, most recently, a Lew R. Wasserman Merit award from Research to Prevent Blindness.

[1] Participating institutions include: University of Pittsburgh School of Medicine; Johns Hopkins University School of Medicine; Duke University School of Medicine; Miller School of Medicine, University of Miami; University of Michigan Medical School; Stanford University School of Medicine; University of California at San Diego, and; West Virginia University School of Medicine.


DOUGLAS J. RHEE, MD

Institute, is studying how psychophysics—or the relationship between a physical stimulus and the subject's perception—can be used to detect the early signs of glaucoma. Using a technique known as *equivalent noise analysis*, Dr. Bex showed that motion sensitivity decreases with age and even further with POAG. This visual function test was sensitive enough to potentially distinguish unhealthy retinal ganglion cells from those that have already died—something that current tests cannot do. These findings were reported June 2007 *in Investigative Ophthalmology and Visual Science,* and Dr. Bex is currently working with Dr. Pasquale to further develop this psychophysical testing method for use in clinical settings.

PREVENTION & NEUROPROTECTION

One of the goals of optic nerve research is to develop novel therapies that ultimately protect the nerve from damage. This endeavor requires understanding the molecular, cellular, and physiological processes of optic neuropathies—including the factors that cause ocular hypertension (increased IOP), which is currently the only treatable risk factor for glaucoma. Ongoing research seeks to improve existing strategies and to find new therapeutic targets for lowering IOP. Because ocular hypertension does not occur in all forms of glaucoma, there is also a great need for additional neuroprotective approaches.


TATJANA C. JAKOBS, MD

Combating ocular hypertension: SPARC-ing interest in the extracellular matrix

In an eye with normal IOP, aqueous humor production is balanced by its drainage through the *trabecular meshwork,* a spongy tissue structure that resides at the "open angle" where the cornea and the iris meet. The trabecular meshwork is impaired in many types of glaucoma (including POAG, the most common form), and many therapeutic strategies focus on improving drainage through this tissue.

It is known that deposits of extracellular matrix material on the trabecular meshwork can block the aqueous humor outflow, and Douglas Rhee, MD, Associate Professor of Ophthalmology, is studying the role of matricellular proteins in maintaining normal IOP. Dr. Rhee previously showed that human trabecular meshwork cells normally express high levels of the matricellular protein SPARC (secreted protein, acidic and rich in cysteine), and hypothesized that this protein may somehow regulate IOP. Thus, Dr. Rhee and colleagues generated mice that are deficient for the gene that encodes the SPARC protein, and found that SPARC-null mice had significantly lower IOP than their wild-type counterparts. This suggests a pivotal role for SPARC in IOP maintenance, and establishes this protein as a novel therapeutic target in glaucoma management. Dr. Rhee is currently investigating the mechanisms SPARC and other matricellular proteins utilize to control IOP.

Protecting the optic nerve by targeting non-nerve cells

Efforts to develop neuroprotective therapies for glaucoma have focused mainly on the retinal ganglion cells that form the optic nerve. HMS Assistant Professor, Tatjana Jakobs, MD is examining how another group of cells called *astrocytes* may affect the retinal ganglion cells. She and her collaborators found that the early signs of optic nerve damage occur just where the optic nerve leaves the retina, in a region called the *optic nerve head* or the *optic disc.* This area contains many astrocytes, and Dr. Jakobs is examining how they affect optic nerve health. Dr. Jakobs and colleagues have closely examined the shape and arrangement of astrocytes around the optic nerve head, and noted that they are clearly altered wherever the optic nerve is damaged. However, it is unclear whether astrocytes serve a neuroprotective role, or if they contribute to optic nerve damage. Dr. Jakobs is currently using a mouse model of glaucoma to address the exact role of astrocytes in optic neuropathy. These studies may potentially lead to novel neuroprotective strategies that target astrocyte function.

Structural remodeling of fibrous astrocytes unveils potential new disease targets

One of the barriers in pursuing these types of studies has been the difficulty in imaging astrocytes and tracking the anatomical changes that occur associated with disease progression. It has long been known that injury to nervous tissue produces a "glial scar," but it has previously been impossible to observe the cellular events that occur during scar formation because the closely packed cells obscure each other. Daniel Sun, PhD, a fellow working with Drs. Jakobs and Masland, solved this problem by using a transgenic mouse strain in which only a few members of the resident astrocyte population express GFP so they could be observed in isolation. They studied astrocytes of the optic nerve, the corpus callosum, and the cortical gray matter. Unexpectedly, they found a multistage remodeling of the fibrous astrocytes. First, they retract and thicken their long processes. In an intermediate stage, the astrocytes appear to migrate. Finally, they re-extend long processes into an unstructured and overlapping fibrillary network, the final scar. These events occur in damaged white matter. This is different from the behavior of protoplasmic astrocytes in gray matter, previously thought to be canonical, which respect to each others' territories. These studies were published in the *Journal of Neuroscience* in 2010 and set the stage for possible points in the disease process where novel interventions can be directed. Co-authors for this study include Drs. Sun, Masland, Jakobs, and research technician, Ming Lye-Barthel.

OPTIC NERVE REGENERATION

Like most neural tissues in the adult central nervous system, the optic nerve cannot regenerate appreciably once injured. Nonetheless, because the optic nerve is readily accessible, it is one of the standard laboratory models in neuroregenerative research. One of the ultimate goals of ophthalmology—and the entire field of neurobiology—is to uncover the mechanisms of optic nerve regeneration.

Overcoming barriers to optic nerve regrowth

Axons in the central nervous system can potentially re-grow after injury, but this normally happens only in the early stages of development. Dong Feng Chen, MD, PhD, discovered that during development, optic nerve cells lose neuroregenerative abilities around the time they stop expressing Bcl-2, a regulator of cell survival. This also coincides developmentally with the maturation of astrocytes, which are cells that form scars around damaged nerves and prevent regrowth. Dr. Chen and colleagues found that by inhibiting astrocytes and inducing Bcl-2 expression, they could stimulate regrowth in severed optic nerve fibers. More recently, Dr. Chen and colleagues used a pharmaceutical approach to promote optic nerve regeneration. They tested the effects of two drugs: lithium, which stimulates Bcl-2 expression, and alpha-aminoadipate, which selectively kills astrocytes. While neither drug alone had significant effects on severed optic nerves, in combination they stimulated robust nerve regeneration in adult mice. These results present a novel therapeutic strategy for inducing neural regeneration in the central nervous system.

Ongoing studies in Dr. Chen's laboratory are targeting the remaining barricades to optic nerve regeneration—such as factors that might prevent nerves from elongating or forming functional connections once they reach their targets. Dr. Chen is also identifying novel epigenetic targets in neurodegenerative diseases, and attempting to activate resident neural stem cells in the eye to potentially restore vision after optic nerve damage.

Links between inflammation, degeneration, and regeneration in the optic nerve

In mature optic nerves, inflammation can have very divergent effects. On one hand, inflammation can lead to death of the retinal ganglion cells (RGCs) that form the optic nerve; on the other hand, inflammation can stimulate neuroregeneration to some extent. These phenomena are some of the main research interests of Larry Benowitz, PhD, Director of the Laboratories for Neuroscience Research in Neurosurgery at Children's Hospital and Professor of Surgery and Ophthalmology at HMS.


LARRY BENOWITZ, PhD

In collaboration with Toru Nakazawa, MD, PhD, and Joan Miller, MD, Dr. Benowitz showed how inflammation might mediate the harmful effects of elevated IOP in a mouse model of glaucoma. In the retinas of mice, elevated IOP induced tumor necrosis factor-alpha (TNF-alpha), a major inflammatory molecule. The elevated TNF-alpha activated immune cells called microglia, which in turn killed the oligodendrocyte cells that produce the protective myelin sheath of nerve fibers. These events resulted in the death of RGCs that form the optic nerve. Using an antibody that blocked TNF-alpha action, these investigators and colleagues were able to prevent the RGC death caused by elevated intraocular pressure. Similar protection of RGCs was seen in mice that lacked either the gene that encodes TNF alpha or one of its receptors. This study suggested that inhibition of TNF-alpha function might offer neuroprotection in elevated IOP. Because drugs that block TNF-alpha are already FDA-approved for treating other conditions, this approach presents (*continued on page 109*)


DONG FENG CHEN, MD, PhD

PROFILE SPOTLIGHT

A niche in eye-movement disorders sheds light on the developing nervous system

Dr. Elizabeth Engle, HMS Professor of Neurology and Ophthalmology, and a Howard Hughes Medical Institute Investigator, never expected to land in her current specialized research niche. But deep curiosity and a single patient encounter led her to become the world's primary researcher probing the genetics of strabismus, or misalignment of the eyes.

Her work, blending genetics with neuroscience, has defined a new category of congenital disorders that leave children unable to move their eyes in specific directions. These conditions impair vision and are often socially isolating; the eyes are fixed in abnormal positions, forcing children to hold their heads in odd positions just to see properly.

In 1992, as a neurology resident at Children's Hospital Boston, Dr. Engle met a little boy with droopy eyelids whose gaze was frozen downward. His father and 20 members of his extended family all had similar conditions. New tools had recently emerged in genetics, and Engle wondered if discovering the mutated gene behind the toddler's disorder might explain how he lost his eye control. Over tea one night in the family's home, she learned of another branch of the family with the condition and got permission to contact them. With enough family samples to do genetic studies, Engle realized she needed to make a foray into laboratory research. "I thought there was no way that I could ever run a lab," she recalls. "I didn't have a PhD and was never officially trained in the lab. I didn't even know how to make chemical solutions."

Nonetheless, Dr. Engle talked her way into a research fellowship in Children's Department of Genetics with Louis Kunkel, PhD, and Alan Beggs, PhD. Aided by their mentorship and resources, she identified the location of the gene mutated in the boy's disorder, then defined its neuropathology by conducting an autopsy of an affected family member. Eventually, she traced the boy's disorder to a single amino acid change in a protein called KIF21A, which carries specific cargo to growing nerve fibers. The subtle change apparently left the cargo stranded—leaving two of the boy's eye muscles without cranial nerve stimulation. Modeling the disorder —congenital fibrosis of the extraocular muscles type 1—in mice, Engle's lab is now studying how the mutations disrupt KIF21A's function, and will determine what its cargo is.

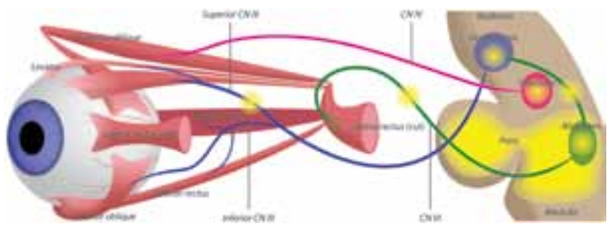
Since that first case, Dr. Engle has searched for other families with unusual congenital eye-movement disorders. She has built a database of more than 1,500 patients, which is large enough to pinpoint many rare genetic defects. She has developed a network of collaborators, allowing her lab to pool cases from all over the world. To date, she's discovered seven different forms of strabismus arising from a variety of genetic errors in brainstem motor neuron development.

Dr. Engle heads a National Eye Institute-designated strabismus diagnostics center at Children's. As a Howard Hughes Medical Institute investigator, she now receives steady financial support that she hopes will help her expand her research and, eventually, translate her discoveries into therapies.

Complex eye-movement disorders also make an ideal model for understanding more common central-nervous-system problems. While the brain contains millions of neurons, making mishaps difficult to identify, the eyes are relatively simple. Just six muscles move the eyeball, controlled by just three sets of cranial nerves, so the number of places things can go wrong is relatively finite.

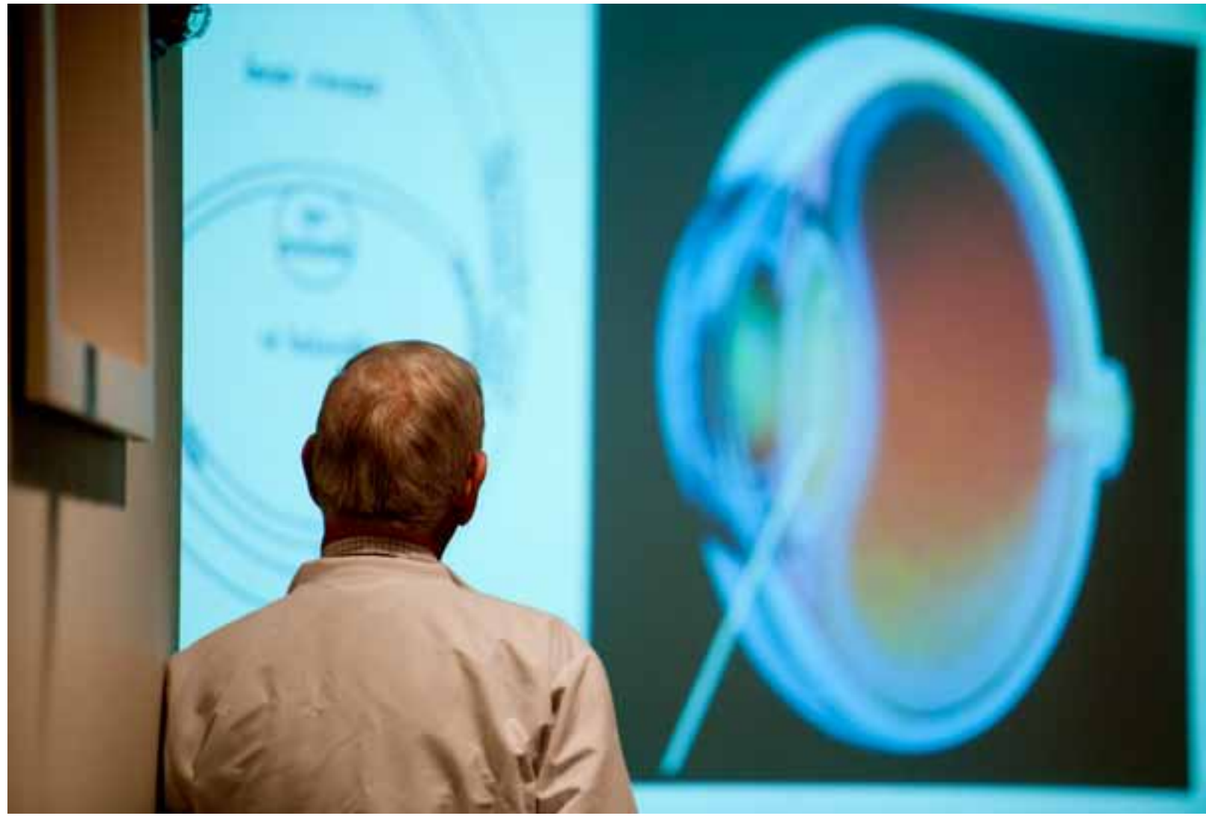
"Think of the U.S. railroad system," Dr. Engle says. "Penn Station, with many trains and switches, is hugely complicated compared to a small Midwestern town with a single train going through daily. Yet understanding how that one train and switch work could help in figuring out Penn Station's complexities."

Excerpted and adapted with permission from the Fall 2008 issue of Vectoronline, a publication of Children's Hospital Boston.



(*continued from page 107*)
a promising neuroprotective treatment for glaucoma. This study was published in 2006 in *Journal of Neuroscience.*

In 2006, Dr. Benowitz and colleagues also discovered that certain immune cells produce a calcium-binding protein called oncomodulin in response to inflammation, and that this protein could actually stimulate regeneration of optic nerves and other neurons of the mature central and peripheral nervous systems. Subsequent studies led by Dr. Benowitz confirmed that oncomodulin was indeed a link between inflammation and axon regeneration in the optic nerve. While examining the molecular mechanisms of oncomodulin in nerve regeneration, Dr. Benowitz and colleagues observed that it activated Mst3b, a signaling protein that could also stimulate regeneration in the optic nerve, as well as in other neurons in both the central and peripheral nervous systems. Because optic nerve regeneration not only requires reactivating axon growth, but also overcoming scar formation and other barriers to nerve regrowth, Dr. Benowitz and colleagues are testing these nerve regrowth factors in combination with other cellular, molecular, and pharmaceutical agents to maximize axon regrowth.



WELCOME TO MEDICAL EDUCATION

"This is a program where learning is valued and the educational experience is tangible. You will learn a vocation, but it differs from many other schools in that HMS is a very academic environment. This is a place where a trainee can approach a faculty member and count on getting help. People coming from other institutions are simply struck by the emphasis we place on medical education."

— Simmons Lessell, MD, Director of Ophthalmic Medical Student Education, Harvard Medical School

Innovate. Train. Mentor. Inspire.

Medical education is integral to the HMS Department of Ophthalmology's mission, and trainees receive the finest ophthalmic education in the world. The department supports full-time faculty in every ophthalmic subspecialty, giving residents a comprehensive grounding in ocular disease and management. Moreover, fellows have the opportunity to gain further clinical expertise or pursue in-depth research in one or more of nine subspecialty areas. Under the exceptional leadership of John I. Loewenstein, MD, HMS Ophthalmology Vice Chair for Medical Education and Director of the HMS Department of Ophthalmology Residency Training Program, recent program innovations have continued to strengthen the department's continuum of medical education. These distinctions culminate in a superb educational experience that offers remarkable depth and breadth to the department's cadre of medical students, residents, and fellows.

The department's greatest asset is its dedicated community of educators. Through their wealth of collective experience, HMS faculty strive to create a supportive and stimulating learning environment at every opportunity: as teachers in the classroom, clinic or lab, and as mentors to students and trainees in their day-to-day interactions. Through close teamwork—and by serving as roles models of effective leadership—their goal is to graduate well-rounded academicians and outstanding clinician scientists who become tomorrow's leaders in ophthalmic medicine, science and education.

SETTING STANDARDS FOR MEDICAL STUDENT EDUCATION

Within the ophthalmology community, there is general consensus of a need to improve the quality of ophthalmic education for medical students, residents, and primary care physicians. Even so, statistics show that ophthalmic education has fallen victim to tightening budgets and shifting priorities in many academic medical schools in the United States. According to a 2004 survey by the Association of University Professors in Ophthalmology, only 30 percent of medical schools nationwide require a formal ophthalmology rotation[1]. Because physicians in many surgical and medical specialties often need to perform eye exams—especially if they are to appropriately manage and triage patients who have ophthalmic complaints—this lack of formal ophthalmic training is of grave concern.

Diverging from this unsettling trend, the HMS Department of Ophthalmology continues to hone its medical student education program. In recent years, major innovations have been implemented, largely due to efforts championed by Simmons Lessell, MD, HMS Director of Ophthalmic Medical Student Education, and Deborah Jacobs, MD, Director of the Core Medicine Clerkship for Harvard Medical School students. Today, the program's revitalized core and elective curriculum emphasizes a dynamic, integrated format that combines didactics with hands-on clinical and research training under a mentor's watchful eye. Core requirements begin in the 2nd year of medical school, when students learn to perform the basic eye exam and use the direct ophthalmoscope in a small-group setting. During their 3rd year internal medicine rotation, students directly engage in clinical activity.

Augmenting these activities, a revitalized Introductory Elective teaches fourth year medical students the principles of basic ophthalmology through hands-on clinical instruction, rather than a traditional lecture-based curriculum. This unique, modified apprenticeship system pairs each student with two active ophthalmic clinicians in different subspecialties, both of whom provide student supervision and feedback. During the four-week rotation, students accompany their mentors in a busy outpatient setting, in the operating room, and at conferences. Early in their rotations, students work in tandem with residents in the 24/7 emergency eye department and trauma center.

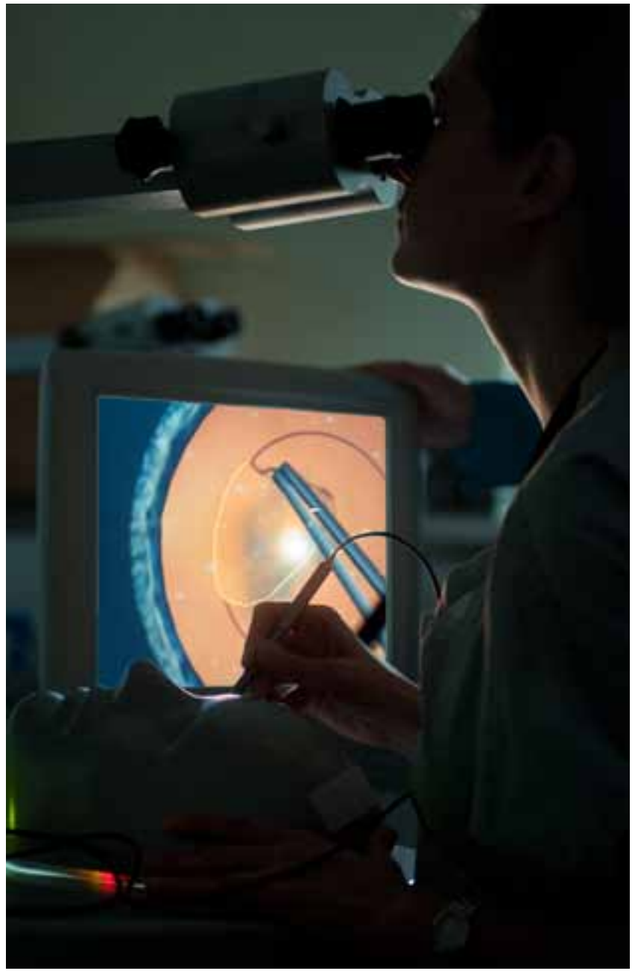
Closely supervised by faculty, students have the opportunity to evaluate, triage, and manage patients, and learn how to use specialized ophthalmic equipment, including the slit-lamp biomicroscope, the tonometer and the ophthalmoscope. Students are also loaned a set of basic ophthalmology textbooks and encouraged to attend Grand Rounds and department lectures to reinforce their training. Faculty guidance and feedback throughout the rotation is an important part of the learning process. A pediatric ophthalmology elective is also available at Children's Hospital Boston for interested students, and directed by Ophthalmologist-in-Chief, David Hunter, MD, PhD.

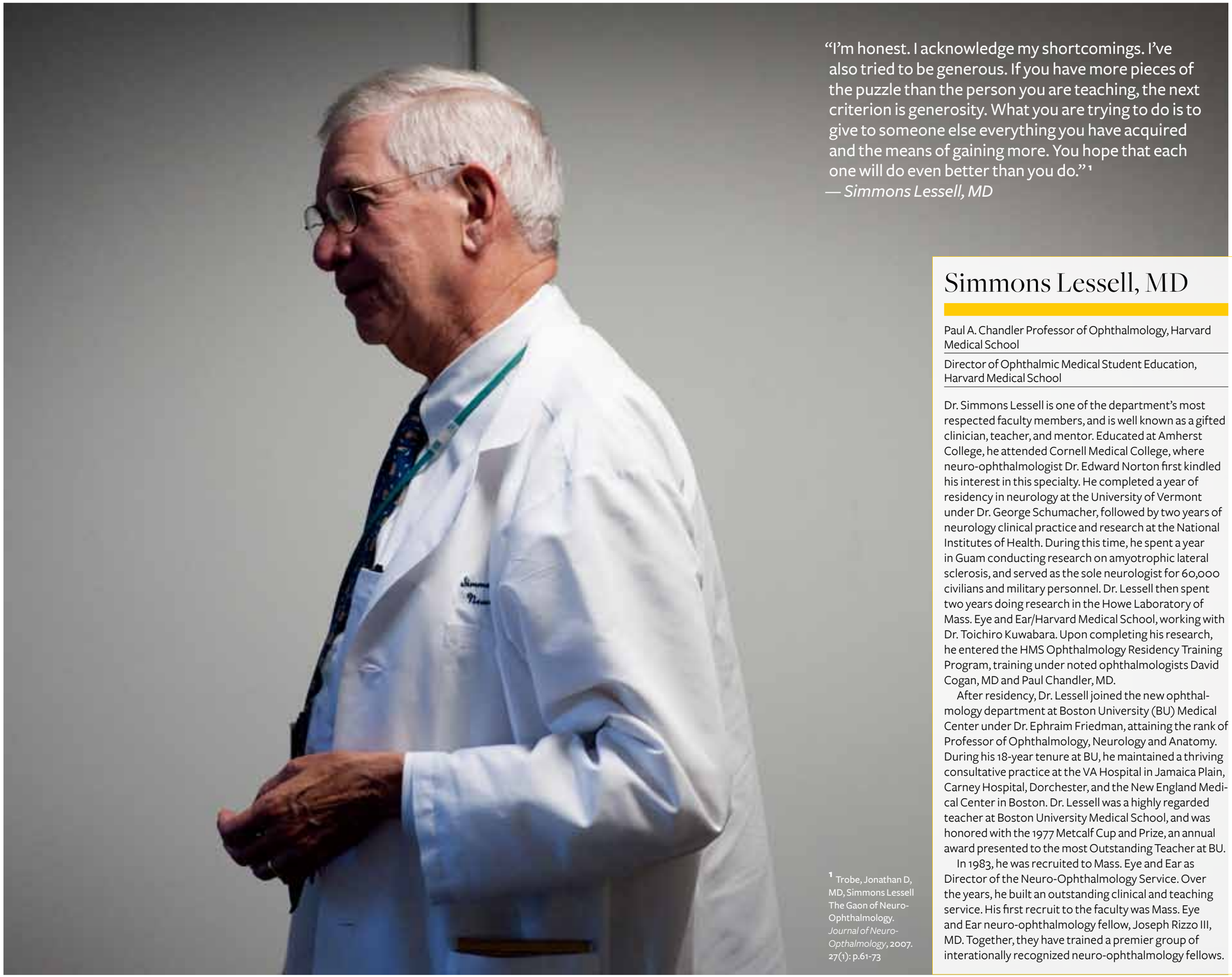
Students who satisfactorily complete the Introductory Elective may choose to take a four-week minimum Advanced Ophthalmology course. At this level, more than 30 electives representing a robust, cross-section of ophthalmic subspecialties are open to students who wish to participate in a focused clinical or laboratory investigation. Students may choose from many exciting areas of study. Some examples include:

- Pathogenesis of age-related macular degeneration (wet or dry)
- Antibiotic resistant bacterial infection
- Human and molecular genetics research with an emphasis on understanding the role of genes in the development of glaucoma
- Behavioral and imaging research to assess visual impairment and monitor progression of retinal diseases
- Diseases of the surface of the eye, including infections and dry eye diseases
- Glyobiology – an expanding field at the forefront of the biomedical sciences that studies the structure and function of the carbohydrate chains (or glycans) present in all living organisms.
- Ocular immune privilege and the pathogenesis of autoimmune uveitis
- Visual functions and developing technologies for visual rehabilitation

According to Dr. Lessell, modified apprenticeship electives excite students about the principles of ophthalmology through "real-life" clinical and research exposure and one-on-one faculty guidance. Students gain first-hand knowledge of the field, giving them an opportunity to decide whether or not ophthalmology is an area of medicine they would like to pursue. Elective rotations also provide excellent training for students who may choose a "sister" specialty such as neurology or neurosurgery. Program feedback from medical students has been highly positive, with approximately 30 students choosing an Introductory Elective each year.

Today, about 1 in 6 ophthalmology department chairs in academic institutions across the U.S. and Canada conducted postdoctoral training at HMS.





"I'm honest. I acknowledge my shortcomings. I've also tried to be generous. If you have more pieces of the puzzle than the person you are teaching, the next criterion is generosity. What you are trying to do is to give to someone else everything you have acquired and the means of gaining more. You hope that each one will do even better than you do."[1]
— Simmons Lessell, MD

[1] Trobe, Jonathan D, MD, Simmons Lessell The Gaon of Neuro-Ophthalmology. *Journal of Neuro-Opthalmology*, 2007. 27(1): p.61-73

Simmons Lessell, MD

Paul A. Chandler Professor of Ophthalmology, Harvard Medical School

Director of Ophthalmic Medical Student Education, Harvard Medical School

Dr. Simmons Lessell is one of the department's most respected faculty members, and is well known as a gifted clinician, teacher, and mentor. Educated at Amherst College, he attended Cornell Medical College, where neuro-ophthalmologist Dr. Edward Norton first kindled his interest in this specialty. He completed a year of residency in neurology at the University of Vermont under Dr. George Schumacher, followed by two years of neurology clinical practice and research at the National Institutes of Health. During this time, he spent a year in Guam conducting research on amyotrophic lateral sclerosis, and served as the sole neurologist for 60,000 civilians and military personnel. Dr. Lessell then spent two years doing research in the Howe Laboratory of Mass. Eye and Ear/Harvard Medical School, working with Dr. Toichiro Kuwabara. Upon completing his research, he entered the HMS Ophthalmology Residency Training Program, training under noted ophthalmologists David Cogan, MD and Paul Chandler, MD.

After residency, Dr. Lessell joined the new ophthalmology department at Boston University (BU) Medical Center under Dr. Ephraim Friedman, attaining the rank of Professor of Ophthalmology, Neurology and Anatomy. During his 18-year tenure at BU, he maintained a thriving consultative practice at the VA Hospital in Jamaica Plain, Carney Hospital, Dorchester, and the New England Medical Center in Boston. Dr. Lessell was a highly regarded teacher at Boston University Medical School, and was honored with the 1977 Metcalf Cup and Prize, an annual award presented to the most Outstanding Teacher at BU.

In 1983, he was recruited to Mass. Eye and Ear as Director of the Neuro-Ophthalmology Service. Over the years, he built an outstanding clinical and teaching service. His first recruit to the faculty was Mass. Eye and Ear neuro-ophthalmology fellow, Joseph Rizzo III, MD. Together, they have trained a premier group of interationally recognized neuro-ophthalmology fellows.

In 2004, Dr. Lessell retired as Director of the Neuro-Ophthalmology Service, and was appointed Director of Ophthalmic Medical Student Education for Harvard Medical School. During his tenure, he has transformed the HMS ophthalmic curriculum by radically redesigning the elective program to emphasize faculty mentorship, conference participation, and emergency room training. He is a master at leading weekly Grand Rounds, and has gained nearly legendary status for his keen insight and quick wit during his presentations.

Dr. Lessell ranks among the top neuro-ophthalmologists in the world, and is frequently sought for consultation by patients and physicians in the U.S. and abroad. During his career, he received RO1 funding from the National Institutes of Health for 13 consecutive years, an objective indicator of his deep intellect and prolific contributions to his field. His depth of knowledge and clinical insight are unmatched, even while he maintains an approachable bedside manner and endearing sense of humor. He demands the best from his residents and fellows, and makes it his personal mission to improve their analytic and diagnostic skills. In describing Dr. Lessell, one resident stated: "To spend a [clinical session] with Dr. Lessell is to see the rare example of an ophthalmologist taking a thorough history and performing a complete exam. In the age of technicians, support staff, and shortcuts, Dr. Lessell knows only to do things completely and accurately himself."

Dr. Lessell embodies the attributes of his teacher, Dr. Chandler, as a physician who exemplifies the highest standards of teaching and patient care. He received the Outstanding Teacher Award in 2004, and in 2006 he was honored as a Distinguished Alumnus at the HMS Department of Ophthalmology Annual Meeting. In 2006, when the Department of Ophthalmology completed funding for the Paul A. Chandler Professor of Ophthalmology, Dr. Lessell was named the first incumbent, reflecting a lifetime of major accomplishments and unparalleled excellence in academic medicine. Dr. Lessell has authored over 200 publications, chapters and reviews, and serves on the editorial board of two premier peer-reviewed journals, *Archives of Ophthalmology* and *Journal of Neuro-Ophthalmology*. At 78 years of age, he remains busy with clinical practice, teaching, and educational administration.

THE HMS RESIDENCY PROGRAM: TRAINING OPHTHALMOLOGISTS, TURNING OUT LEADERS

The HMS Department of Ophthalmology Residency Training Program, directed by John Loewenstein, MD, and Associate Director, Carolyn Kloek, MD is ACGME accredited and ranked by *Ophthalmology Times* as one of the top five programs in the country. With the program's stellar reputation, securing one of the department's eight junior residency slots is highly competitive. Each year, the program attracts an average of 450 elite physician applicants from around the globe.

Mentored by some of the finest educators in ophthalmology, residents receive superb comprehensive and subspecialty training. Many faculty members are renowned internationally for their specialized expertise in ocular melanoma, macular degeneration, retinal degenerations, keratoprosthesis, diabetic eye disease, ocular surface disease, glaucoma, ocular genetics, amblyopia, and ocular pathology. In this rich and dynamic teaching environment, our gifted academicians and clinician scientists nurture, inspire, and challenge residents at every turn while carefully balancing the needs and safety of their patients. Residents complete this synergy by bringing vital contributions, energy, and insight to bear across the department.

Residents work closely with junior and senior faculty to pursue novel scientific and clinical investigations; their efforts often lead to publication of scholarly papers in peer-reviewed journals. Residents also give presentations at national meetings and conferences such as Association for Research in Vision and Ophthalmology (ARVO) and American Academy of Ophthalmology. In 2011, 70 percent of HMS ophthalmology residents were invited to present at ARVO's annual spring meeting.

HMS Department of Opthalmology national rankings

U.S. News & World Report
#4 "America's best hospitals" (2011–12)

Ophthalmology Times
#5 "Overall best program"
#3 "Best research program" (2010–11)

BROAD PATIENT EXPOSURE

With a strong emphasis on leadership development, the residency program is structured to give trainees broad patient exposure and increasing responsibility during their three years of training. Residency training is firmly integrated into all aspects of patient care so that trainees gain expertise in diagnosing and treating an extensive array of ocular conditions.

Residents develop finely tuned surgical and clinical skills as they rotate through the comprehensive and subspecialty programs of our world-class HMS affiliates, including Mass. Eye and Ear, Massachusetts General Hospital, Children's Hospital Boston, Beth Israel Deaconess Medical Center, and the VA Boston Healthcare System. Residents also provide inpatient consultations and 24/7 emergency eye care and trauma coverage to patients at Mass. Eye and Ear, and many Harvard-affiliated hospitals. Additional clinical and surgical experience is gained through senior rotations at the Togus VA in Maine and elective rotations at Aravind Eye Hospital in India.

With 11 affiliate and partnering institutions, HMS's broad-based organizational structure brings tremendous educational value to our residency program. Diverse patient populations give residents exposure to a myriad of pathologies and the opportunity to provide highly specialized care to patients both young and old. Residents directly benefit from the international reputations of our faculty; patients come from around the world seeking specialized care, and residents work in tandem with faculty to diagnose and treat some of the most difficult and unusual ocular pathologies. Each affiliate setting is unique, and residents gain valuable insights from the varied philosophies of treatment and surgical techniques of individual institutions and their faculty.

HMS resident graduate statistics

A Five-Year Review: Academic Years 2007–2011

97% seek fellowship training

57% choose HMS fellowships

60% pursue academic careers after fellowship

24/7 Emergency Department

The Mass. Eye and Ear Emergency Department (ED) is one of only three dedicated eye facilities in the country, and New England's only specialized referral center for eye trauma. This busy facility handles an average of 12,000 patient visits each year, and provides a tremendously valuable teaching environment for residents, complementing their already robust clinical exposure. During ED rotations, junior residents learn to function independently and manage the medical and surgical care of patients with various ocular pathologies, conditions, and injuries. By year three, senior residents perform open-globe repairs on patients under the supervision of the Chief Resident - who also serves as Director of the Eye Trauma Service — and supervise junior residents in minor procedures.

Aravind Eye Hospital, India

During senior year, most residents choose to do an international elective at the Aravind Eye Hospital in India. This unique opportunity allows HMS ophthalmology residents to broaden their clinical and surgical experience in an international setting.

At Aravind, residents witness an impressive international health care system that delivers high-quality eye care to a large volume of patients in a cost-efficient manner. Residents have the opportunity to participate in the cornea, glaucoma, and uveitis clinics with exposure to end-stage inflammatory and infectious diseases that are uncommon in the United States. Residents also spend half of each day in the operating room, and serve as primary surgeons for cataract surgeries (both extra-capsular and phaco-emulsification).

HANDS-ON LEARNING

Numerous program innovations have created a more effective learning environment for trainees. State-of-the art training tools and technology enable residents to fine-tune their surgical skills outside of the operating room.

Progressive surgical curriculum

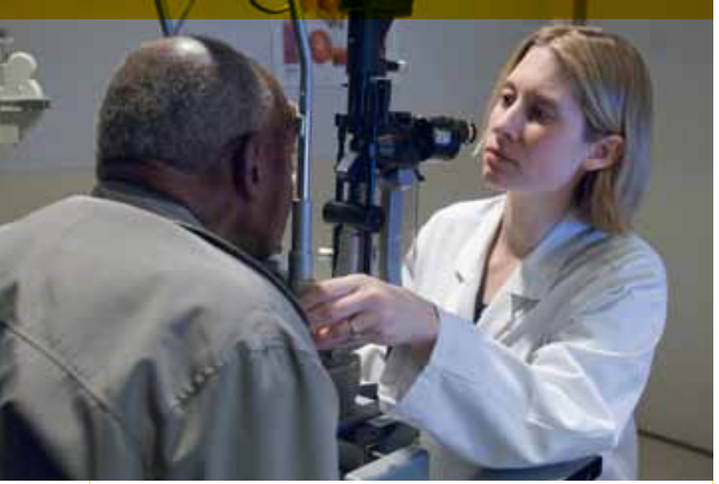
Beginning in the first year of residency, a progressive surgical curriculum provides a graduated learning process for trainees, as well as greater surgical exposure with a cataract rotation in Year 2. "We're always looking at ways to give our residents the best experience possible," says Carolyn Kloek, MD,

HMS residency highlights

Year 1: (PGY-2)
- Ophthalmology fundamentals gained through daily lectures, core clinical rotations, and "high-value" exposure in the Emergency Department and Eye Trauma Service
- Observe in the operating room and serve as primary surgeon for several operative cases

Year 2: (PGY-3)
- Refine exam, diagnostic, and surgical skills rotating through subspecialty clinics
- Independently consults for HMS affiliates (w/attending supervision)
- Emphasis on surgical skills (oculoplastics, strabismus, vitreoretinal, and cataract surgeries)
- Perform intravitreal injections, as well as retina and glaucoma laser procedures

Year 3: (PGY-4)
- Refine knowledge, judgment, technical skills, and professional maturity
- Intensive ophthalmologic surgical training in cataract, glaucoma, anterior segment, open-globe, and retina surgeries
- Elective surgical rotation at Aravind Eye Hospital, India



Carolyn E. Kloek, MD

Associate Director, Residency Program in Ophthalmology, Harvard Medical School

Instructor in Ophthalmology, Harvard Medical School

Editor-in-Chief, *Digital Journal of Ophthalmology*

Dr. Carolyn Kloek is a comprehensive ophthalmologist at Mass. Eye and Ear who provides consultation and treatment for cataracts, eye injuries, and various other ocular disorders. A *magna cum laude* graduate of Dartmouth College, Dr. Kloek received her MD from Harvard Medical School and completed an internship in Internal Medicine at Brigham and Women's Hospital. Dr. Kloek completed her ophthalmology residency at Mass. Eye and Ear, where she served as Chief Resident.

Dr. Kloek is actively involved in medical student and resident education. She routinely serves as a lecturer at HMS, and is a preceptor for medical students rotating in ophthalmology at Mass. Eye and Ear. As Associate Director of the HMS Residency Program in Ophthalmology, Dr. Kloek assists residency program director, Dr. John Loewenstein, in the administrative leadership of the program, and serves on several HMS committees, including the Graduate Medical Education Committee and Residency Selection Committee. She developed and implemented the progressive Harvard Ophthalmology Residency surgical curriculum to improve the learning experience for trainees. She also spearheaded a 360-degree evaluation system for HMS residents. She continues to teach ophthalmology residents in both the clinic and operating room; in 2008, Dr. Kloek was selected by Harvard ophthalmology residents to receive the HMS Teacher of the Year Award, reflecting her outstanding mentoring skills and efforts in medical education.

Dr. Kloek's research activities complement her dedication to teaching and focus on advancing ophthalmology education. She served as co-Principal Investigator for a study assessing residency experience for the progressive surgical curriculum, which was presented at the 2011 annual Educating the Educators meeting. For Academic Year 2009-10, she received the HMS Shore Fellowship to support her contributions to develop the innovative Mass. Eye and Ear Cataract Surgery Mentor. She is also collaborating with faculty at the Division of Sleep Medicine at Brigham and Women's Hospital to investigate the effect of sleep deprivation on the learning of surgical skills on a simulator. Recently, she was honored with a prestigious Harvard Medical School Rabkin Fellowship in Medical Education to develop a standardized online ophthalmology curriculum designed to enhance the training of U.S. medical school students, and to prepare graduates to more effectively triage and manage a wide variety of ophthalmic diseases. The case-based program will feature a series of guided interactive modules on topics covered in *Basic Ophthalmology*, a textbook published by the American Academy of Ophthalmology.

"Our goal with the Mass. Eye and Ear Cataract Surgery Mentor is to minimize clinical risk while providing residents with the best "real-life" experience possible for learning cataract surgery. We fully expect this virtual training tool to boost skills and confidence, and to better prepare residents for their experience in the operating room." *—John Loewenstein, MD*

Associate Director of the Residency Program. In collaboration with Dr. Loewenstein and Lynn Poole Perry, PhD, MD, Dr. Kloek has worked over the last several years to enhance the curriculum. "These enhancements redistribute the traditional third-year 'blast' of surgical training so that residents get surgical exposure much earlier in their careers," explains Dr. Kloek. "Gradual exposure allows time to reinforce core surgical principals and to build key skills that trainees can scale up over time. It's a more effective way to learn."

Another program improvement that complements clinic experience is a structured schedule of customized wet lab sessions, which are formally proctored by faculty and fellows. In 2009, the department also invested in a state-of-the-art wet lab that is equipped with the most advanced teaching tools available. Trainees can now hone their surgical skills 24/7 using an Eyesi Virtual Reality Simulator and other high-tech training tools.

Step-wise phacoemulsification

Drs. Loewenstein and Kloek have also introduced modular stepwise training of phacoemulsification surgery beginning in Year 2. This has made the intricacies of cataract surgery, one of the most difficult and complex to master, easier for second-year residents to grasp. In lieu of having residents perform the procedure from start to finish for each surgery, they execute individual steps (such as lens insertion) for every case that day guided by the attending physician. By the end of their 7-week cataract rotation, residents have mastered every step of phaco. A recent survey of trainees indicates that the new stepwise model helps them learn more efficiently, improves recall of surgical steps, and creates a more relaxed environment for residents and attendees. The new model has also led to an increase in cataract surgery numbers in Year 2, and better prepared senior residents for busy cataract rotations at the Togus VA and, if elected, Aravind Eye Hospital.

VIRTUAL SUCCESS:

The Mass. Eye and Ear Cataract Surgery Mentor

Cataract surgery—one of the most frequently performed eye surgeries in the United States—is notoriously difficult to master. Residents typically train in a "wet lab" scenario before moving directly to live patients. Making this leap can potentially cause surgeons-in-training and their teachers a good dose of anxiety. Moreover, finding good teachers and patients who will agree to let a resident participate in their surgery so they can gain real-life training experience can be challenging. Several years ago, HMS Residency Program Director John Loewenstein, and Bonnie Henderson, MD, FACS, former Director of Comprehensive Ophthalmology and Cataract Consultation Service at Mass. Eye and Ear, set out to find a better way to ameliorate some of these hurdles and better prepare residents for the operating room."

The "better way" that emerged was the Mass. Eye and Ear Cataract Surgery Mentor, a virtual reality training tool being developed by Drs. Henderson and Loewenstein. Adam Neaman, PhD was instrumental in the conception of the program, and several other Mass. Eye and Ear cataract surgeons have made significant contributions. The simulator contains a screen that shows surgical animations and videos of real surgical examples, complete with expert discussions on details of the surgery. There is also a help and reference section, and at any given moment, questions may pop up that are specific to that step in the surgery. The self-guided, interactive program not only anticipates typical questions that a beginner would ask, but also allows users to access a full reference section.

Text options for actions in the surgery appear during the training session; these actions are then illustrated on the central video portion. If the surgeon-in-training makes a serious error, the program provides immediate feedback in the form of an expert video, explaining how the problem occurred, what to do to fix it, and how to avoid making the same mistake again. This essentially allows new surgeons to master life-like surgery without risking injury to a patient. Moreover, the computer simulation tool allows residents to practice surgery at any time, even without a teacher or instructor present. This promotes more rapid learning while drastically reducing a host of issues, such as cost, management, and scheduling. "We want to make sure that future ophthalmologists can be taught in a safer and more effective manner," says Dr. Henderson.

To test the effectiveness of the Mass. Eye and Ear Cataract Surgery Mentor, Drs. Henderson, Loewenstein and colleagues conducted a prospective, multi-center, single-blind, controlled trial using ophthalmology residents from seven academic institutions. The residents received traditional surgical training along with either written teaching materials or training using the Mass. Eye and Ear Cataract Surgery Mentor. The residents who utilized the computer simulation tool scored significantly higher on post-training tests, and rated the tool more enjoyable to use and more likely to be used repetitively. This study, published in the February 2010 issue of the journal *Ophthalmology*, demonstrates that the Mass. Eye and Ear Cataract Surgery Mentor could be an effective supplement to traditional teaching.

"Our goal with the Mass. Eye and Ear Cataract Surgery Trainer is to minimize clinical risk while providing residents with the best "real-life" experience possible for learning cataract surgery," says Dr. Loewenstein. "We fully expect this virtual training tool to boost skills and confidence, and to better prepare residents for their experience in the operating room." The developers are now exploring licensing the program that would make it accessible to training programs and practitioners nationwide.

CAROLYN E. KLOEK, MD

SPOTLIGHT:

THE EXPERIENCE OF ONE HMS RESIDENT

Rajesh Rao, MD

"The retina has long fascinated me. Here, a thin sheet plastered to the back of the eye seethes with millions of bustling, firing neurons that translate light to information we use to understand and interact with the world around us."
—Dr. Rajesh Rao, HMS Department of Ophthalmology Resident, class of 2011

Determined to improve the lives of patients through scientific and clinical innovation, Dr. Rajesh Rao was drawn to the HMS Department of Ophthalmology's Residency Training Program for a number of reasons: high-caliber programs, broad clinical exposure, and extensive research and educational opportunities—all delivered by a world-class faculty mostly comprised of clinician scientists. Dr. Rao was chosen from an impressive pool of more than 500 applicants to fill one of eight highly competitive residency slots for the Class of 2011.

Dr. Rao graduated this spring, and by his account, the HMS residency program exceeded his expectations—not only in gaining exposure to wide-ranging subspecialty areas and patient populations, but also in opportunities to pursue novel research. In the laboratory of Dong Feng Chen, PhD, an internationally renowned Schepens researcher, Dr. Rao had a rare opportunity to carry out independent investigations in the burgeoning new field of retinal epigenetics. Dr. Chen underwrote the expense of his experiments and provided generously of her time and other resources. Dr. Rao's original research yielded several presentations and a publication in the December 2010 issue of the journal *Investigative Ophthalmology and Visual Science*. It also garnered him a Retina Research Foundation Award at the 2011 Association for Research in Vision and Ophthalmology meeting. Dr. Rao's research has yielded so much promise that Dr. Chen has continued this new direction of investigation in her laboratory.

Dr. Rao considers clinical and surgical mentoring to be one of the great strengths of the HMS residency program. As he progressed in his residency, Dr. Rao was entrusted with gradually increasing roles in clinical eye care. He also mastered increasingly complex and delicate surgical procedures through the newly implemented surgical training block for second-year residents, complete with state-of-the art training equipment, including an Eyesi virtual reality simulator. In every facet of training—clinic, classroom, lab, OR, and ED—his mentors provided an exceptional learning environment.

In Dr. Rao's final year of residency, the line between trainee and ophthalmic professional continued to blur as he fine-tuned his clinical, surgical, and leadership skills. Like his colleagues, he often began his day with an early meeting or Grand Rounds presentation. He gained experience in patient advocacy, ethics in patient practice, and issues with transparency and conflict-of-interest, underscoring the department's firm commitment to providing a leadership-driven education. At least once a month, he typically presented clinical or research topics at one of several scheduled conferences, rounds or symposia. Despite a brimming schedule, Dr. Rao continued to pursue his sophisticated and productive investigative work at Schepens.

From the start of residency, he found a supportive and congenial cohort among his fellow HMS trainees. This support network created a sense of community for Dr. Rao and other trainees—many of whom are far from home, family, and friends, and all juggling heavy workloads with rigorous training demands. He credits the support of his peers as one of the most important factors in his success.

"Dr. Rao enjoyed a stellar career at HMS," notes residency program director, John Loewenstein, MD. "He has a deep-seated appreciation for the challenges and complexities of retinal pathophysiology, and relishes the opportunity to contribute his energy, expertise, and compassion to improve the lives of his patients. I know he will contribute immensely to his chosen field of retinal medicine and science."

Like nearly all of his residency classmates, Dr. Rao has parlayed his exceptional skills and considerable knowledge into fellowship training so he can delve more deeply into the nuances of ophthalmic retinal diseases. For the next two years, he will be training as a vitreoretinal fellow at Barnes Retina Institute (BRI) at Washington University in St. Louis. Ultimately, he aims to have an academic career that combines clinical practice, teaching, and research – the three-fold mantra of a clinician scientist. In his view, the possibilities are enticing. "The retinal field is poised to benefit from recent pharmacological, regenerative, and surgical innovations that may soon cure retinal disease, not just slow disease progression," he says.

For Dr. Rao, the promise of HMS's residency program is all about putting theory into action, working with world-class teachers and mentors, pursuing original research, and utilizing his clinical training to treat a breadth of patients and pathologies. "Doctors typically help one patient at a time," he notes. "However, as a clinician scientist, you can potentially help thousands more by deciphering the critical mechanisms of a disease." As a fellow at BRI, Dr. Rao will continue to pursue his passion—refining his skills and knowledge that one day may punctuate a new generation of discoveries.

As a clinician scientist, his journey is just beginning.

A DAY IN THE LIFE

CLINICAL FELLOWSHIP PROGRAMS OFFER UNRIVALED OPPORTUNITIES

The Ophthalmology Fellowship Programs of Harvard Medical School are comprised of nine clinical subspecialty programs at several affiliate hospitals. Together, these individual programs pursue a single goal: to train superb specialists in ophthalmology. These programs not only prepares fellows to evaluate and manage the most difficult clinical cases, but also provides an atmosphere that fosters professional development through teaching and research. This unrivaled breadth of opportunity serves to mold the next generation of educators and leaders in the field of ophthalmology.

Organization and facilities

The following clinical fellowship programs are available within the Harvard Medical School Department of Ophthalmology:

- Cornea, Refractive Surgery, and External Disease Fellowship
- Glaucoma Fellowship
- Oculoplastic and Reconstructive Surgery Fellowship
- Ophthalmic Pathology Fellowship
- Neuro-Ophthalmology Fellowship
- Ocular Immunology and Uveitis Fellowship
- Vitreoretinal Fellowship
- Medical Vitreoretinal Fellowship
- Pediatric Ophthalmology and Adult Strabismus Fellowship

All eligible fellowship programs are either currently certified or pending certification by the Association of University Professors of Ophthalmology. Of the 30 clinical fellows enrolled in the Ophthalmology Clinical Fellowship Program for Academic Year 2011-12, 24 are based at Mass. Eye and Ear, three are based at the Beetham Eye Institute of Joslin Diabetes Center, and three are based at Children's Hospital Boston. These fully equipped and state-of-the-art institutions enable fellows to master innovative diagnostic and surgical techniques.

Exceptional clinical experience

During training, fellows will care for patients with a wide variety of complex ocular conditions, advancing their clinical skills for a diverse array of ophthalmic disorders. Fellows participate in all aspects of patient care including routine examinations, patient consultation, emergency and on-call services, and surgery. The devotion to teaching and mentoring of our accomplished faculty members provides a rich academic and clinical experience for fellows.

Unparalleled research opportunities

The HMS Department of Ophthalmology Fellowship Training Program strives to complement its extensive clinical fellowship experience with academic stimulation and research. Abundant and unparalleled opportunities for clinical collaborations exist at several HMS affiliate hospitals and other universities in the Boston area. Ophthalmology clinical fellows who demonstrate strong research potential are given careful consideration for competitive career development grants that offer junior faculty status and protected time for research.

Excellence in education

Historically, HMS Ophthalmology fellows have played an active role in the education of residents and medical students. In addition to serving as attending staff in the Emergency Department, fellows help organize conference cases, write didactic reviews for ophthalmology textbooks and journals, and deliver presentations to residents, students, and other fellows. This tradition of excellence in education not only enriches the academic experience of ophthalmology fellows, but is also appreciated and recognized by their trainees. Each year, students and residents honor this tradition of teaching excellence with the Fellow of the Year Award. Fellows are also encouraged to attend and present at national and international meetings, and travel reimbursements and awards are available.

CLINICAL FELLOWSHIP OPPORTUNITIES

Chair, Fellowship Committee, Dean M. Cestari, MD

Cornea, Refractive Surgery, and External Disease Fellowship

Program Director: Reza Dana, MD, MPH, MSc

Founded in 1958 by Dr. Claes Dohlman, the Cornea, Refractive Surgery, and External Disease Fellowship is an intensive one-year program that equips fellows with advanced diagnostic and surgical skills for the entire spectrum of corneal and external eye disorders. Fellows care for a wide variety of patients with complex disorders in the Cornea Service of Mass. Eye and Ear and at nearby Mass General Hospital. Conferences and teaching activities provide forums for ongoing education and collaboration. Numerous graduates of this fellowship go on to serve in positions of clinical and academic leadership throughout the world. An optional second year is offered in cornea research.

Oculoplastic Fellowships

Program Directors: Suzanne K. Freitag, MD and Aaron M. Fay, MD

The Ophthalmic and Orbital Plastic Surgery Service at Mass. Eye and Ear offers three training programs: 1) a two-year Oculoplastic Fellowship that is accredited by the Accreditation Council for Graduate Medical Education (ACGME) 2) a two-year Oculoplastic Fellowship that is accredited by the American Society of Ophthalmic Plastic and Reconstructive Surgeons (ASOPRS), and 3) a one-year Oculoplastic International Fellowship that provides exceptional training opportunities to applicants from underserved areas of the world. Each program has a comprehensive orbital and oculoplastic surgery curriculum that includes clinical and surgical care, academic research and writing, and cosmetic surgery. Research is mandatory in these rigorous training programs, and there are many opportunities for interdepartmental collaboration.

Glaucoma Fellowship

Program Director: Louis R. Pasquale, MD

The Glaucoma Fellowship Program is an intense one-year training program conducted at the Glaucoma Service of Mass. Eye and Ear. In this full-service facility, outfitted with state-of-the-art diagnostic and surgical equipment, fellows learn the medical management of glaucoma cases, as well as the pre- and postoperative care of surgical cases. In addition, fellows can explore career development at Mass. Eye and Ear through teaching and research. While 80 percent of the fellow's time is dedicated to patient care, many opportunities for clinical, basic science, and translational research exist in collaboration with investigators of the Howe Laboratory of Mass. Eye and Ear.

Ophthalmic Pathology Fellowship

Program Director: Frederick A. Jakobiec, MD, DSc

The Ophthalmic Pathology Fellowship at Mass. Eye and Ear is an interdepartmental curriculum coordinated between the David G. Cogan Ophthalmic Pathology Laboratory, the Ophthalmic and Orbital Plastic Surgery Service, and the Mass General Hospital Department of Pathology. In the Ophthalmic Pathology portion of the curriculum, fellows receive training in eye anatomy and histopathology. In the Ophthalmic Pathology and Oculoplastics portion, fellows learn to evaluate patients with conditions

Dean M. Cestari, MD

Assistant Professor of Ophthalmology, Harvard Medical School

Chair, Fellowship Committee, Massachusetts Eye and Ear Infirmary

Dr. Dean Cestari is one of the few ophthalmologists worldwide who is board-certified in both neurology and ophthalmology. A graduate of Colgate University in Hamilton, NY, Dr. Cestari received his MD from the Sackler School of Medicine of Tel Aviv University in Israel. He completed an internship in internal medicine and a residency in neurology at New York Presbyterian/Weill Cornell Medical College. After a one-year fellowship in neuro-ophthalmology at Mass. Eye and Ear, Dr. Cestari returned to New York Presbyterian/Weill Cornell Medical College. There, he completed a residency in ophthalmology, serving as Chief Resident in his final year. Dr. Cestari then rejoined the HMS Department of Ophthalmology and Mass. Eye and Ear in 2006 as Instructor of Ophthalmology, and became Assistant Professor in 2008.

Dr. Cestari's primary clinical interests include optic nerve disorders, strabismus, and intracranial hypertension of unknown causes. An integral member of Mass. Eye and Ear's Neuro-Ophthalmology Service, he runs an active medical and surgical practice, performing medical and surgical intervention for adult strabismus and evaluating patients with various neuro-ophthalmic disorders. Also an active clinician-scientist, Dr. Cestari hopes to elucidate the underlying mechanisms of optic nerve disease. His efforts to develop preclinical models and novel neuro-protective strategies for optic neuropathies are supported by a Harvard Medical School Catalyst Grant.

As Assistant Professor of Ophthalmology at HMS, Dr. Cestari is committed to training and mentoring students, residents, and fellows. He has been invited to participate in several training programs, including the Lancaster Course in Ophthalmology and the Kevin Hill Seminar in Ophthalmology. Dr. Cestari is also recognized for his leadership skills. Since 2007, he has served on the Digital Media Committee of the American Academy of Ophthalmology and on the Curriculum Development Committee of the North American Neuro-Ophthalmology Society. At Mass. Eye and Ear, he chairs the Clinical Fellowships Committee and leads the Clinical Fellowship Program, which spans nine sub-specialties.

of the eyelids, conjunctiva, orbit, and periorbital compartments using advanced techniques. This one—to two-year program imparts the skills necessary to rapidly and differentially diagnose rare and complex eye disorders. Alternatively, fellows may choose to complete a one-year program dedicated exclusively to Ophthalmic Pathology.

Neuro-Ophthalmology Fellowship

Program Director: Joseph F. Rizzo III, MD

The Neuro-Ophthalmology Fellowship at Mass. Eye and Ear provides intense training in both ophthalmology and neurology. Fellows learn to evaluate and manage a broad spectrum of neuro-ophthalmic cases, including optic neuritis, ischemic optic neuropathy, various other neurological or neuromuscular conditions that affect the eye, and cases of unexplained vision loss. Working closely with the neurologists and neurosurgeons of Mass General Hospital, fellows provi⁰ de services for inpatients on a regular basis. World-renowned for its strong translational research, the Neuro-Ophthalmology Service of Mass. Eye and Ear also provides cutting-edge research opportunities for fellows in this program.

Ocular Immunology and Uveitis Fellowship

Program Co-Directors: George N. Papaliodis, MD and Lucia Sobrin, MD, MPH

The Ocular Immunology and Uveitis Fellowship, conducted at multiple clinics within Mass. Eye and Ear and Mass General Hospital, is an intensive one-year program that provides advanced diagnostic, therapeutic, surgical, and research training for ocular inflammatory disorders. Various assigned clinics provide the necessary skills for delivering high-quality and comprehensive patient care. Through collaborations with the Rheumatology Department of Mass General Hospital, Ocular Immunology and Uveitis fellows may gain clinical experience in the non-ophthalmic effects of inflammatory disorders. Ample research opportunities are also available at Schepens Eye Research Institute, where ongoing research projects are delineating immunological and inflammatory responses within the eye.

Vitreoretinal Fellowship

Program Director: Shizuo Mukai, MD

Established in 1977, the Vitreoretinal Fellowship is offered through Mass. Eye and Ear's Retina Service, a fully equipped clinical facility with advanced clinical technology. Here, fellows receive comprehensive training in the surgical and medical management of diseases of the retina, vitreous and choroid. The program includes strong components in ocular tumors and pediatric retina. The two-year fellowship provides a uniquely intense clinical experience that allows ample time for academic pursuits. As a result, this program produces vitreoretinal specialists with significant experience in basic or applied ophthalmic research. Many graduates go on to serve as professors of ophthalmology, private-practice retina specialists, retina service directors, and academic leaders.

Medical Retina Fellowship

Lloyd Paul Aiello, MD, PhD

Conducted at the Joslin Diabetes Center, the Medical Retina Fellowship allows exceptional research opportunities along with strong clinical training in the management of diabetic eye disorders. State-of-the-art diagnostic and therapeutic technology is readily accessible in this full-service diabetes eye treatment and research center, which is located in the heart of Boston's Longwood Medical Area. Fellows receive excellent training in the history, diagnosis, and treatment of diabetic retinopathy, and interact daily with internationally recognized experts. In addition to attending diabetes and ophthalmology clinics within the local medical community, fellows also have ample opportunities to participate in national and international meetings.

Pediatric Ophthalmology and Strabismus Fellowship

Program Director: Deborah K. Vanderveen, MD

The Pediatric Ophthalmology and Strabismus Fellowship is a one-year fellowship program conducted at Children's Hospital Boston. The clinical experience includes broad exposure to every aspect of pediatric ophthalmology, including innovative procedures for pediatric oculoplastic surgeries, cataracts, strabismus, and glaucoma. This fellowship also provides comprehensive training for the clinical management of complex adult strabismus. Fellows have access to advanced diagnostic equipment, as well as the broad research activity and academic stimulation of the Longwood Medical Area. Mandatory research projects are conducted under the guidance of the diverse and internationally respected faculty of Children's Hospital Boston.

Community-based clinical fellowships

The Department of Ophthalmology sponsors four additional clinical fellowship opportunities with several distinguished community ophthalmologists who hold part-time academic appointments at Harvard Medical School, and practice privately in the Boston area. As experienced mentors and teachers, they offer trainees an outstanding clinical fellowship experience in the following subspecialties:

Glaucoma Fellowship:
Preceptor: Mark A. Latina, MD (Reading Health Center)

Ocular Immunology and Uveitis Fellowship:
Preceptors: C. Stephen Foster, MD and David Hinkle, MD (Massachusetts Eye Research and Surgery Institute)

Retina Fellowships(2):

- *Preceptors: John J. Weiter, MD, PhD, and Sheldon M. Buzney, MD (Retina Specialists of Boston)*
- *Preceptors: Arnold J. Kroll, MD (Zero Longfellow Place, Charles River Park), Peter L. Lou, MD (Andover Eye Associates), Edward A. Ryan, MD (microsurgical eye consultants), and Tatsuo Hirose, MD (Boston Eye Group)*

PEDRAM HAMRAH, MD

RESEARCH FELLOWS IN OPHTHALMOLOGY

At any given time, the Department of Ophthalmology trains approximately 100 research fellows who represent a new generation of clinician scientists. Integral to the translational work of the department, our research fellows embody the department's focus on bench-to-bedside research.

Research fellows may be actively involved in both the basic science and clinical aspects of translational studies—bridging investigations between the laboratory and the clinic. As a research fellow working with Dr. Reza Dana, Mohammad Dastjerdi, MD, conducted the initial laboratory investigations of bevacizumab for corneal neovascularization; he then tested the antiangiogenic regimen in prospective human studies, and further refined his therapeutic strategies in the laboratory before additional clinical trials. Research fellows like Dr. Dastjerdi are key players in each stage of the translational research process—from experimental design to clinical evaluation to publication and implementation.

In the Department of Ophthalmology, there are also research fellows who work exclusively on human studies; as such, fellows may work with a variety of scientists and clinicians to implement new and innovative interventions. For example, research fellow Andrea Cruzat, MD, worked with Dr. Pedram Hamrah to study the use of *in vivo* confocal microscopy in patients with different corneal pathologies. Their work has revealed many new applications for this technology—greatly influencing ophthalmic research and practice, and further strengthening the Ocular Surface Imaging Center of the Mass. Eye and Ear Cornea Service.

Research fellows may have far-reaching impact that extends beyond the department. The therapeutic regimens designed by Dr. Dastjerdi are now used throughout the world in clinical testing and practice; similarly, the information gained from Dr. Cruzat's research has been central to the growing use of corneal imaging worldwide in both laboratory and clinical investigations. Research fellows also serve as liaisons between multiple groups—not only working with primary investigators, but also with patients, other scientists in different fields, and even pharmaceutical companies. Research fellows in the Department of Ophthalmology thus fill a fundamental niche in the concept of translational medicine—within our department and beyond.

HIGH-VALUE EDUCATION PROGRAMS

A robust didactic curriculum comprises ophthalmology Grand Rounds, symposia, lectures, workshops, conferences, courses, and special events. This structure offers exceptional breadth and depth of discussion for residents, fellows, and faculty. Program offerings span enduring educational venues such as the Lancaster Course in Ophthalmology - now in its 65th year – to the department's new AMD International Symposium, which draws faculty from around the world to discuss emerging trends in AMD research.

International symposia
AMD International Symposium NEW
International Cornea Conference

Ophthalmology Grand Rounds
(CME credit available)

Visiting Professors and Invited Lectures
Paul A. Chandler Visiting Professorship
Cornea Visiting Professor Lecture Series
Ephraim Friedman Lecture
Murphy/Chylack Lecture
Harvard Visiting Professorship & Residents' Course
Boston Ophthalmic Pathology Lecture Series
Pediatric Ophthalmology Visiting Professor Lecture Series
Schepens Distinguished Lecture Series

Special Courses, Workshops, Lectures & Seminars
Macula Conference
Mass. Eye and Ear Resident Lecture Series
Pathology Rounds
Dr. Pei-Fei Lee Lectureship in Ophthalmology NEW
Monthly Cornea Conference
Neuro-Ophthalmology Fall Festival
Annual Harvard Vitrectomy Course NEW
Annual Harvard Intensive Cataract Surgical Training Course
Lancaster Course in Ophthalmology
Weekly VA Journal Club
Weekly VA Surgical Conferences
Molecular Bases of Eye Diseases Course
Cornea Research Seminars and Conferences
AMD Journal Club
Glaucoma Focus Group NEW
Surgical Retina Conference (twice monthly)
Longwood Medical Area Ophthalmology Conferences (monthly, September-June)
New Frontiers in Corneal Disease NEW
Biennial SportVision Conference

Continuing Medical Education
Presentation of the Red Eye (HMS on-line)
Genetics: Macular Degeneration (HMS on-line) NEW

International
Digital Journal of Ophthalmology

Department of Ophthalmology Annual Meeting & Alumni Reunion
Frederick A. Jakobiec Lecture in Ophthalmology
Mariana D. Mead Lecture
Distinguished Alumni Awards and Lectures

HIGHLIGHTS

Ophthalmology Grand Rounds & Visiting Professor Lecture Series at Mass. Eye and Ear, Schepens Eye Research Institute, and Children's Hospital Boston feature more than two dozen lectures each year, including many named or honorary lectures taught by distinguished HMS Faculty and lecturers from around the world. Grand Rounds presentations at Mass. Eye and Ear are moderated by Simmons Lessell, MD, the Paul A. Chandler Professor of Ophthalmology. The department has also utilized videoconferencing to conduct international Grand Rounds with colleagues at Aravind Eye Hospital, and Shanghai Eye and ENT Hospital at Fudan University. More of these collaborative venues are planned for the future.

Annual **Mass. Eye and Ear Vitrectomy Course,** co-developed by HMS Ophthalmology Vice Chair for Medical Education, John Loewenstein, MD, and HMS Assistant Professor of Ophthalmology, Demetrios Vavvas, MD, PhD, is designed exclusively for first-year vitreoretinal surgical fellows. This unique and comprehensive one-day workshop course gives beginning fellows a brief but comprehensive introduction to techniques in vitreoretinal surgery, and prepares them for fellowship OR experience. Consisting of lectures, wet labs, and "dry labs" using virtual reality simulators, the course is taught by renowned faculty from the U.S. and abroad and features a 2:1 student/teacher ratio. Dean Eliott, MD, is course director.

"This meeting was a great platform to engage colleagues from all over the U.S. and abroad, and an opportunity to collaborate with some of the best minds in AMD research. Having speakers on hand from related disciplines added to the breath of discussion and gave the meeting a very unique flavor."
-Anthony P. Adamis, MD, Vice President and Global Head of Ophthalmology, Genentech, Inc.

The Department's first **AMD International Biennial Conference**, launched in 2010, drew a distinguished and diverse group of clinicians and researchers from around the U.S. and abroad to discuss current topics and challenges in AMD research. The interactive format engaged participants in thought-provoking discussion on numerous topics including genetics, inflammation, stem cells and tissue engineering, imaging, animal models, and neurodegenerative disease. Participant feedback spoke to the depth of discussion and meaningful dialogue with colleagues. Plans for the 2012 event are in progress. For more information, visit www.schepens.harvard.edu/amd_symposium


SIMMONS LESSELL, MD

The Biennial Cornea Conference, now in its 27th year, explores current basic and laboratory research developments of the cornea and ocular surface, building links between this exciting new information and the numerous disease entities that afflict this portion of the eye. Two days of lectures typically feature some 30 national and international speakers. Session topics include Ocular Pain and Sensation, Dry Eye and Ocular Surface, Infection, Inflammation and Angiogenesis, Stem Cells and Regenerative Medicine.

The **Annual Harvard Intensive Cataract Surgical Training Course** is the premier cataract surgery training course for ophthalmology residents in the United States. Founded in 2005 by Bonnie An Henderson, MD, FACS the course has been co-directed since 2006 by Dr. Henderson, Sherleen Chen, MD, and Roberto Pineda II, MD. The course attracts distinguished faculty from across the country, and offers a complete preparatory program covering all aspects of cataract surgery to more than 100 second-year residents each year. The course is unique in several respects. First, distinguished faculty from around the country are nominated by their respective department chairs as the best representative cataract surgeon/teacher of their institution so the level of instruction is unsurpassed. Additionally, the course consists of lectures and a 20-station wet lab so residents receive focused instruction on each step of cataract surgery while learning varying techniques from preceptors. The course is also foundation-sponsored and free to participating residents.

The Department of Ophthalmology launched a reinvigorated and expanded **Annual Meeting & Alumni Reunion** in 2011. The 3-day weekend features a new integrated format that combines scientific exchange with networking events and social activities for faculty, alumni and newly graduated residents and fellows. The department's Annual Meeting - launched in 2004—leads the festivities with a day of featured speakers, including the traditional Mariana D. Mead Lecture, and Distinguished Alumni Awards and Lectures. The inaugural Alumni Reunion was dedicated to ten graduating classes from 1961 to 2006, and featured the observations and career achievements of a representative from each five-year anniversary class. Participants were treated to a celebratory dinner, toured new Mass. Eye and Ear facilities, and capped off their weekend with visits to the Museum of Fine Arts and Fenway Park.

DAVID G. COGAN LABORATORY OF OPHTHALMIC PATHOLOGY

The Eye Pathology Service, housed in the David G. Cogan Laboratory of Ophthalmic Pathology, serves as a regional and national diagnostic center, and is an integral part of training physicians and researchers in ocular pathology. The Cogan Laboratory has access to a wide spectrum of ancillary supports, such as flow cytometry, histochemical and immunoperoxidase staining, and electron microscopy facilities. To provide the best care possible, the Eye Pathology Service utilizes a variety of clinical ophthalmology services to assist in diagnosis and case management. The laboratory collaborates extensively with the Massachusetts General Hospital Pathology Service to evaluate challenging cases, provide enhanced diagnostic services,

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- Original research
- Grand Rounds case reports
- Knowledge review
- Patient information
- 2,000 registered users from 100 countries

FOCUS ON FACULTY

Frederick A. Jakobiec, MD, DSc

Henry Willard Williams Professor of Ophthalmology, Emeritus, Harvard Medical School

Professor of Pathology, Emeritus, Harvard Medical School

Director, David G. Cogan Laboratory of Ophthalmic Pathology, Massachusetts Eye and Ear Infirmary

Frederick Jakobiec, MD, DSc, graduated from Harvard College magna cum laude in 1964. He received his MD from Harvard Medical School in 1968 and a DSc from the College of Physicians and Surgeons at Columbia University in 1971. He interned at Stanford University Medical Center, and completed residencies in both pathology and ophthalmology at Columbia Presbyterian Medical Center. His fellowship in ophthalmic pathology was conducted at the Armed Forces Institute of Pathology in Washington, D.C.

Dr. Jakobiec served as Chief and Chair of Ophthalmology at Harvard Medical School/ Mass. Eye and Ear from 1989 until 2002 when, because of ill health, he stepped down. Upon his recovery, he was welcomed back in 2007 as Director of the David G. Cogan Laboratory of Ophthalmic Pathology at Mass. Eye and Ear, where he also serves as an attending surgeon and pathologist. Dr. Jakobiec's clinical and research interests have centered on inflammation and tumors of the eye and surrounding tissues. As a clinician he advanced cryotherapy for conjunctival melanomas and squamous carcinomas as well as concentrated on orbital tumors, particularly lymphomas, and was responsible for a 450 page chapter on orbital diseases in Spencer's four volume definitive textbook on *Ophthalmic Pathology*.

Throughout his career, Dr. Jakobiec has focused much of his efforts on ophthalmology education. He has served a myriad of visiting lectureships and professorships at over 50 institutions and societies, and has been given numerous awards and medals. For ten years, he was the course director for the Lancaster Course in Ophthalmology, which is the largest and most distinguished curriculum for ophthalmology residents. He also participated in the Armed Forces Institute of Pathology Course in Ophthalmic Pathology for two decades. Since 2007, Dr. Jakobiec has served as Program Director for the HMS/Mass. Eye and Ear Clinical Ophthalmic Pathology Fellowship, and offers daily supervision and teaching of residents, clinical fellows, and medical students, rotating in the Ophthalmic Pathology Laboratory.

As director, Dr. Jakobiec continues to enhance eye pathology education in the department. He developed a pathology-based, visiting professor lecture series covering all aspects of ophthalmic pathology. This popular teaching venue, now in its fourth year, attracts speakers who are national leaders in ophthalmic pathology; lectures are open to all HMS and BU Medical School residents and fellows in ophthalmology and pathology. Dr. Jakobiec also conducts Ophthalmic Pathology Rounds for trainees and faculty from all HMS affiliate institutions. Held monthly, the rounds are comprised of a comprehensive review of cases presented by residents and fellows on all subspecialty services. They are offered as "unknowns" to Dr. Jakobiec who covers the clinical features, differential diagnosis, pathological features, and management issues of each case.

In addition to his exceptional clinical and scientific leadership, Dr. Jakobiec has written over 300 journal articles and book chapters, and has edited more than 20 volumes devoted to eye tumors and eye pathology. He was Co-Editor of Albert and Jakobiec's *Principles and Practice of Ophthalmology*, which is now in its third edition and is considered the gold standard of ophthalmology reference texts.

train residents and fellows, and pursue clinico-pathology research projects.

Founded by Benjamin Joy Jeffries in 1868 and dedicated to David G. Cogan in 1982, the Cogan Laboratory is one of the oldest ocular pathology facilities in the United States. Starting as a simple cabinet that held pathological specimens and drawings, the Cogan Laboratory has grown to include an extensive slide collection, an eight-head teaching microscope, digital photography capabilities, and numerous reference books. Future enhancements include acquisition of a twelve-headed microscope, a plasma screen for viewing slides by large groups, conferencing abilities, and TeleMed sessions.

Frederick Jakobiec, MD, DSc, Director of the Cogan Laboratory, has been preceded in this role by a distinguished list of directors including Drs. Frederick Verhoeff, David Cogan, Taylor Smith, Daniel Albert, and Thaddeus Dryja.

Dedicated to every facet of their work, faculty receive first-rate and well-deserved support from Department of Ophthalmology executive leaders. Equally requisite support comes from Jeffrey S. Flier, MD, HMS Dean, Faculty of Medicine, and the leadership of HMS affiliate institutions. Since taking the helm in 2003, HMS Ophthalmology Chair Joan Miller, MD, has championed a progressive and rewarding 21st century workplace environment for HMS faculty While these actions require a substantial investment of resources and leadership, Dr. Miller anticipates that future returns—in the form of advances in "personalized" patient care, accelerated research and discovery, an increasingly collaborative learning environment, and top-notch faculty recruitment—will be well worth the investment. Some of these newest efforts have led to:

- New funding & mentoring supports
- A streamlined promotion and reappointment track
- Expanded programs for professional development
- A faculty mentorship program
- Establishment of five fully funded HMS professorships in the last two years
- Gender-neutral policies that promote women to leadership roles
- Numerous venues for professional recognition

A few of these efforts are highlighted in the following pages.

HMS Ophthalmology Today

Faculty and Trainees by the numbers

- 235 Faculty
  - 140 Full-Time
  - 34 Full Professors
- 24 Residents
- 43 Clinical Fellows
- 100 Research Fellows
- Postdocs (some overlap with research fellows)
- PhD students, Medical Students

20 percent of full-time HMS Ophthalmology faculty holds the title of Professor

MATTHEW F. GARDINER, MD

STAYING ON TRACK

Guided by HMS Ophthalmology Vice Chair for Promotions and Reappointments, Dr. David Hunter, the department has made a concerted effort to streamline the promotions and appointment process. Since 2008, 12 faculty members have been honored with promotions to Professor of Ophthalmology or Clinical Professor of Ophthalmology.

- Mark B. Abelson IV, MD, CM
- Lloyd P. Aiello, MD, PhD
- Larry I. Benowitz, PhD (secondary appointment)
- James Chodosh, MD, MPH
- Robert J. D'Amato, MD, PhD
- Reza Dana, MD, MPH, MSc
- Anne B. Fulton, MD
- David G. Hunter, MD, PhD
- Andrius Kazlauskas, PhD
- Deborah P. Langston, MD
- Joseph F. Rizzo III, MD
- Lois M. Smith, MD

HMS Ophthalmology Clinician Scientists Receive Broad Funding Support

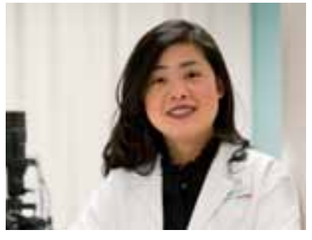
The road of a clinician scientist can be a difficult one to traverse. On one hand, clinician scientists possess unique skills and perspectives; they help forge multidisciplinary collaborations in translational medicine, and bridge the efforts of academia and industry to expedite treatments and cures. On the other hand, they face the challenge of fluctuating government and industry funding, which is often compounded by increasing financial pressures to boost clinical productivity in many U.S. academic medical institutions. These added demands can make it difficult for rising young investigators to find the time and resources to pursue investigative work. Not surprisingly, the ophthalmology community has questioned the viability of this career path, even though its rewards often prove rich in scientific discovery and patient care.

The HMS Department of Ophthalmology has a long history of successfully sustaining the efforts of its clinician scientists. Examples include: the introduction of cataract surgery to New England by Mass. Eye and Ear co-founder, Dr. John Jeffries; development of the cornea subspecialty and a corneal prosthesis (Kpro, Dr. Claes Dohlman); and the development of photodynamic therapy and anti-VEGF therapies to treat AMD (HMS Angiogenesis Research Group). This commitment has remained rock solid and, since 2004, the department has made substantial headway to broaden funding supports so that junior faculty members are encouraged to pursue research careers. HMS clinician scientists now receive support through a number of sources, including the K12 program, Scholar funds, endowed chairs, as well as multi-purpose funding to boost salaries, create programs and fund individual academic pursuits. Some of these efforts are described here.

MEET OUR SCHOLARS

On average, researchers receive their first RO1 or equivalent award at the age of 42, a statistic that underscores the critical need for intermediary funding between mentored K awards and independent funding. Scholar funds are a new funding mechanism designed to address this need and maintain momentum in our overall research efforts.

In 2011, six exceptional faculty members were named to funded scholar positions in retina, cornea and glaucoma. The program is supported primarily through the award and continuing royalties to Mass. Eye and Ear from the department's successful QLT judgment – itself the outcome of successful translational research in the field of wet age-related macular degeneration. Additional multi-purpose funding helps support individual research programs throughout the department, including stem cell studies and other translational research projects in the cornea, glaucoma, and retina services.



Ivana K. Kim, MD
Evangelos S. Gragoudas Distinguished Scholar in Retina Research

Director, AMD Unit, Mass. Eye and Ear

Dr. Kim joined the full-time faculty of Mass. Eye and Ear's Retina Service in 2003. As a key member of the HMS angiogenesis research group (HMSARG), she has been involved in numerous clinical and translational studies directed toward the development of new therapies for age-related macular degeneration (AMD) and other ocular conditions involving choroidal neovascularization. Her preclinical research utilizes genetic analysis to identify both risk factors and new pathways associated with pathological disease processes investigating both melanoma and macular degeneration. One area of recent focus explores the use of animal models to study the pathophysiology and progression of dry AMD to geographic atrophy and blindness. She is also working with colleagues to test the safety and efficacy of antiangiogenic therapies for various other ocular diseases.

Demetrios G. Vavvas, MD, PhD
Joan W. Miller Scholar in Retina Research

Dr. Vavvas is on the full-time faculty of Mass. Eye and Ear's Retina Service. His laboratory research spans neuroprotection, ocular cancer, angiogenesis, and retinopathies of prematurity and diabetes. He is participating in ongoing studies to find safer and less toxic therapies for treating retinoblastoma in infants, and aims to develop therapies that prevent the growth of primary and metastatic tumors in uveal melanoma. In collaboration with Dr. Joan Miller, he is also pursuing neuroprotection strategies that can prevent photoreceptor death, and potentially preserve vision in many retinal diseases. Together with Drs. Miller and Kim, he is also developing the first dry AMD primate model.

Ula V. Jurkunas, MD
Department of Ophthalmology Scholar

Dr. Jurkunas is a full-time member of Mass. Eye and Ear's Cornea and Refractive Surgery Service and Assistant Scientist at Schepens Eye Research Institute. Her studies focus on translational research related to corneal dystrophies and stem cell-based therapies for other diseases of the cornea. In 2006, she was one of the first HMS junior clinician scientists to receive a K12 Harvard-Vision Clinical Scientist Development Program award, monies that supported her award-winning research into the pathophysiology of Fuchs' Endothelial Corneal Dystrophy (FECD). In addition, her translational research to bring corneal stem cell therapy into clinical practice has been accepted by the Production Assistance in Cellular Therapies program of the National Heart Lung and Blood Program.

Pedram Hamrah, MD
Henry Allen Cornea Scholar

Dr. Hamrah is a full-time faculty member of Mass. Eye and Ear's Cornea and Refractive Surgery Service. He directs the newly formed Ocular Surface Imaging Center in the Cornea Service, where he is interested in

Lucia Sobrin, MD, MPH
Department of Ophthalmology Scholar

K12 Grant Gives HMS Clinician Scientist Time to Grow

Dr. Lucia Sobrin is a full-time clinician scientist with the Retina and Uveitis Services. She completed her ophthalmology residency training at Bascom Palmer Eye Institute in 2003, followed by a medical and surgical retina fellowship at the Mass. Eye and Ear in 2005 and a uveitis and ocular immunology fellowship at the Massachusetts Eye research and Surgery Institute (MERSI) in 2006. That year, she joined the Department's Retina and Uveitis Services as one of the Department's first Harvard Vision Clinical Scientist Research Program (K12) recipients, receiving a four-year grant to study the genetics of macular degeneration and diabetic retinopathy under the mentorship of David Altshuler, MD, PhD, Joan Miller, MD, and Johanna Seddon, MD, ScM.

One of Dr. Sobrin's primary research interests is elucidating the genetics of diabetic retinopathy in African Americans. She was the first ophthalmologist to be awarded funding under the HMS Catalyst Grant Program, and is principal investigator for a study entitled, "Epidemiology and Genetics of Diabetic Retinopathy in the Jackson Heart Study." In 2011, she was honored with the ARVO/Alcon Early Career Clinician Scientist Research Award.

Here, Dr. Sobrin describes her experience as a K12 recipient.

Has the K12 program enabled you to advance your career as a clinician scientist?
Yes, it gave me protected time so I could learn the field of complex disease genetics. I didn't have a background in genetics apart from what I learned in medical school. With salary support and protected time to attend seminars and courses in genetics and biostatistics, I was able to gain the skills I needed to do research effectively in this field. It also provided me with time for on-the-job learning of statistical genetics, which is very time consuming. Finally, it provided me with the funds to start the study of diabetic retinopathy in African Americans that I have initiated in the Jackson Heart Study.

How has K12 support directly benefitted your research efforts?
The K12 funded a study coordinator and fundus photography for the initial year of our diabetic retinopathy study. It also supported my tuition for a Masters in Public Health at the Harvard School of Public Health. In a nutshell, the K12 funded my education so I could pursue the research and then funded the essentials of getting the study started.

Did the K12 award influence your decision to join the MEE retina and uveitis services in 2006?
It did. I wanted a position that would support me in my initial years of trying to become a clinician scientist. I still needed training in research techniques, specifically biostatistics and genetics, in order to become an effective clinician scientist. The K12 gave me the time and resources to complete this training while allowing me to continue my clinical work.

Has the K12 program met your expectations?
Definitely. It's given me the protected time necessary to train in biostatistics and genetics, and under the mentorship of some of the best minds in science – Drs. David Altshuler, Joan Miller, and Johanna Seddon. It has also supported my early stage research and subsequent scientific work that has been the basis for applications for independent funding. I've been able to train to become an independent investigator while also continuing to see and treat patients in one of the largest and most prestigious academic medical school environments in the world.

developing live imaging techniques and using *in vivo* confocal microscopy for image-guided therapy. Dr. Hamrah's research focuses on immune cell trafficking in immune and infectious diseases of the cornea, including viral and microbial keratitis, corneal transplant tolerance and rejection, neurotrophic keratopathy, and ocular surface disease. From 2008 through May 2010, his research was supported by a K12 Harvard-Vision Clinical Scientist Development Program award. Recent research funding includes a Grant-in-Aid award from Fight for Sight, two grant awards from Alcon Research, LTD, and a Research to Prevent Blindness Career Development Award.

Louis R. Pasquale, MD
Distinguished Scholar in Ophthalmology

Dr. Pasquale is the director and a full-time faculty member of Mass. Eye and Ear's Glaucoma Service. Dr. Pasquale's research focuses on primary open-angle glaucoma (POAG), and seeks to improve early detection of the disease and improve the understanding of its pathogenesis. He is principal investigator of several NIH-funded studies that examine gene-environment interactions related to POAG. Together with Janey Wiggs, MD, PhD, Dr. Pasquale is co-leading the NEIGHBOR Consortium—a multi-center cohort study that includes 8,000 glaucoma cases and controls gathered from Mass. Eye and Ear, the Nurses' Health Study (NHS), the Health Professionals Follow-up Study, and eight other institutions. Funded through the National Human Genome Research Institute, this work has generated the largest known group of POAG cases, and seeks to eventually identify the full complement of gene-gene and gene-environment interactions associated with POAG.

SHATTERING THE GLASS CEILING

More than at any other time in the department's history, HMS women faculty are achieving an unprecedented array of leadership positions in patient-care, teaching, research, and administration. Guided by the vigorous support and gender-neutral policies of department chair, Joan Miller, MD, significant resources have been directed to ensure academic and professional advancement of women faculty, and to redress the inherent balancing act of career and family. This support has come in many forms - administrative policy changes, financial support and scholarship awards, and encouragement and mentorship - to enrich the careers and lives of many outstanding HMS women faculty. Since 2009, the department reached several milestones:

- Established the first short-term disability program for medical leave for professional staff at Mass. Eye and Ear
- Awarded three of six Mass. Eye and Ear Scholar Funds to women faculty
- First women appointed to the following positions at Mass. Eye and Ear:
  - Vice Chair for Basic Research
  - Associate Chief for Clinical Research
  - Associate Director of the Howe Lab
  - Director of the Genetics Diagnostics section of the new Ocular Genomics Institute
  - Associate Director of the HMS Ophthalmology Residency Training Program
  - Chief Quality Officer in Ophthalmology for Mass. Eye and Ear.
- Promoted two women physicians to full Professor with a third in the pipeline
- Created the first HMS Professorship that will be named for a woman: The Joan Whitten Miller Chair (to be named upon Dr. Miller's retirement; currently named in honor of her father, Charles Edward Whitten).

HMS ENDOWED CHAIRS

In part through the establishment of endowed chairs, the HMS Department of Ophthalmology attracts and supports the endeavors of world-class clinician scientists and investigators. Endowed chairs offer research and training support to incumbents while giving them the freedom to pursue independent research without the burden of financial risk. These endowments are a wonderful tribute to the past success of their namesakes, and serve as a building block for future endeavors. They are also powerful recruiting tools, attracting visionary leaders whose contributions historically have forged many paths in medicine and science. Prior to 2008, just four chairs had been completed; today, that number has shot to 12 thanks to generous department and institutional support, private foundations, and the philanthropy of HMS ophthalmology friends and alumni. These gifts will help ensure that generations of outstanding HMS ophthalmology faculty thrive in perpetuity.

Endowed Chairs in Ophthalmology	Incumbent 2011	Completed
Henry Willard Williams Professorship	Joan W. Miller, MD	1893
David Glendenning Cogan Professorship**	Richard H. Masland, PhD	1969
William Frederick Chatlos Professorship	Eliot L. Berson, MD*	1978
Paul Austin Chandler Professorship	Simmons Lessell, MD*	1986
Charles L. Schepens Professorship	Vacant	2008
Sir William Osler Professorship	Michael S. Gilmore, PhD*	2003
Claes Henry Dohlman Professorship	Reza Dana, MD, MPH* MSc	2008
David Glendenning Cogan Professorship (2)	In process	2010
David Glendenning Cogan Professorship (3)	In process	2011
Charles Edward Whitten Professorship	Evangelos S. Gragoudas, MD*	2011
Stelios Evangelos Gragoudas Professorship	In process	2011
Solman and Libe Friedman Professorship	In process	2011

*signifies inaugural incumbent
**The David Glendenning Cogan Professorship was divided into three chairs in 2010 and 2011.

GIFTS PAY TRIBUTE TO EPHRAIM FRIEDMAN, MD (1930-2011)

Dr. Ephraim Friedman, ophthalmologist and past President of the Massachusetts Eye and Ear Infirmary, passed away on June 18, 2011. He was a friend to many within the HMS Ophthalmology community, a loving family man, skilled clinician and retinal surgeon, sculptor, educator, researcher, and administrator.

Dr. Friedman was drawn to ophthalmology while serving as a captain in the Air Force, and completed his residency at Harvard Medical School/Mass. Eye and Ear under Dr. David Cogan in 1961. For the next four years, he was a research fellow at the Howe Laboratory of Ophthalmology at Mass. Eye and Ear. The author of 36 scholarly articles focusing on circulation in the eye, Dr. Friedman developed the vascular model for the pathogenesis of age-related macular degeneration (AMD), the leading cause of blindness in the developed world. He served as Dean of the Boston University Medical School (1970-1974) and Dean of the Albert Einstein College of Medicine (1974-1983) before returning to the Mass. Eye and Ear as President (1983-1990). A life-long sculptor, Dr. Friedman retired from administration in 1990 to spend more time with his art, family, research, and the log home he built in Maine.

In 2006, a gift from Friedman Family Foundation initiated the Ephraim Friedman Lecture in honor of Dr. Friedman's extraordinary teaching, research, and service to the field of ophthalmology and AMD. On the occasion of his 80th birthday in 2011, another family legacy gift was established: the Solman and Libe Friedman Professorship in Ophthalmology at Harvard Medical School. Named for Dr. Friedman's parents, the professorship was made possible through a very generous gift from the Friedman Family Foundation with contributions from additional donors and the Foundation of Mass. Eye and Ear Infirmary.

"Generations of HMS ophthalmology faculty and trainees will benefit from these gifts as they endure through the 21st century and beyond," said Dr. Miller. "They commemorate dedication to learning that is a Friedman family hallmark, and create a lasting tribute to a man who gave so much to our institution, our profession and our patients."

"I do have a basic philosophy that the only thing you have left when you die is what you gave away."
—Norman Knight, Philanthropist

FUNDING & PHILANTHROPY

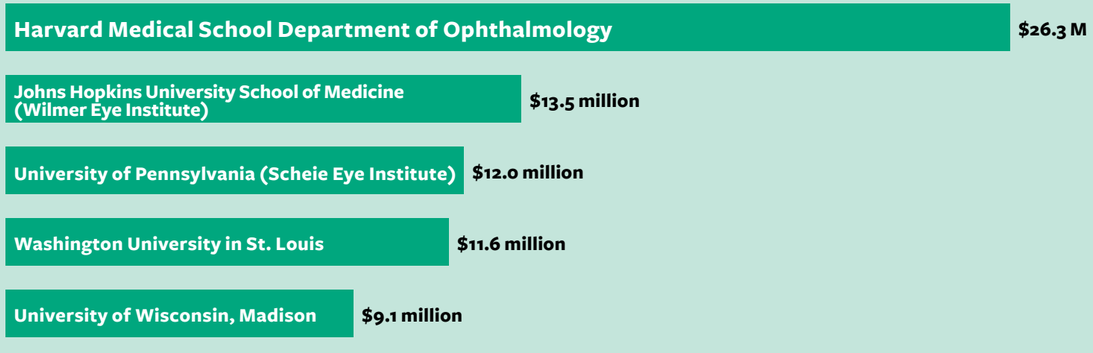
THE GIFT OF SIGHT

The clinical, educational, and scientific endeavors of the HMS Department of Ophthalmology faculty garner support from many sources. Private funds from individuals, families, or foundations, as well as corporate and government grants, all provide for the essential infrastructure that allows faculty to improve the quality of life for countless individuals with vision loss. Today, significant inroads into many areas of ophthalmic medicine and science have set the stage for potential breakthroughs: regenerating optic nerves and repairing damaged retina cells with stem cells, providing "personalized" care to patients using an individual's genetic blueprint, even restoring some sight to the blind with a retinal prosthetic. Once fodder for fiction, the realm of scientific possibility and patient care is widening rapidly, and there is new hope on the horizon for millions of sight-challenged people around the globe.

As these exciting efforts continue to unfold, we would like to highlight the extraordinary support of several of the department's key foundation partners, alumni, and generous friends. In his quote introducing this section, Mr. Norman Knight, one of the department's most ardent and loyal supporters, reminds us that the unflagging commitment and generosity of every supporter continues to make the department's mission possible. Their gifts, large or small, continually change lives in many ways—whether it's support to accelerate critical areas of vision research, acquire highly specialized equipment for ophthalmic procedures, support the training of promising young ophthalmologists, or perform life-changing surgeries on children.

NIH/NEI funding support

The HMS Department of Ophthalmology leads the country in acquiring support for eye research from the National Institutes of Health (NIH). Numerous grants (R-01, R-08 and K-12 grants, among others) reflect the diversity of our research programs and the significant caliber of our investigators. Total NIH vision research funding in 2008 to HMS Ophthalmology topped $26 million, according to a 2009 ranking by *Ophthalmology Times*. This is more than twice the level of funding received by any other academic ophthalmology department in the United States.



DONOR PROFILE:

NORMAN KNIGHT

A generous friend to all

There is perhaps no greater friend to Mass. Eye and Ear than Norman Knight. A self-made broadcast pioneer and media mogul, this humble man has supported the department's clinicians, scientists, and nurses with the same vision, drive, and passion that propelled him to the top of his field.

Norman Knight is a man who cares deeply about people and seeks out opportunities to empower individuals to achieve their best. Through scholarships for aspiring nurses, leadership awards for rising clinician scientists, and support for employees faced with personal crises, his impact is broad, personal, and profound.

His philanthropy has helped put Mass. Eye and Ear on the forefront of major clinical and research initiatives, including hyperbaric medicine, head and neck cancer research, and nursing excellence. In the HMS Department of Ophthalmology, Mr. Knight endowed The Norman Knight Leadership Development Award, which provides critical seed funding to young ophthalmologists at the start of their academic careers. Recent recipients include Ivana Kim, MD (Retina); Dean Cestari, MD (Neuro-Ophthalmology); and Ula Jurkunas, MD (Cornea). "The Norman Knight Award had a great impact on my research career," says Dr. Jurkunas, whose research into stem cell therapy may lead to novel treatments for corneal diseases. "I'm absolutely amazed at his spirit and his willingness to help."

Mr. Knight's interests extend to technology as well. In recent years, his generosity has led to the purchase of two anterior segment optical coherence tomography (AS-OCT) scanners (see sidebar) for the Retina and Cornea Services, and a pulse dye laser in the Ophthalmic Plastic and Reconstructive Surgery Service. This equipment is used every day to maximize the care and treatment of patients and further the department's research efforts.

"Over the years, Norman's selfless spirit has touched so much of what we do at Mass. Eye and Ear, and for that we are truly grateful," says HMS Department of Ophthalmology Chief and Chair, Dr. Joan Miller. "Thanks to Norman's many generous endowments, Mass. Eye and Ear and countless patients will continue to benefit from his philanthropy for generations to come."

When asked to reflect on his own generosity, Mr. Knight characteristically turned the attention back to the hospital. He asked, "What would you do if Mass. Eye and Ear wasn't here? Where would you get treated for eye diseases that no one else can handle?"

Thanks in large part to Mr. Knight's generosity, that's a question that may never need an answer.

A gift in action

Thanks to Mr. Knight's generosity, the Cornea Department at Mass. Eye and Ear now utilizes a high-tech, AS-OCT ophthalmic scanner—a noncontact imaging modality—that provides detailed cross-sectional cornea images. With this tool, HMS cornea faculty can optimize patient care and conduct research to improve current treatments. AS-OCT is used to:

Patient Care

- Assess corneal pathologies
- Diagnose and manage corneal infections
- Detect corneal melts by measuring/monitoring corneal thickness
- Immediately evaluate post-surgical success of lamellar transplants in patients with Fuchs' Dystrophy and bullous keratopathy ; this capability has enabled fast resolution of complications and significantly improved success rates.

Current Research Trials

- Develop an algorithm to differentiate scar tissue from inflammation; this will minimize the use of steroids on patients, which can have harmful side effects.
- Analyze the thickness of deadly ocular surface tumors prior to excision; depending on its thickness, a surgical procedure may be eliminated by combining a biopsy of the lymph nodes.

DONOR PROFILE:

PHILIP & MARJORIE GERDINE

Creating a legacy

Some time ago, visual impairments literally jeopardized the careers of Drs. Philip and Marjorie Gerdine. Dr. Philip Gerdine, an international finance executive, was diagnosed with Fuch's Dystrophy in 1994; his wife Marjorie, a clinical child psychologist, learned of her age-related macular degeneration (AMD) in 2003. Both sought help from several major medical institutions, and were delighted by the integrated approach offered at Mass. Eye and Ear.

The Gerdines have been quite impressed by the quality of care provided by Joan W. Miller, MD, Chief of Ophthalmology, and a leading expert in treating AMD. Dr. Marjorie Gerdine's concerns about the disease were considerably allayed once she met Dr. Miller, who explained that she had a mild case of the dry form of AMD, which is less severe and progresses much more slowly than the wet form. Her husband's care has been guided by Dr. Miller for almost six years and he has progressed to the point where his vision, with help, is almost normal. Both were able to productively continue their professional lives.

In appreciation for their care at Mass. Eye and Ear, they became interested in encouraging young physicians to come to Mass. Eye and Ear to pursue research initiatives in their own specialties, and to take advantage of its rich and diverse urban clinical environment. This led the Gerdines to a decision to leave a bequest of $1.3 million to permanently endow the *Marjorie and Philip Gerdine Fellowship in Ophthalmology*. "Our care at this institution, which for many years has occupied a pre-eminent role in medical research, education and clinical practice, has proven invaluable," said Dr. (Philip) Gerdine. "We are grateful for the opportunity to help support the institution's goals."

What will your legacy be?

Generous gifts propel our efforts forward and help seed discoveries that provide lasting legacies to society.

Finding Cures
Breakthroughs happen every day. By making a gift to support the research of your physician or a particular subspecialty area, you will help to accelerate the development of new treatments, and make an impact on people all over the world.

Training the Next Generation
The HMS Department of Ophthalmology trains the top medical residents and fellows in the country, helping to ensure that specialty care is available to people wherever they live. When you make a gift to support teaching funds and endowments, you are investing in a healthier future.

Providing Exceptional Care
Maintaining the highest level of patient care depends on continuously upgrading equipment, facilities, and technology. When you make an unrestricted gift, your support is used where it is needed most.

To learn more about gift-giving programs, please contact Melissa Paul, Chief Development Officer for Mass. Eye and Ear, at melissa_paul@meei.harvard.edu or call 617-573-4168.

DONOR PROFILE:

BOB NASER

Generous friend issues challenge for low vision study

"Generous" is the first word that comes to mind when one thinks of Bob Naser. The phrase "A man of action" follows soon after. Mr. Naser wants to make a difference, and wants to help encourage others to do so as well. That's why after sitting down with Dr. Mary Lou Jackson, Director of the Vision Rehabilitation Center at Mass. Eye and Ear, to learn about the opportunity and promise of research to evaluate patient outcomes after vision rehabilitation services, he couldn't stay idle.

"How can I help?" he asked.. Dr. Jackson explained that the department needed $120,000 to launch a new study that would ultimately impact how vision rehabilitation services are delivered in the future; moreover, the study had the potential to significantly improve the care and quality of life for many thousands of low vision patients. To this, Mr. Naser issued a challenge: he would give half of the funds if Mass. Eye and Ear could raise a matching amount from other patients and friends.

And that is exactly what Dr. Jackson and others did. "We were very excited about Mr. Naser's challenge; it gave us a wonderful reason to call people who we knew were passionate about vision rehabilitation – and to ask for their help," Dr. Jackson says. "We were so pleased to be able to meet his challenge, and to exceed it, with $10,000 in additional funds raised. This important project may never have happened without Bob's inspiration and generosity."

When asked about his generous gift, he simply said, "I was inspired and I heard the need. I was in a position to help."

This isn't the first time that Mr. Naser has issued a challenge to the Mass. Eye and Ear.. In 2007, he made his first challenge grant of $55,000 to support the work of Dr. Steven Rauch in his research on balance. Once again, the department exceeded its goal and raised over $130,000. This grant was used to develop an ambulatory vestibular monitoring device.

Wycliffe Grousbeck, MBA, JD

Chair, Massachusetts Eye and Ear Infirmary Board of Directors

Wycliffe "Wyc" Grousbeck was elected Chair of Mass. Eye and Ear's Board of Directors in January, 2010. Wyc has been devoted to research and educational initiatives relating to vision and the search for cures to blinding conditions that are genetically-based, such as Leber congenital amaurosis, which causes blindness or severe visual impairment at birth or during the first months of life; and retinitis pigmentosa, another congenital condition which leads to progressive vision loss, often in the first decades of life. Wyc's wife, Corinne, founded and serves as chair of the Trust Board at Perkins School for the Blind, in nearby Watertown, MA. This institution is devoted to educating blind and blind/deaf students worldwide and they are both active in other vision-related causes.

Wyc and Corinne were the innovators behind the successful October 2010 gala "Sense-ation," for Mass. Eye and Ear's newly created *Mass. Eye and Ear Cure for Kids Fund*. The event raised more than one million dollars. The proceeds will fund innovative research in pediatric vision and hearing disease, provide care for needy kids who come to Mass Eye and Ear for treatment, and form a basis for a foundation that will continue to support these efforts into the 21st century and beyond.

A graduate of Princeton University, Wyc received a JD from University of Michigan and an MBA from Stanford. He currently serves as CEO of the Boston Celtics basketball team. Previously he worked in venture capital and was as an investor in many successful healthcare and medical technology companies.

On being elected chair of the Board, Wyc declared: "This institution is at the forefront of preventing and restoring vision and hearing loss, which is a personal mission of mine.... I am looking forward to supporting the efforts of the extraordinary vision and hearing researchers, educators, physicians, and patient care professionals of Mass. Eye and Ear."

"It is an amazing feeling to support the dedicated people at Schepens Eye Research Institute who have fantastic dreams which, when realized, could change so many lives."

DONOR PROFILE:

CHARLES DE GUNZBURG

A personal experience with vision loss is what drives Charles de Gunzburg when it comes to supporting the work of the Schepens Eye Research. Retinal detachments in both eyes nearly blinded him, but his vision was restored by Dr. Charles Schepens. Since then he has maintained and nurtured a strong, supportive relationship with the Institute.

Mr. de Gunzburg is Chairman of First Spring Corporation, a private New York-based investment company, and a founder of FdG Associates, a leverage buyout firm. He has a bachelor's degree from Dartmouth College and a Master's degree in Public Administration from Harvard's Kennedy School of Government. Mr. de Gunzburg resides with his wife and family in New York City and Concord, MA.

In recent years, Mr. de Gunzburg has focused his energy and generosity on the regenerative medicine component of eye research, believing that for many struck by degenerative diseases, it holds the greatest promise of a cure. Reassured by this belief, he contributed substantial resources to create the Minda de Gunzburg Center for Retinal Transplantation Research. The center, now the Minda de Gunzburg Center for Ocular Regeneration, is dedicated to the development of therapies aimed at regenerating tissues of the eye that have been damaged by disease or trauma. One of the Institute's most generous benefactors, he has also endowed the de Gunzburg Director of that center, a position held by Dr. Michael Young, a world leader in the use of stem cell and other tissue regenerating techniques to restore vision.

"Schepens scientists have already made enormous progress in this fledgling, fascinating field," says Mr. de Gunzburg. "I was already a believer, but in the past few years, my commitment has grown even greater. It is an amazing feeling to support the dedicated people at Schepens Eye Research Institute who have fantastic dreams which, when realized could change so many lives," he says.

A trustee of the Institute since 1986, he has also assumed leadership responsibilities for the Institute's future by chairing the Nominations Committee to recruit board members sharing his commitment to advance vision research.

DONOR PROFILE:

FRED & INES YEATTS

Generous support propels AMD research

For Fred and Ines Yeatts, research to develop new treatments for age-related macular degeneration (AMD) is an interesting, exciting, and important means to an end. Long-time friends and supporters of hearing research at Mass. Eye and Ear, Fred and Ines recently extended their philanthropy to include a new partnership with Drs. Joan Miller, HMS ophthalmology chair, and Demetrios Vavvas, HMS Assistant Professor of Ophthalmology. Their support has seeded a highly innovative research program in neuroprotection, a burgeoning area of investigation that aims to rescue retinal cells that are at risk of dying, before they die, and potentially preserve vision in many retinal diseases.

"We enjoyed meeting Drs. Miller and Vavvas very much," said Ines Yeatts. "They made us aware of just how complex and difficult it can be to hit every research milestone in their search for a cure. We were impressed by their energetic pursuit of the problems."

Research at Mass. Eye and Ear is fueled with the help of thoughtful and generous individuals like the Yeatts. "Neuroprotection offers tremendous promise in many areas of medicine, and especially in preserving vision," explained Dr. Miller. "This is an area that is very exciting to us and, with the Yeatts' help, we've been able to dive into it and start to make progress in a short time. We could not be more appreciative of their keen interest in our work and their outstanding generosity."

Fred Yeatts is an engineer who spent his career in the defense industry. Now retired, his passion for science continues ever strong through his interest in medical research. "We know that these are tough problems that will take a long time to solve," said Fred. "We enjoy hearing about the obstacles and strategies and the victories, and we're happy that we can play a role in advancing their efforts to find a cure for AMD."

DONOR PROFILE:

DEWALT ANKENY

DeWalt (Pete) Ankeny's commitment to eye research came to him as a legacy from his parents. It is a legacy that he has whole-heartedly embraced and one he hopes to pass on to the next generation. Building on that legacy, Pete has supported the Institute's mission to cure blinding eye disease along with support from The Ankeny Foundation and the Ankeny Family Fund of the Minneapolis Foundation. In addition to his leadership at these foundations, Pete has also been a devoted member of the board of trustees of Schepens Eye Research Institute. His daughter, Sally Ankeny-Reiley, has taken up the cause in recent years, contributing as a member of the development and public relations committee at The Institute.

It all began in the late 1950s, when his father, DeWalt H. Ankeny, Sr., suffered two retinal detachments. At that time, detached retinas were not easily repaired and often resulted in blindness. He and Marie, his wife, sought the help of Dr. Charles Schepens, who was able to restore his vision with a new technique he developed at the Retina Foundation (the precursor to Schepens Eye Research Institute). Decades later, Marie also needed Dr. Schepens' skill to reattach her retina. These experiences resulted in Marie's great fondness for Dr. Schepens and forged her commitment to support the Institute and eye research. Not only did they endow the Institute's DeWalt and Marie Ankeny Director of Research position but Marie's sister, Theodora, also generously gave to the Institute through a charitable remainder trust.

Over the years, Pete, who had a distinguished career in banking and who is now at Meristem in Minnesota, has been dedicated to ensuring that the Foundations continue to meet the needs of the Institute's mission. Through the two foundations, he has made sizable contributions to the building of new laboratories, the annual fund and the Center for Age-related Macular Degeneration Research at the Institute, even following closely in his parents' footsteps to endow the Ankeny Scholar of Retinal Molecular Biology, held by Dr. Pat D'Amore. He continues to keep a close watch on the Institute's progress, always remembering how its creative innovation helped save the sight of both of his parents.

Life-changing surgery honors Ray Tye: a man who changed lives

Dr. Fay shares a happy moment with Andrea Nemethi. Dr. Fay is an Assistant Professor of Ophthalmology at Harvard Medical School and a surgeon in Mass. Eye and Ear's Ophthalmic Plastic Surgery Service. He specializes in Ophthalmic Oncology and is a founding member of the Mass. General Hospital Hemangioma and Vascular Malformations Clinic. His clinical interests focus on vascular lesions around the eye, such as hemangiomas, Sturge Weber syndrome, and port-wine stains. For many complex conditions faced by patients, Dr. Fay has performed innovative and life-changing solutions, including eyelid reconstruction, tear duct surgery, and laser therapies. Dr. Fay was recognized by the Vascular Birthmarks Foundation as Physician of the Year in 2007.

Twelve-year-old Andrea Nemethi smiles as she tries on eyeglasses inside Mass. Eye and Ear's Optical Shop. The fact that she can wear glasses at all is amazing; up until recently, Andrea had a tumor behind her right eye that had grown to the size of a grapefruit, destroying the eye and pushing it out of the socket. Doctors from her home country of Romania told her family that she had an inoperable tumor with just months to live. The tumor continued to grow for eight years with no help in sight—until the English teacher in her small, rural middle school searched the Internet, and through many connections found out about Mass. Eye and Ear.

The daughter of a retired pediatrician, the teacher was increasingly concerned with Andrea's right eyeball, which had become a huge bulge covering half of her face and stretching the eyelid almost to the point of bursting.

"According to the school doctor, in case of an unexpected turn for the worse, at school or elsewhere, we would be unable to do anything to assist her," wrote the teacher in an email to Mass. Eye and Ear's Ophthalmic Plastic Surgery Service. "The haunting possibility of such an evolution makes us desperate enough to try to look for assistance all over the world."

Dr. Aaron Fay, Director of Mass. Eye and Ear's Ophthalmic Plastic and Reconstructive Surgery Service, reviewed Andrea's case. Having helped many children with life-threatening facial tumors, Dr. Fay thought he could help. In a case involving an international child without funding, Mass. Eye and Ear would have immediately turned to the Ray Tye Medical Aid Foundation for assistance. "Ray Tye was a thoughtful man who led a meaningful life. He never missed a chance to help people, especially children," Dr. Fay explains. "When I saw the photos of this young Romanian girl, I thought of Ray. Helping this girl is exactly what Ray would have done."

Unfortunately, Mr. Tye was not to know of Andrea's situation, having passed away shortly before her case arose. The request for assistance came at a fortuitous moment, however. Camille Condon, Director of the International Office at Mass. Eye and Ear, along with the institute's doctors and administrators, had been trying to think of a meaningful way to honor the memory of Ray Tye. "During his lifetime, Ray donated hundreds of thousands of dollars to help patients in need," says Camille. "Knowing that Ray would have jumped at the chance to help this courageous and strong young lady, the physicians volunteered their services in his honor."

Andrea and her father came to the United States in the summer of 2010, and the local Romanian community hosted the family. Dr. Fay and his team performed several surgeries—the first of which was a seven-hour operation to remove the tumor. Thankfully, the tumor was benign, and the team was able to preserve Andrea's eyelid and surrounding muscles. In subsequent surgeries, Dr. Fay rebuilt her eye socket and implanted an artificial eye—all of which have dramat/ically changed her appearance. A future surgery will further refine her eyelid.

These procedures changed the way she looks, but more importantly they have also changed her life. She has grown into a beautiful, self-confident young lady who enjoys being back in school, able to play with her classmates in the school yard without fear of injury. She can enjoy swimming and bicycling, activities that she could not do before. "This was an extremely emotional journey for all who were involved," Camille says. "Our only regret is that Ray Tye did not have the opportunity to meet Andrea." His widow, Eileen Tye, met Andrea and was touched by the experience. "Unlike an honor where you are handed a plaque or a bowl, this is an honor from the heart," Mrs. Tye remarked. "Ray would have loved helping Andrea. The two of them would have been great friends."

Andrea and her family are grateful for all the love and support they received, but mostly to the man they never had the chance to meet but who continues to help those in need. "He must have been a great man," says Andrea's father, Petru, through an interpreter. "With a big heart," Andrea adds.

FOUNDATION PROFILES

The HMS Department of Ophthalmology is extremely grateful to its long-standing partners in vision research, including the Massachusetts Lions Clubs, Research to Prevent Blindness, and Foundation Fighting Blindness. Their stalwart and steady financial support enables the department to continue its mission of research, education and care on many fronts.

Foundation Fighting Blindness

The Foundation Fighting Blindness (FFB) was established in 1971 by a passionate group of individuals who were driven to overcome vision-robbing retinal degenerative diseases that were affecting them or their loved ones.

Gordon Gund, FFB's chairman, co-founded the organization with the late Ben Berman. Mr. Gund, who is blind from retinitis pigmentosa, is chief executive officer of Gund Investment Corporation, and was the principal owner of the NBA's Cleveland Cavaliers and co-founder and part owner of the San Jose Sharks. Mr. Berman was a real estate executive with two daughters affected by retinitis pigmentosa.

The Foundation's goal was clear: To drive the research that would lead to preventions, treatments, and cures for the entire spectrum of blinding retinal degenerative diseases—including macular degeneration, retinitis pigmentosa and Usher syndrome—that together affect more than 10 million Americans and millions more throughout the world. At the time of FFB's founding, very little was known about these conditions. Today, thanks to the Foundation's efforts, much progress has been made in the effort to prevent or cure retinal degenerations.

Through private individual contributions, corporate philanthropy, and community-based fundraising activities, FFB has raised more than $425 million since its inception. In addition to being the largest private funder of retinal research in the world, the organization also conducts a robust outreach program, and hosts symposia and conferences to raise public awareness of retinal degenerative diseases.

The Berman and Gund families met over forty years ago when both were seeking ways to foster research into discovering the causes of and treatments for retinal degenerative diseases. In 1974, the FFB provided funding for the Berman-Gund Laboratory at Mass. Eye and Ear, dedicated to investigating blinding retinal diseases. The Foundation also established the William F. Chatlos Professorship of Ophthalmology, which came about through the pivotal efforts of William Chatlos, a dedicated member of the FFB who has served in key leadership roles since the mid-70's (including Vice Chairman). Dr. Eliot L. Berson, regarded as one of the world's top retinal clinicians and researchers, has been Director of the Berman-Gund Laboratory since its inception, and has held the Chatlos Professorship since its creation in 1978. Under Dr. Berson's leadership, clinical and research teams in the Berman-Gund Laboratory have made critical discoveries about the etiology of blinding retinal diseases and treatments to slow their progression. Dr. Eric Pierce, who has served on the FFB's Scientific Advisory Board since 2003 and as chair since 2005, joined Mass. Eye and Ear and Dr. Berson as the Associate Director of the Berman-Gund Laboratory in 2011, further enhancing the relationships among these pre-eminent organizations.

Lions Clubs International

Founded in 1917, the Lions Clubs International is the world's largest service club organization with nearly 1.35 million volunteer members in approximately 45,000 clubs throughout the world. The Lions aid in numerous philanthropic causes and are recognized particularly for their strong commitment and service to sight conservation. Today, through countless local and international efforts, Lions clubs donate over $500 million and provide 71 million hours of service each year in the United States and worldwide.
In 1925, the Lions Clubs began to focus efforts on the blind and visually impaired when Helen Keller, noted author and activist with both vision and hearing loss, challenged the Lions to be "Knights of the Blind." In 1952, eye research was voted to be the official project of the Massachusetts Lions, and six years later, the project was formally incorporated as the Massachusetts Lions Eye Research Fund, Inc. (MLERF). The origins of MLERF date back to the summer of 1950, when the plight of so-called "blind babies" or "retrolental fibroplasia babies" came to the attention of a Lions District Governor, E. Daniel Johnson. First discovered by a Massachusetts physician in 1941,

"The opportunity I bring to you, Lions, is this: To foster and sponsor the work of the American Foundation for the Blind. Will you not help me hasten the day when there shall be no preventable blindness; no little deaf, blind child untaught; no blind man or woman unaided? I appeal to you Lions, you who have your sight, your hearing, you who are strong and brave and kind. Will you not constitute yourselves Knights of the Blind in this crusade against darkness?"
Excerpted from Helen Keller's Challenge to the Lions, 1925 International Convention, Cedar Point, Ohio, June 30, 1925

the disease we now know as retinopathy of prematurity (ROP) was, at that time, afflicting four out of five premature babies weighing four pounds or less. The disease baffled the medical community, which had no dedicated resources for research. Several Lions members mobilized together with Al Hirshberg (Sports Writer for the Boston Post and Chairman of the Foundation for Eye Research) and Dr. Edwin B. Dunphy (Chief of Staff at Mass. Eye and Ear). The group produced and mailed a pamphlet telling this story to all Lions in Massachusetts, and to District Governors in the U.S. and Canada. In his accompanying cover letter, Mr. Johnson wrote a passionate call to action. "The attached leaflet tells briefly about the lack of research in the field of blindness," the letter stated. Mr. Johnson went on to write, "it is unbelievable that so little money is spent on trying to prevent a malady...and I shudder to think that probably a child or grandchild of mine or yours might well be the victim of this." The condition, which Mr. Johnson called "baby blindness" and noted to strike "rich and poor alike," drove him to call for the underwriting of eye research. "It seems that this is a challenge to the Lions of Massachusetts, yes to the country!" he declared.

"...it is unbelievable that so little money is spent on trying to prevent a malady...and I shudder to think that probably a child or grandchild of mine or yours might well be the victim of this." The condition, which Mr. Johnson called "baby blindness" and noted to strike "rich and poor alike," drove him to call for the underwriting of eye research. "It seems that this is a challenge to the Lions of Massachusetts, yes to the country!"
—E. Daniel Johnson

From 1951 to 2006, Massachusetts Lions raised and donated nearly $26 million to eye research in Massachusetts. Several HMS ophthalmology affiliates—including Mass. Eye and Ear, Children's Hospital Boston, Schepens Eye Research Institute, and Joslin Diabetes Center—have directly benefitted from this philanthropy. MLERF funds have provided critical financial support for numerous eye programs, outreach efforts, research initiatives, and technologies that have enabled many medical advances and helped tens of thousands of Massachusetts residents to avoid or mitigate vision loss. Today, Lions support remains steadfast and continues to drive our mission forward.

Research to Prevent Blindness

For half a century, Research to Prevent Blindness (RPB) has cultivated and sustained the careers of thousands of vision researchers whose highly innovative work has, in turn, propelled ophthalmic science forward and transformed millions of lives. Since its founding in 1960, RPB has awarded 3,381 research grants totaling more than $290 million in research support to fund the invention of new technologies, test innovative concepts, and develop potential treatments. In 2010 alone, the organization funded 89 new grants and actively supported more than 151 scientists at 57 departments of ophthalmology at medical schools across the United States.

Since 1961, RPB has been a key foundation partner to the HMS Department of Ophthalmology. Funding provided by RPB to date tops $6.97 million. Thanks to this generous and ongoing support, many major developments in eye research and treatment have come to fruition at Harvard Medical School. For example, RPB has consistently invested resources in the evolution of anti-VEGF investigations that have led to the development of intravitreal drug treatments. Millions of patients have benefitted from these treatments, which can slow, halt, or sometimes reverse the effects of advanced age-related macular degeneration (AMD).

Throughout this decades-long partnership, RPB support has driven innovative research across a broad range of subspecialty areas and scientific disciplines. RPB individual investigator awards have recognized the efforts of numerous HMS faculty at every career level; these include the Jules and Doris Stein RPB Professorships, RPB Walt and Lilly Disney Award for Amblyopia Research, RPB Career Development Awards, RPB Senior Scientific Investigator Awards, RPB Lew R. Wasserman Merit Awards, RBP Physician Scientist Awards, and RPB Special Scholar Awards.

Along with individual grants, RPB has provided significant unrestricted grant support to the department. During the last several years, this funding has helped to mobilize vigorous new initiatives to expand and enhance the department's academic programs. The steady influx of RPB unrestricted grants also has enabled faculty to pursue new teaching initiatives and to hone HMS residency and fellowship programs. Significant funding also has provided for laboratory renovations and the purchase of state-of-the-art equipment.

ALUMNI GIVING SOCIETY

Seeding a Culture of Excellence

HMS Ophthalmology alumni know first-hand the importance of supporting the vital work of our trainees and faculty. Launched in 2010, the Alumni Giving Society of HMS Ophthalmology at Mass. Eye and Ear shines a light on their philanthropy by recognizing gifts of $1,000 or more to the department within the fiscal year (October 1-September 30). In its first year, over 100 HMS alumni and current or former medical staff signed on; their generous donations totaled more than $300,000. In year two, this generous philanthropy has intensified, with several inspirational gifts celebrated in this section.

The department extends its sincerest thanks to all Alumni Society Giving members—past, present and future —whose investments in our institution drive innovation, entrepreneurial spirit, and success across every corner of the campus.

Richard J. Simmons and Ruthanne B. Simmons Fellowship Fund

This gift was initiated by Dr. Richard Simmons, a 1957 graduate of Harvard Medical School who completed his ophthalmology residency at Mass. Eye and Ear in 1962. For four decades, Dr. Simmons enjoyed a career as a pre-eminent glaucoma specialist in Boston, first, as student and colleague of Mass. Eye and Ear luminaries, Drs. Paul Chandler and Morton Grant, and later, as the mentor of an entire generation of glaucoma specialists. He was President of the Professional Staff of Massachusetts Eye and Ear Infirmary, President of New England Ophthalmological Society (NEOS), one of the four Founders of the American Glaucoma Society, one of the four Founders of the Chandler Grant Glaucoma Society, author of more than 66 peer-reviewed papers, and author of numerous book chapters on glaucoma. Dr. Simmons taught intensively as a fellowship preceptor and as a frequent guest lecturer nationally and internationally.

Dr. Simmons' daughter, Ruthanne Simmons, followed in her father's footsteps. Thirty years after her father, she too, graduated from Harvard Medical School with her MD. Upon completion of her residency and glaucoma fellowship at Duke University Medical Center, Ruthanne, joined her father in his ophthalmology practice. Later they practiced together at Ophthalmic Consultants of Boston. She operated at Mass. Eye and Ear and taught in the HMS Department of Ophthalmology. Like her father, Ruthanne was also active in many professional societies, including the American Academy of Ophthalmology, the American Glaucoma Society, NEOS, and others. She was an active researcher and author.

Tragically, Ruthanne Simmons' journey was cut short. In 1996, she was diagnosed with breast cancer. She stopped practice for a year to undergo aggressive treatment and successfully returned to active practice for four more years. Sadly, the cancer returned again, and this time, it overcame her. It was a great loss when Ruthanne passed away in 2002.

In honor of his daughter, Dr. Simmons began an effort to raise $250,000 to create a Richard and Ruthanne Simmons Fellowship Fund at Harvard Medical School. He seeded the fund and personally gave $135,000. Mass. Eye and Ear reached out to ask others to join in, and 46 colleagues and friends did just that, making generous gifts to bring the fund to the $250,000 minimum threshold.

Income from the Simmons Fellowship Fund will provide partial fellowship support to a succession of Simmons Fellows in the Glaucoma Service at Mass. Eye and Ear and help to ensure well-trained specialists for decades to come.

Dr. Richard Simmons with his wife, Anne

Pei-Fei Lee, MD

Dr. Pei-Fei Lee Lectureship in Ophthalmology

Paul Lee, MD, JD received his medical degree from the University of Michigan in 1986 and his law degree from Columbia University that same year. He went on to complete his glaucoma fellowship at Mass. Eye and Ear in 1991. Today, he is Professor of Ophthalmology and Vice Chair of Ophthalmology at Duke University School of Medicine. Earlier this year, Dr. Lee honored the memory of his father with a pledge of $50,000 to endow the Dr. Pei-Fei Lee Lectureship in Ophthalmology. The lectureship will be held biannually with first preference given to glaucoma-related topics.

Dr. Pei-Fei Lee, who passed away in 2009 at the age of 83, was a dedicated clinician scientist. His son notes that Mass. Eye and Ear held a special place in his father's heart. Dr. Pei-Fei Lee was Mass. Eye and Ear's first glaucoma fellow, and was mentored by two Mass. Eye and Ear luminaries, Drs. Paul Chandler and Morton Grant. According to his son, the late Dr. Lee "conveyed not only the thinking but also the importance of the principles and character of both his mentors." On a personal level, Dr. Lee felt indebted to Mass. Eye and Ear for the outstanding training and education he received during his fellowship. After he retired, the senior Dr. Lee devoted himself to building educational bridges between the U.S. and China. Dr. Paul Lee's gift not only commemorates his father's dedication to education, but will continue to advance the education of future ophthalmologists. The gift also holds special significance as the department seeks to build new international bridges—most recently in exploring an academic partnership with Shanghai Eye and Ear, Nose, and Throat Hospital at Fudan University in China.

The Abelson Family Fellowship in Cornea at Massachusetts Eye and Ear Infirmary

In 1974, Mark Abelson, MD arrived at HMS' Department of Ophthalmology to pursue a joint fellowship in cornea and external disease research at Mass. Eye and Ear and Schepens Eye Research Institute. Under the mentorship of Dr. Claes Dohlman, and advisor Dr. Mathea Allansmith, he completed his fellowship two years later and joined Schepens Eye Research Institute in 1976. At Schepens, Dr. Abelson developed a passionate interest in ocular surface inflammation and allergy response—areas where little research was being done and funding from sponsoring industry and government agencies was scarce.

With Dr. Dohlman's encouragement, Dr. Abelson set out to build a clinical practice and a clinical research organization to develop therapies for allergy and ocular surface disease. He was extremely successful in both activities. The research organization, Ophthalmic Research Associates (Ora), has been involved in the development of over one-third of the world's currently marketed ophthalmic pharmaceutical products.

Throughout his career, Dr. Abelson has maintained his connection and support of Schepens, where he is currently a Senior Clinical Scientist and Trustee. In recent years, he has joined in HMS departmental activities more broadly—editing a section on pharmacology and contributing chapters for all three editions of Albert & Jakobiec's *Principles and Practice of Ophthalmology*. In addition, Dr. Abelson lectures at department meetings, and teaches HMS students. In 2011, he was promoted to Clinical Professor of Ophthalmology at Harvard Medical School.

Left to Right: Joan W. Miller, MD; Mark Abelson, MD; and Claes Dohlman, MD, PhD.

The Abelson family—including Dr. Abelson and his wife Annalee, their son Stuart (who now heads Ora and is a Trustee of Mass. Eye and Ear) and wife Kathryn, their son Richard and wife Mariana, and other Abelson family members—wanted to give back to Mass. Eye and Ear; they partnered with his mentor, Dr. Dohlman, to establish a fellowship fund at Mass. Eye and Ear. The Abelson family has pledged $600,000, matched with $600,000 from Mass. Eye and Ear from the proceeds of the Boston Keratoprosthesis, to create the Abelson Family Fellowship in Cornea at Massachusetts Eye and Ear Infirmary.

"This gift from the Abelson family is extraordinary on many levels," says Dr. Joan Miller, Chief and Chair of the HMS Department of Ophthalmology. "Dr. Abelson is a shining example of an HMS Ophthalmology fellow who has gone on to establish a prominent career in bench-to-bedside research. Not only is Dr. Abelson a quintessential clinician scientist, but his family has also perpetuated his far-reaching impact with their ongoing work. We are extremely proud of Dr. Abelson's achievements, and truly honored to carry on his legacy with the Abelson Family Fellowship in Cornea."

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—Joan W. Miller, MD

"Massachusetts Charitable Eye Infirmary partly originated in the fact that one of its founders had the happiness of restoring a beloved father to sight by the operation for cataract. The tender relation in this case of surgeon and patient, becoming extensively known among the small population then composing our community, brought to his observation, a large number of Ophthalmic patients....The great majority of all these cases belongs to the humbler ranks of society; and have their prolific parentage in the various privations and sorrows unavoidably consequent upon poverty."

— Edward Reynolds, MD, in his address at the dedication of the Massachusetts Charitable Eye and Ear Infirmary, 1850[1]

[1] Snyder, Charles. Massachusetts Eye and Ear Infirmary: Studies on Its History. 1984. Massachusetts Eye and Ear Infirmary, Boston

REACHING OUT

Founded on the principal of caring for the community and inviting "the poor, afflicted with diseases of the eye to come there for gratuitous aid[1]," the Massachusetts Charitable Eye Infirmary was established in 1824 by Edward Reynolds, MD, and John Jeffries, MD. It would eventually grow into the Massachusetts Eye and Ear Infirmary and form the nucleus of the HMS Department of Ophthalmology. In 1824, Drs. Reynolds and Jeffries were at the cusp of great changes in medical education, including enormous advances in the diagnosis and treatment of eye diseases. By the 1870's, HMS established subspecialty departments (including a Department of Ophthalmology), reflecting the enormous growth in medical knowledge and the increasing trend toward medical specialization. Today, the HMS Department of Ophthalmology comprises over 300 faculty and trainees who provide care to thousands in need—around the corner and around the globe.

AROUND THE CORNER

The adage "charity begins at home" forms the cornerstone of the department's community outreach mission. Every year, HMS physicians, fellows, and residents provide free care, information, and screenings to thousands of area residents. Collaboration is key to these efforts, and the department joins with numerous organizations to target populations in need of eye care but otherwise may not have access to ophthalmic services.

Since 1995, Mass. Eye and Ear and Children's Hospital Ophthalmology Foundation (CHOF) staff have provided pediatric vision screenings to the Neighborhood Charter School in Dorchester, which is home to 400 children of diverse backgrounds. For the last two years, HMS staff members have provided vision screenings at Camp Harbor View, a summer camp held on Boston Harbor's Long Island, for 600 at-risk, low-income youth. HMS staff also collaborates with Massachusetts Vision Coalition to provide eye exams to children at the West End House Boys and Girls Club in Allston, MA, as well as vision screenings to young adults in the *Year Up Boston* program, which prepares young urban adults for successful careers. Those in need of eyeglasses have received free pairs courtesy of Vision Coalition Massachusetts and the Mass. Eye and Ear Optical Shop. Each year, CHOF, Mass. Eye and Ear, and other affiliates join with the Massachusetts Lions Clubs to collect used eyeglasses for refurbishing and distribution in underserved or impoverished areas. CHOF staff also has provided free eye exams at the Children's Museum Boston during Child Life Week, and visits local Girl Scout groups for informational presentations on eye health.

Mass. Eye and Ear staff participate in adult eye screenings at numerous community centers, such as the Harriet Tubman House in Boston's South End, the Center for Adult Learning Experiences in Somerville, and the Blackstone Senior House in Boston. Businesses such as the Boston Omni Parker House Hotel have also arranged eye screenings for employees. HMS ophthalmologists give informational presentations at Massachusetts Lions Club meetings throughout the state, and participate in many of their mobile screening van programs. Vision screenings and "ask a doctor" sessions target regional health fairs such as Partners Health Expo and Runners Health Expo. HMS faculty members regularly provide free public lectures and presentations on topics such as glaucoma, age-related macular degeneration (AMD), and pediatric glaucoma. Open forums for the community feature a range of topics, such as "Update on AMD."

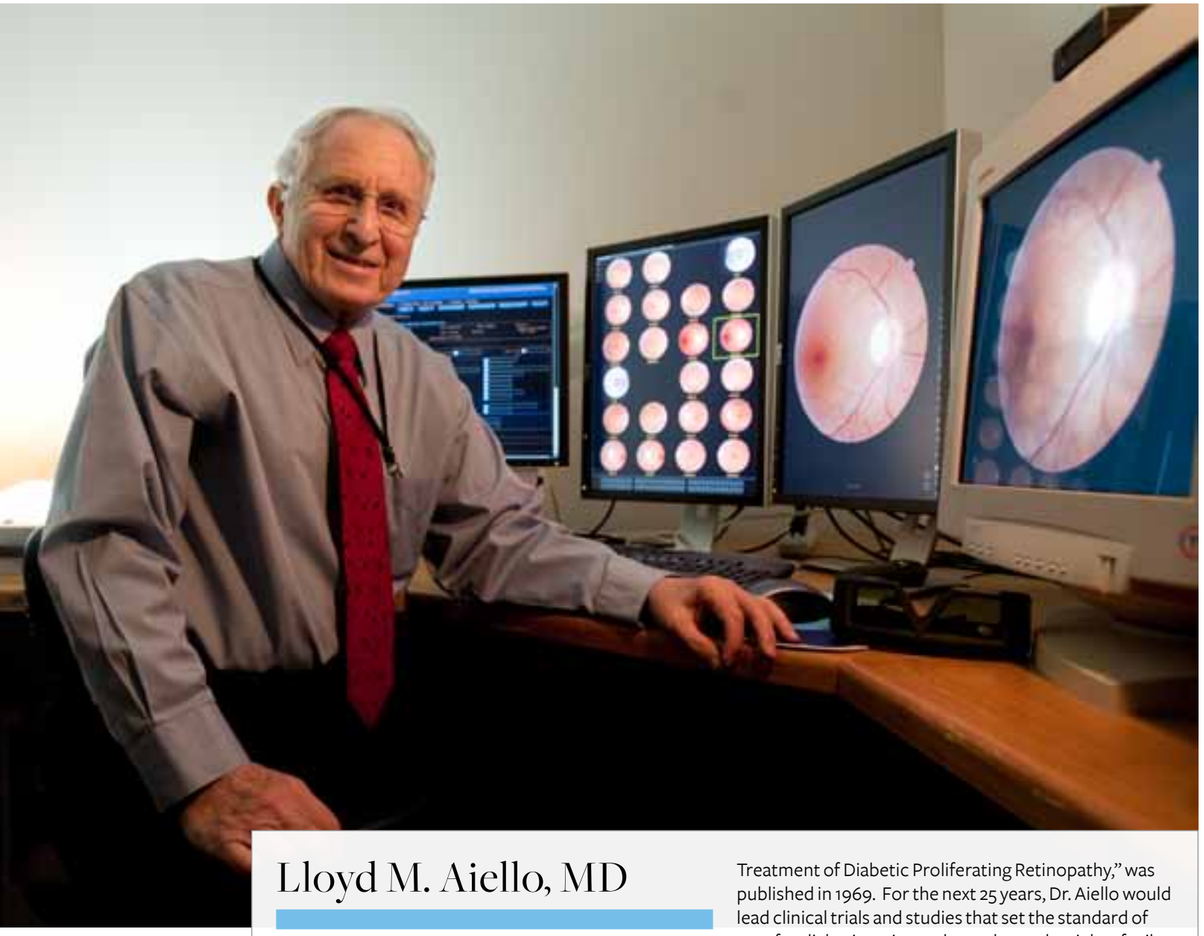
Each year, as participants in the World Health Organization's World Sight Day, Schepens Eye Research Institute and Mass. Eye and Ear provide screenings and raise awareness of gender inequities in vision loss. This international day of awareness, held annually in October, focuses on the global issue of avoidable blindness and visual impairment. Schepens also invites the public to its annual Eye & Vision Research Symposia, which highlight the Institute's latest research and current clinical advancements. These free symposia series are designed to empower patients and their families by providing the latest information about vision research and interventions for vision loss. A display of low vision aids is also provided. Events are held in Boston, Cape Cod, and in several Florida locations.

Joslin Vision Network reducing barriers to eye care

The Joslin Vision Network (JVN), a national telemedicine program targeting diabetic retinopathy, was pioneered by Lloyd M. Aiello, MD at the Joslin Diabetes Center. Dr. Aiello sought to mitigate the terrible consequences of diabetic retinopathy, in which abnormal blood vessels proliferate, bleed, and detach in the retina, leading to cell death and blindness.

In the 1960s, Dr. Aiello worked with Dr. William P. Beetham to develop the pan-retinal laser treatment for diabetic retinopathy, and oversaw the clinical trials that showed the technique to have a 96 percent success rate in patients. Despite their success, however, diabetic retinopathy continued to be the leading cause of blindness in the United States, mostly due to a shortage of skilled diabetic eye care in many areas of the country. Dr. Aiello teamed with colleague Sven-Erik Bursell, PhD, who used video technology in his research laboratory at Joslin. The two developed a plan for a diagnostic system composed of a specialized camera to take retinal photographs, and a video transmittal system to send the images to Joslin's highly skilled clinicians for reading and interpretation.

Today, the JVN utilizes custom software and a unique digital retinal-imaging device to screen and evaluate diabetes patients. The JVN systems are set up in central areas, such as medical center pharmacies, to optimize patient access. Imaging takes 15 minutes, and requires no pupil dilation. The brief encounter also permits patient education staff to reinforce the importance of medications, monitoring, and life-style modifications. The non-dilated diabetic eye evaluation (considered the gold standard of imaging), coupled with broad access to the JVN service and 48-hour turnaround for results and



Lloyd M. Aiello, MD

Clinical Professor of Ophthalmology, Harvard Medical School

Founding Director, Beetham Eye Institute at Joslin Diabetes Center

Dr. Lloyd M. Aiello received his medical degree from Boston University, and completed postgraduate work at HMS and Mass. Eye and Ear. In 1971, he was appointed Director of Joslin's Beetham Eye Institute, and in 2005 he was named Founding Director. From 1990 to 2001, Dr. Aiello headed the Section on Eye Research, which is now led by his son, Lloyd Paul Aiello, MD, PhD.

Dr. Aiello is the second of three generations of Joslin ophthalmologists. Working with his father-in-law, William P. Beetham, MD, Dr. Aiello revolutionized the diagnosis and treatment of diabetic retinopathy. Prior to the pioneering work of Drs. Aiello and Beetham, there was a 75 to 80 percent risk of blindness for patients with diabetic retinopathy. In 1967, Aiello and Beetham developed a pan-retinal laser technique that reduced the risk of blindness to less than two percent in patients diagnosed and treated early in addition to careful follow-up. The landmark paper, "Ruby Laser Photocoagulation in Treatment of Diabetic Proliferating Retinopathy," was published in 1969. For the next 25 years, Dr. Aiello would lead clinical trials and studies that set the standard of care for diabetic retinopathy, and save the sight of millions of people.

Dr. Aiello has authored more than 95 original articles and 37 book chapters and review articles. He has served as a Trustee of Joslin Diabetes Center, a member of the Executive Committee of the HMS Department of Ophthalmology, and President of the New England Ophthalmological Society. Dr. Aiello's numerous honors include the Warren Alpert Foundation Prize, the David Rumbough Scientific Award of the Juvenile Diabetes Foundation International, the Lighthouse Pisart Vision Award, the Leo R. Breitman Excellence in Research Award from the Juvenile Diabetes Foundation Massachusetts Affiliate, the Massachusetts Society of Eye Physicians and Surgeons Man of the Year, the American Diabetes Association Outstanding Physician Clinician in Diabetes Award. In 2003, Dr. Aiello received the American Telemedicine Association President's Award (for his contributions in the development of telemedicine and its advancement worldwide), and the Gertrude D. Pyron Award for Outstanding Achievement in Retina Research, recognizing his lifelong contribution to the understanding and treatment of diabetic retinopathy.

recommendations, has dramatically increased compliance among the diabetes population, especially in the early stages of disease (which are often asymptomatic). For thousands of patients, early detection and treatment has prevented devastating vision loss. In recent years, the JVN has expanded its reach across Massachusetts and to borders beyond.

Local: In an ongoing collaboration with Massachusetts Lions Clubs, Joslin staff provides diagnostic support and evaluation of retinal images acquired by the Massachusetts Lions EyeMobile service. The EyeMobile has logged more than 9,000 miles throughout western Massachusetts—traveling to over 180 Lions' events and serving some 4,500 residents and visitors.

National: The Indian Health Service-JVN Teleophthalmology Program is leading the way to improve early identification of American Indians and Alaskan Natives at risk of vision loss due to diabetic retinopathy. These populations often live far from health care centers that provide nationally accepted standards of eye care, including eye exams that can diagnose high-risk candidates for diabetes-related blindness. The HIS-JVN Program addresses this health care gap by using telemedicine technology to reduce the incidence and severity of diabetes-related vision loss; to date, the program has imaged more than 21,000 patients.

Global: The JVN-Venezuela program was established in Caracas in 2006 through the Foundación M.M.G. with the support of Morella Mendoza Grossman, Joslin Diabetes Center Trustee, and Dr. Lloyd M. Aiello, JVN founder. The program is an American Telemedicine Association, category 3 ocular telehealth program, and has provided high-level diabetes eye care to more than 83 children. More recently, the program was expanded to include pregnant women and adult patients. The program serves as a model for the international eye care initiatives of the JVN, enabling extensive retinal image analysis in pediatric populations to identify novel retinal lesions. By potentially predicting future severe retinal diseases, this program may allow earlier interventions that protect against vision loss.

Teleretinal imaging program captures high risk patients

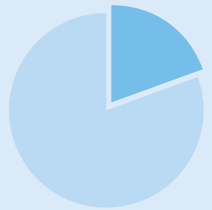
In 2008, Mass. Eye and Ear and Massachusetts General Hospital (MGH) collaborated to establish the Ocular Telemedicine Program at MGH's Chelsea Health Center to screen high-risk, diabetic patients for diabetic retinopathy. The center serves an urban, indigent, and predominantly Hispanic population. As an ethnic group, Hispanics are far less likely to get regular annual screenings than other ethnic groups and also have an increased prevalence and more rapid progression of diabetic retinopathy.

On-site retina photographs are sent electronically to Mass. Eye and Ear and screened for diabetic retinopathy or other pathologies. Findings are posted securely using the Longitudinal Medical Record (LMR) system, which allows a network of shared information among Harvard's 17 hospitals and affiliates. If results warrant, a clinical alert is sent to the patient's primary care doctor who can refer patients to Mass. Eye and Ear or another facility for further diagnosis and follow-up. The LMR enables fast, accurate, and prompt medical decision-making at every clinical level. For patients with diabetic retinopathy, the teleretinal program can mean early intervention and sight-saving diagnosis and treatment.

In a study conducted from 2008 to 2010, approximately 20 percent of the population evaluated through the teleretinal program presented with some degree of diabetic retinopathy; nearly five percent of these patients had indications of severe disease. According to Louis Pasquale, MD (HMS Associate Professor of Ophthalmology and director of Mass. Eye and Ear's Ocular Telemedicine Program), the program is continually evolving in an effort to encourage patient compliance and follow-up. Patient screening is now offered five days a week. Health center staff members, who were initially trained to just take the images, have received additional training so they can identify and flag potentially high-risk candidates. In such cases, Mass. Eye and Ear's expert clinician readers are notified promptly and, if warranted, results are relayed to patients within 24 hours.

"We continue to make improvements to the program by expanding its reach and dropping every barrier we can think of to ensure that patients with detectable diabetic retinopathy are notified by their PCP and get prompt follow-up and treatment," says Dr. Pasquale. "Not only are we saving sight, but we're also reducing the burden on the healthcare system by treating diabetic retinopathy in its early stages."

Percentage of Patients with Diabetic Retinopathy on Imaging



233 patients imaged with 3-field views using non-mydriatic camera in an urban primary care clinic.

All 233 images reviewed by trained telemedicine readers who referred patients to ophthalmology.

73 patients (31.3%) referred to ophthalmology for clinical evaluation.

AROUND THE WORLD

More than ever before, the interconnected global community is bringing the plight of eye disease into sharp focus. The statistics are sobering; according to the World Health Organization, 314 million people suffer from visual impairment, and 45 million of them are blind. Nearly nine out of 10 people who suffer from blindness or visual impairment live in developing countries that have minimal or no access to quality, affordable healthcare.

Many HMS Department of Ophthalmology physicians, optometrists, and support staff are determined to change these statistics by joining volunteer medical missions that serve communities across the far reaches of the globe. Missions are wide-ranging and include: providing eye exams, performing sight-saving surgery, conducting vital skills-based training for local medical staff, and establishing self-sustaining ophthalmology clinics and programs. HMS faculty and staff have joined medical missions to El Salvador, Guatemala, Nicaragua, Cambodia, and in many other locations throughout the world. Here are some of their stories.

Womenseyehealth.org envisions a better future for women

Earlier this decade, an analysis of 70 epidemiological studies revealed that two out of three people who are blind or visually impaired in the world are women. Reasons vary as to why women bear a greater burden of blindness and vision loss. In industrialized countries like the United States, women live longer than men; many potentially blinding eye diseases, such as age-related macular degeneration, increase in frequency with age. Statistics also show that some ocular conditions (such as dry eye) are more intrinsic to women than men; autoimmune diseases that affect the eye, such as Sjögren's Syndrome, may also be more prevalent in women. In developing nations, infectious diseases like trachoma are more prevalent in women, and in some areas of the world, social or economic factors can impede a woman's access to health care.

Beyond these troubling statistics is the fact that three-quarters of blindness and visual impairment is preventable, according to the World Health Organization. Recognizing the critical need for public advocacy and education, HMS Professor of Ophthalmology, Ilene Gipson, PhD, teamed with colleagues in the United States and abroad to form WomensEyeHealth.org (WEH.org), an online education and advocacy group that raises public awareness about women's eye health, and supports blindness prevention research and programs.

The group's core mission is to alert women to their increased and disproportionate risk of eye disease; the organization also encourages life style changes and actions that optimize eye health, such as having regular eye exams and not smoking. The group promotes their message through their website (www.womenseyehealth.org) as well as a variety of outreach venues including health fairs, lectures, and literature campaigns. And word is spreading quickly: WEH.org chapters are being established in many U.S cities and in nations around the globe. Recently, chapters were formed in Spain, Portugal, and China.

"When we preserve sight, we improve life," notes Dr. Gipson, WEH.org Chair. "When we preserve a woman's sight, we improve the lives of her children, spouse, and community. We want women to know that they can take steps to optimize their eye health. And in parts of the world where women may be deprived of the best health care, we want to educate people that the precious gift of sight benefits them not only directly but also encourages more productive and supportive family situations in the community."

"When we preserve a woman's sight, we improve the lives of her children, spouse, and community. We want women to know that they can take steps to optimize their eye health."

—Ilene K. Gipson, PhD, Chair, Women's Eye Health.org

HMS ophthalmologist, Dr. Roberto Pineda II, MD, performs cornea surgery on a patient during an ORBIS mission to Myanmar in 2008.

HMS ophthalmologists on a mission to advance global health

HMS Assistant Professors Aaron M. Fay, MD, and Roberto Pineda II, MD, have made a commitment to improving global eye health as medical volunteers for ORBIS International. ORBIS was founded nearly three decades ago as a non-profit organization dedicated to saving sight and eliminating avoidable blindness worldwide. In 1982, its now-iconic Flying Eye Hospital—at the time a converted DC8 outfitted as an ophthalmic teaching hospital and surgical center—flew its first mission to Panama. Seventy-five countries and hundreds of flying missions later, ORBIS's unique and highly lauded program has evolved into a broad-based, "capacity building" effort that is dedicated to helping developing countries create sustainable, accessible, and affordable eye health care within their communities.

Central to the ORBIS mission are the services of a core group of 500 volunteer faculty members. Drs. Fay, Pineda and other ophthalmology experts provide high-level, hands-on surgical and clinical training to local staff. Dr. Fay, of Mass. Eye and Ear's Ophthalmic Plastic and Reconstructive Surgery Service, traveled with ORBIS to India to teach oculoplastics techniques. Dr. Pineda, director of Refractive Surgery at Mass. Eye and Ear, is a 12-year veteran of ORBIS. Since 1998, he has traveled on ten missions to remote communities in Ethiopia, Uzbekistan, Burma [Myanmar], India, China, Cuba and, most recently, Indonesia (Java). He has trained hundreds of local physicians in the techniques of cornea surgery (including corneal transplants), cataract surgery, and other anterior segment surgeries.

ORBIS's strong focus on educating and training a complete medical "core" of personnel—from doctors to nurses and OR staff—is a philosophy that appeals to academic clinicians like Dr. Pineda. "The ORBIS program is unique in that it's very comprehensive and very structured. As visiting volunteer faculty, my role is both clinician and teacher," says Dr. Pineda. I'm screening patients, doing surgical demonstrations, giving lectures, and teaching—even fixing equipment! Missions typically last just for a week, but my contributions have a high impact." There is continuity as well; local doctors can continue to communicate and consult with Dr. Pineda once he returns to Mass. Eye and Ear through an on-site, web-based interface that allows them to share information and images.

Tapping the expertise of highly skilled clinicians like Drs. Pineda and Fay has multiple benefits. Pineda notes, for example, that lack of funds, government restrictions, and political strife may prevent most local doctors in these developing countries from traveling overseas for specialized training opportunities. "Our involvement fills a training gap by helping local doctors broaden their skill sets," he said. Dr. Pineda's commitment to ORBIS also has been a conduit for striking up new collaborations with other ophthalmologists. He notes that his involvement in establishing a keratoprosthesis clinic in Ethiopia came about as a direct result of his experience with ORBIS.

In November 2010, as a guest speaker at an ORBIS fundraiser in New York City, Dr. Pineda lauded the organization's broad social impact on global health. "ORBIS volunteers and staff work hand-in-hand with the unique requirements and customs of governments around the world," he says. "In doing so, they pull together all the elements needed to establish a working and sustainable health care infrastructure in developing communities. In this way, ORBIS heightens awareness of eye disease globally and at every level of government. I'm proud to be part of an effort that effects real and positive change around the world."

As Director of the Refractive Surgery Service at Mass. Eye and Ear, Roberto Pineda II, MD, regularly performs refractive surgeries and serves as co-investigator in excimer laser FDA clinical trials while also developing tools used in managing LASIK complications. His clinical interests also include complex reconstruction procedures, such as Descemet's stripping endothelial keratoplasty for toxic anterior segment syndrome. In collaboration with with other Mass. Eye and Ear clinician scientists, including Drs. Ula Jurkunas and Claes Dohlman, Dr. Pineda is also developing strategies for reducing complications after various corneal procedures—including LASIK, PRK, and Boston KPro.

"These...simple interventions can have a huge, life-changing impact for a child who has a blinding eye disease but is otherwise healthy."
— Danielle Ledoux, MD

Dr.Ledoux (far right surgery, back to camera) coaches a local Guatemalan ophthalmologist through a cataract surgery. Surgeries are run side by side in the same OR to maximize resources and save time, a medical practice forbidden in the US.

HMS ophthalmologist gives hope — and sight — to children around the world

Long before she became a pediatric ophthalmologist, Danielle Ledoux, MD, had a strong desire to serve children in underprivileged communities, which helped shape her future medical career. "I chose ophthalmology because I knew it would allow me to do the international work I wanted to do," says Dr. Ledoux, whose busy pediatric ophthalmology practice at Children's Hospital Boston is focused on cataract and strabismus surgery.

Her desire to be involved in global outreach was fueled during her pediatric fellowship at the Medical University of South Carolina (MUSC). She was mentored by M. Edward Wilson, MD, Chair of the Department of Ophthalmology at MUSC, who is well known in the international medical community for his longstanding outreach work in developing countries. Through Dr. Wilson's collaboration with a private family foundation, Danielle had the perfect venue to put her skills—and her heart—to work. The U.S.-based foundation, which funds several global outreach programs, established one of its most successful endeavors in Guatemala: a pediatric, cataract surgery program at Hermano Pedro Hospital in Antigua.

Patients and family members wait in line at Hermano Pedro Hospital to register for surgery.

For the last five years, she has traveled to the hospital as part of a weeklong mission to perform cataract and, more recently, strabismus surgery on children from impoverished areas of that region. "These are relatively straightforward and simple interventions, but can have a huge, life-changing impact for a child who has a blinding disease but is otherwise healthy," remarks Dr. Ledoux. "This is especially true of children from poor, remote villages whose life circumstances are already challenging."

According to Dr. Ledoux, young patients are screened ahead of time by a local ophthalmology team to determine if they are candidates for surgery. The program's original focus was cataract surgery, but has been expanded to include strabismus surgery. The cost for surgery, room and board, and short-term follow-up care, is fully funded through the foundation, which also subsidizes the travel expenses of family members who accompany patients. Dr. Ledoux is one of a team of three pediatric surgeons (including Dr. Wilson) who perform a total of about 50 surgeries during their weeklong stay.

The work is not without its challenges. Although Hermano Pedro hospital is clean and well run, it is not a full-service hospital; not only does it have limited inpatient facilities, but it also does double duty as the local orphanage. Lacking resources, staff, and technology that other hospitals in wealthier countries have readily at hand, Dr. Ledoux says she has to consider the implications of each surgery she performs knowing that the hospital has limited resources, and that most patients will return to a remote village with little or no access to long-term medical care. "Depending on the individual needs of each patient, my approach and methods may vary in order to ensure the best outcome possible," she says.

Dr. Ledoux notes that the program also has helped cross a cultural divide. In past years, patients and their families have been reticent to seek treatment or follow-up care because of the stigma attached to these diseases. This is slowly changing, she explains, as the program builds momentum through education and word-of-mouth. "I've noticed more and more patients are willing to return for follow-up care and families of potential patients are seeking out our help," says Dr. Ledoux. "It's gratifying to see how the program is creating this continuity of care which, ultimately, will enable us to help more young patients."

In February 2011, Dr. Ledoux put her experience and talent to work on a month-long mission at the Nepal Eye Hospital in Tripureshwor, Kathmandu. There, she worked with a local pediatric ophthalmologist who has established a pediatric ophthalmology department and

training program. She credits her outreach opportunities to the strong web of support she receives from the International Health Services Program at Children's Hospital Boston—particularly to David Hunter, MD, PhD, the hospital's Ophthalmologist-in-Chief. "I have received incredible support from the hospital, especially from Dr. Hunter, who has encouraged my outreach efforts from the beginning," says Dr. Ledoux. These experiences have helped me grow personally and professionally. It's simply an amazing feeling to have such a real and lasting impact on the health of children around the world."

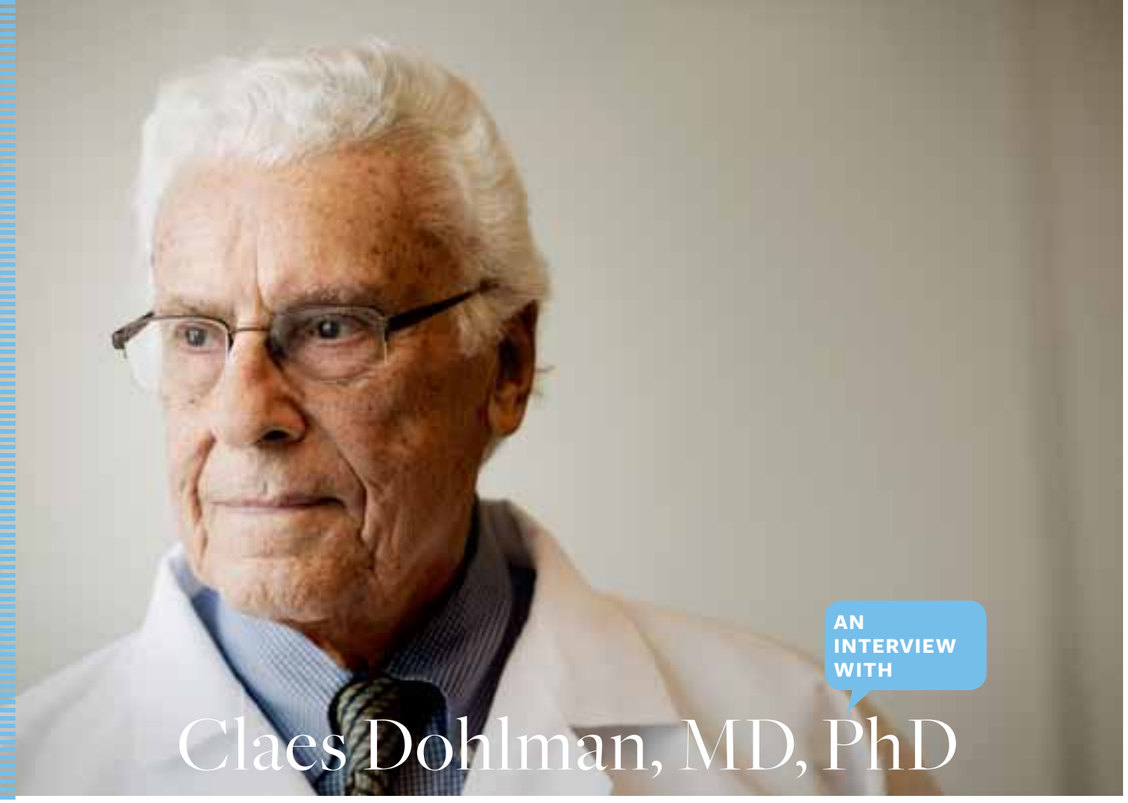
Vision on the go: global demand increases for boston keratoprosthesis

An estimated eight million people in the world are blind from corneal disease, and the majority of patients live in developing countries. For some patients, conventional cornea transplantation offers a successful and life-changing solution. But sometimes transplants fail, while other patients suffer from conditions that make them poor candidates for traditional transplantation. HMS Emeritus Professor of Ophthalmology, Claes H. Dohlman, MD, PhD, has devoted much of his life's work to solving this problem. Dr. Dohlman, founder of the cornea specialty, invented the Boston Keratoprosthesis (KPro), which combines a corneal prosthesis with a synthetic supporting structure that sometimes can be used as a successful alternative to conventional cornea transplants. Approved by the FDA nearly two decades ago, the KPro is now used in 150 centers in the United States and around the world, offering sight to thousands of people who would otherwise remain blind.

Pilot programs in developing nations around the globe are bringing KPro's sight-saving benefits to these populations. Programs exist in India, China, Thailand, Central and South America, Africa, and, most recently, Sudan. Cornea experts James Chodosh, MD, and Roberto Pineda II, MD, also have worked to broaden the availability of the Boston KPro worldwide. Dr. Chodosh has performed and assisted with artificial cornea implantation surgery in India, Italy, England, and Israel. Recently, he began a project to develop a $50 keratoprosthesis for use in underdeveloped countries.

In 2008, Dr. Pineda led the effort to establish the first KPro center in Africa. His team traveled to Addis Ababa, Ethiopia to teach surgical implantation techniques to ophthalmologists and medical support staff. Dr. Pineda's team also offers training on the follow-up care needed for successful outcomes. Establishing self-sustaining, long-term KPro clinics in poorer demographic areas like Addis Ababa is not without challenges. Scarcity of medications and advanced microbiology labs, along with maintaining rigorous patient protocols, can make an already-challenging task even more difficult. Dr. Pineda notes that careful up-front planning helped the process run smoothly. Today, the clinic is self-sustaining. Back in Boston, the KPro team is in the third year of a five-year longitudinal study to study the viability of the Boston KPro in developing countries and hone the program as needed.

Drs. Roberto Pineda and Aaron Fay with a Kpro patient in Ethiopia.



AN INTERVIEW WITH

Claes Dohlman, MD, PhD

How does someone approach the formidable task of creating a new ophthalmic subspecialty?
You have to have a somewhat fanatical interest and focus. It's not a part-time undertaking, not something you do now and then. You have to stick with it because it's so time-consuming. It's not only a career but rather a life you live.

What were some of the challenges?
When I first came to the U.S. in 1958, there was no formal Cornea Service; it was just me for many years and that was the biggest challenge. I was fortunate in that, once I established the Cornea Service and a structured fellowship program, we were able to attract many students who had academic ambitions. Drs. Sweebe, Boruchoff, Martola and Wiedman were important early faculty collaborators. Over the years, the faculty has trained more than 200 clinical fellows. Eighty of those individuals have become full professors and more than 40 have become department chairs. We were very lucky to get great people who have gone on to become pioneering researchers and leaders in the field.

How did people react when you decided to develop an artificial cornea?
With a lot of skepticism—as I did! My original results, in the 50s and 60s, were pretty disastrous. We started to get some good outcomes after that but it wasn't until the 1970s that the prosthesis began to show promise. However, when I became chief and chair of the Department in 1974, I had to stop KPro research for 15 years simply because I had too many other commitments.

And what happened?
When I retired from my administrative duties in 1989 I decided to concentrate on something practical – the KPro – and the prosthesis has been the centerpiece of my work for the last twenty years. I'm glad I did because developing an artificial cornea has been very exciting. It has been a lesson in patience and perseverance - not just time consuming but fraught with complex and difficult challenges. As I said, it was years before we realized some promising outcomes.

You use the term "we."
Absolutely. The clinical success of the KPro has required a great collaborative effort among Harvard's ophthalmic research community and close research partners at MIT. Turning the KPro into a viable, clinical reality for patients has required multi-disciplinary expertise not only in surgery but in biomaterials, bioengineering, optics, inflammation, bacteriology, glaucoma, retinal detachment, plastics and contact lenses. None of these disciplines are my areas of expertise so, over the years, I have enlisted the collaboration of numerous HMS faculty as well as partners like MIT.

Who are some key members of the KPro team?
Presently Dr. James Chodosh – who is an astute researcher on a professorial level - is addressing autoimmune issues; Drs. Ilene Gipson and Eli Peli from Schepens, are foremost experts in enzymes and optics respectively. Dr. Kathryn Colby is refining surgical development techniques; Dr. Irmgard Behlau, an infectious disease expert at Mass. Eye and Ear, examines bacteriology issues; Dr. Joseph Ciolino, has developed a drug releasing contact lens in collaboration with several researchers from Professor Robert Langer's laboratory at MIT, supervised by Dr. Daniel Kohane who now runs his own lab at MIT. Dr. Roberto Pineda is our ambassador abroad and has established KPro clinics in some of the poorest nations. Dr. Samir Melki is developing telemetric techniques for measuring the intraocular pressure. I also have seven international research fellows working on KPro improvements. Of course, there are many other individuals here and abroad who have provided key guidance and expertise in helping us to develop the KPro and to spread the word.

What have been some of the KPro milestones?
There have been two primary ones in recent years. Historically, post-operative bacterial infections caused some disastrous failures, especially in patients with autoimmune diseases. In the early part of this decade, Dr. Marlene Durand (Director of Infectious Disease at Mass. Eye and EAr) suggested vancomycin prophylactically, which dramatically lowered infection rates. It was a revolutionary improvement in treatment. A second challenge we've addressed is tissue melt around the cornea. In 2000, we redesigned the KPro and added holes in the back plate of the collar button shaped prosthesis; this improves nutrition to the holding graft. We also started to use a soft contact lens to protect against dehydration. Both advances have mitigated tissue melt by almost 100 percent in non-autoimmune eyes.

What are the challenges that lay ahead?
Despite recent successes in improving clinical outcomes with the KPro, I temper my enthusiasm with the caveat that we are only halfway to the train station – we still have some significant challenges to overcome. Autoimmune disease and chemical burns remain problematic because they can lead to tissue disintegration. We're working on several fronts to address these issues. Another troubling KPro outcome is that it can trigger glaucoma, a complication that can be particularly vicious in patients with chemical burns. We have worked closely with Mass. Eye and Ear's glaucoma service, specifically Drs. Cynthia Grosskreutz and Lucy Shen who have helped us to develop new procedures, while one of my fellows at MIT is working on a new type of shunt.

You and your team have made a significant effort to promote the Boston KPro to some of the world's poorest nations. Why?
Most of the world's 8 million people with corneal blindness live in the developing world and they need a safe and inexpensive cornea prosthesis. Our goal with the KPro is simple: get it out there so it is doing some good and helping as many people as possible. That's why we've established self-sustaining KPro clinics in some of the poorest nations, most recently in Sudan and Ethiopia. Logistically, these efforts have gone remarkably well thanks to Dr. Pineda. Cost, unfortunately, still remains an issue.

Can you elaborate?
For many developing countries, the cost of the KPro procedure is prohibitively expensive. Even if the device were provided free of charge, there are additional costs associated with physician time, long-term medication, contact lenses, follow-up care, etc. We've mitigated this situation some by providing the KPro to some countries at a substantially reduced cost – in some cases for free – in order to make it affordable and available to those who need it. Even so, it remains out of reach for many people.

You've inspired thousands of fellows, students and colleagues through the years. Who inspired you?
As a fellow at the Wilmer Institute (Johns Hopkins) in the early 1950s, I had the good fortune to study under Dr. Jonas Friedenwald who, at the time, was one of the country's premier eye researchers. Another inspiration was Dr. Charles Schepens, renowned for his work on retinal detachment and for creating and building the Schepens Eye Research Institute into a foremost eye research facility. He had an enormous talent for focusing on a single problem, and then building up an organization, research, and fellowship training around it. His advice was invaluable to me after I arrived in Boston (1958) and began to build a cornea specialty and structured cornea fellowship program.

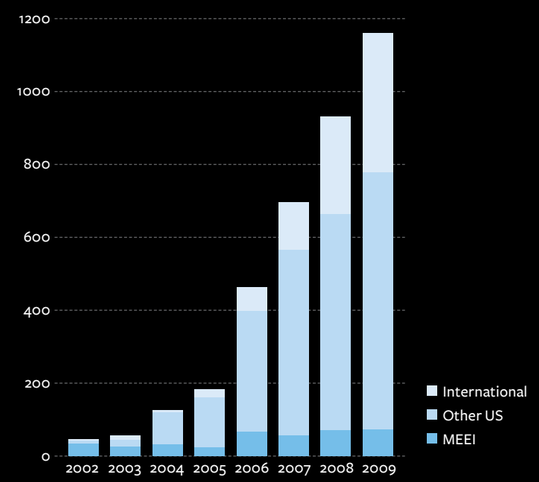
Now in your ninth decade, you remain an active member of the Cornea Service. How do you spend your time?
I teach and mentor, run a small, specialized KPro patient clinic and direct a program of clinical R&D. I also like to keep up with my colleagues and others who ask for my advice so I make an effort to answer my correspondence. I stopped operating in the spring (2010)—I'm 88 so I have a good excuse. I'm still having fun, though, and especially enjoy teaming up fellows with the right expertise to tackle the remaining KPro issues. Even though we've made a lot of progress there is still so much to accomplish. I am convinced that we will continue to have the most talented cornea team in the world, headed by Dr. Reza Dana, to carry on at Harvard when I eventually retire.

You've made indelible contributions to ophthalmic science and research. How do you want people to remember you? Your work?
I don't know. I have been very lucky in my work and I have always been happy doing it – never bored. I would like to pay tribute to my wonderful family who has been extraordinarily supportive. My great wife has done so much to support my career. I have a lot to be grateful for!

"What the developing world needs is a safe, long-term and inexpensive corneal prosthesis. Our goal with the KPro is simple: get it out there so it is doing some good and helping as many people as possible." *— Dr. Claes Dohlman*

KPRO USAGE COUNTRIES:

“What the developing world needs is a safe, long-term and inexpensive corneal prosthesis. Our goal with the KPro is simple: get it out there so it is doing some good and helping as many people as possible.” *— Claes Dohlman, MD, PhD*



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40. **Portugal**
41. **Saudi Arabia**
42. **Singapore**
43. **South Africa**
44. **Spain**
45. **Syria**
46. **Taiwan**
47. **Thailand**
48. **Turkey**
49. **United States**
50. **Venezuela**

HMS DEPARTMENT OF OPHTHALMOLOGY MAJOR NATIONAL AND INTERNATIONAL AWARDS

2005 – 2011

Faculty Member	Award	Organization	Year
Anthony P. Adamis, MD	The Ernst H. Bárány Prize	International Society for Eye Research	2008
Lloyd M. Aiello, MD	Warren Alpert Foundation Prize	HMS	2009
Lloyd Paul Aiello, MD, PhD	Charles Schepens Award in Research and Lecturer	Schepens International Society, Vancouver, BC	2005
	Mary Jane Kugal Award	Juvenile Diabetes Research Foundation Int.	2006
	ARVO/Pfizer Ophthalmics Translational Research Award	ARVO/Pfizer	2007
	Award of Merit in Retina Research and the Charles L Schepens Lecture	Retina Society	2007
	Senior Achievement Award	AAO	2007
	Special Research Scholar Award	RPB	2007
	Paul Henkind Memorial Lecture	Macula Society	2009
	Lew R. Wasserman Merit Award	RPB	2010
Eliot L. Berson, MD	Ludwig von Sallmann Prize in Ophthalmology	International Congress of Eye Research	2006
	The Award of Merit in Retina Research	The Retina Society	2010
Alex R. Bowers, PhD	Irvin and Beatrice Borish Award	American Academy of Optometry	2010
Constance L. Cepko, PhD	Alfred W. Bressler Prize in Vision Research	The Jewish Guild for the Blind	2011
Dong Feng Chen, PhD	Sybil B. Harrington Scholar	RPB	2006
	Outstanding Scientific Achievement Award	RP International and the Vision Awards	2008
Teresa C. Chen, MD, FACS	Achievement award	AAO	2009
Kathryn A. Colby, MD, PhD	Achievement Award	AAO	2007
Kip M. Connor, PhD	William Randolph Hearst Fund Award	Harvard Medical School	2008
Patricia A. D'Amore, PhD, MBA	Senior Scientific Investigator Award	RPB	2006
	A. Clifford Barger Excellence in Mentoring Award	Harvard Medical School	2006
	American Society for Investigative Pathology Rous-Whipple Award	AIP	2010
Reza Dana, MD, MPH, MSc	Physician Scientist Merit Award	RPB	2005
	Service Recognition Award	AAO	2006
	Alcon Research Institute Award	Alcon	2008
	Lew R. Wasserman Award Merit Award	RPB	2009
Francois Delori, PhD	Roger H. Johnson Prize for Macular Degeneration Research	University of Washington, Seattle	2008
Thaddeus P. Dryja, MD, PhD	Zimmerman Medal and Lecture	American Association of Ocular Pathology	2005
	Ophthalmic Pathology Award	International Council of Ophthalmology	2006
Claes H. Dohlman, MD, PhD	Cornea World Congress Medal	The Cornea Society	2005
	Alcon Research Award	Alcon	2005
	Claes H. Dohlman Award for Excellence in Teaching and Education	The Cornea Society	2006
	Laureate Award	AAO	2007
	Prize for Vision Research	Helen Keller Foundation	2010
	European Union Cornea Society Medal	European Union Cornea Society	2010
Ilene K. Gipson, PhD	The Friedenwald Award	ARVO	2007
	Endre A. Balazs Prize	International Society for Eye Research	2008
Evangelos S. Gragoudas, MD	Mildred Weisenfeld Award	ARVO	2006
Meredith Gregory-Ksander, PhD	Sybil B. Harrington Special Scholar Award	RPB	2009-10
Pedram Hamrah, MD	Career Development Award	RPB	2011
David G. Hunter, MD, PhD	Walt and Lily Disney Award for Amblyopia Research	RPB	2005-6
	Lew R. Wasserman Merit Award	RPB	2005
	Outstanding State Advocate Award	RPB	2007
Ula V. Jurkunas, MD	ARVO/Alcon Early Career Clinician Scientist Research Award	Alcon Foundation/ARVO Foundation for Eye Research	2008
	Physician Scientist Award	RPB	2011
Andrius Kazlauskas, PhD	Republic of Lithuania Academic Award	Lithuanian Academy of Sciences	2009
Ivana K. Kim, MD	Physician Scientist Award	RPB	2009
Gabriel Kreiman, PhD	New Innovator Award	National Institutes of Health	2009
	NIH Director's Award	National Institutes of Health	2009
	Career Award	National Science Foundation	2010
Deborah P. Langston, MD	Phillips Thygeson Plaque and Lecture	Ocular Microbiology & Immunology Group	2005
Tiansen Li, MD, PhD	Board of Directors' Award	Foundation Fighting Blindness	2008
Richard H. Masland, PhD	Proctor Award	ARVO	2010
Joan W. Miller, MD	Pfizer Ophthalmics Translational Research Award	ARVO	2006
	M. Donald Gass Medal	The Macula Society	2009
	Joseph B. Martin Dean's Leadership Award for the Advancement of Women Faculty	Harvard Medical School	2010
	Suzanne Veronneau-Troutman Award	Women in Ophthalmology	2010
	Paul Henkind Memorial Award	The Macula Society	2011
Louis R. Pasquale, MD	Achievement Award	AAO	2006
	Physician Scientist Award	RPB	2010
	Secretariat Award	AAO	2010
Eliezer Peli, MSc, OD	The Pisart Vision Award	Lighthouse International	2006
	Alcon Research Institute Vision Award (shared with Robert Massof, PhD)	Alcon	2009
	The William Feinbloom Award	American Academy of Optometry	2009
	The Helmoltz Lecture	The Helmoltz Institute, Utretcht, Holland	2010
	The Otto Schade Prize	The Society for Information Display	2010
	The Edwin H. Land Medal	Optical Society of America and the Society for Imaging Science and Technology	2010
Douglas J. Rhee, MD	Achievement Award	AAO	2007
	Physician Scientist Award	RPB	2007
Joseph F. Rizzo III, MD	Senior Achievement Award	AAO	2007
Magali Saint-Geniez, PhD	NIH Director's New Innovator Award	NIH	2009
Lois E. H. Smith, MD, PhD	Alfred W. Bressler Prize in Vision Research	The Jewish Guild for the Blind	2005
	Alcon Research Institute Award	Alcon	2007
	Fridenwald Award for Outstanding Research in the Basic/Clinical Sciences as Applied to Ophthalmology	ARVO	2008
	NIH Director WALS Lecturer for Outstanding Contributions to Science	National Institutes of Health	2009
	Research to Prevent Blindness SeniorInvestigator Award	RPB	2009
Lucia Sobrin, MD, MPH	Career Development Award	RPB	2008
	Early Clinician Scientist Award	ARVO	2011
David A. Sullivan, PhD	Lifetime Achievement Award	Governing Board of the Tear Film & Ocular Surface Society (TFOS)	2010
Jennifer K. Sun, MD, MPH	Early Career Clinician Scientist Research Award	ARVO/Alcon	2008
Janey L. Wiggs, MD, PhD	Lew R. Wasserman Merit Award	RPB	2011
Michael J. Young, PhD	Special Research Scholar Award	RPB	2008

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Michael Gerard Morley, MD *Assistant Clinical Professor of Ophthalmology*
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