Leading the Fight Against Glaucoma

Bascom Palmer’s Clinicians and Researchers Deploying New Strategies and Technologies to Help Patients Preserve Vision

For more than 50 years, Bascom Palmer’s researchers and clinicians have been leading the fight against glaucoma, one of the leading causes of blindness throughout the world. Now, advancements in optical imaging technology have provided insights into the structural changes in the eye that can signal a loss of vision.

Other researchers are studying the genetic linkages – why glaucoma rates are higher in certain groups of people and the genes that may cause or increase the risk of developing glaucoma.

On the clinical side, Bascom Palmer’s physicians are trying medical approaches and surgical advancements to delay or halt the progression of the disease. And perhaps most exciting of all, studies are well underway on finding neuroprotective medications that could prevent the death of nerve cells in the retina and stop the disease in its tracks.

“The battles against glaucoma are being fought on many levels,” says Richard K. Parrish, II, M.D., professor and Edward W.D. Norton Chair of Ophthalmology. “While we still don’t understand the basic mechanism, we have made great strides in diagnosing glaucoma – even before symptoms occur – and in treating this blinding disease through medication and surgery.”

Glaucoma affects more than three million Americans and is responsible for 15 percent of world blindness. It is a family of ocular diseases characterized by progressive damage to the retinal ganglion cells that capture visual images, and the optic nerve, which carries those images to the brain. Vision loss from glaucoma is irreversible.

Bascom Palmer’s researchers are making significant progress in identifying genetic, metabolic and chemical precursors to the disease, using experimental and clinical models, as well as cutting-edge optical imaging technology developed at Bascom Palmer and not available anywhere else in the world.

Treating high eye pressures

Glaucoma often involves high levels of pressure inside the eye. The front part of the eye is filled with a clear fluid called aqueous humor that nourishes nearby tissues and then leaves the chamber through drainage channels at the “angle” where the iris inserts into the “sclera,” or white of the eye. Usually, the fluid flows smoothly through the trabecular network, a meshwork-like drainage system, keeping eye pressure at a normal level.

But in open-angle glaucoma, the most common type, the eye drainage system does not work properly. Instead, the fluid builds up, creating high intraocular pressure (IOP) that damages the sensitive optic nerve and results in gradual vision loss. However, there are other forms of the disease as well, including angle closure glaucoma, which is more prevalent in people of Asian origin, pseudo-exfoliation glaucoma, pigmentary glaucoma, angle recession glaucoma and neovascular glaucoma.

Bascom Palmer’s ophthalmologists see glaucoma patients from newborn infants to seniors. Individuals with high risk for glaucoma include people over age 60, those with a family history of glaucoma and people of African descent over age 40. Hypertension, diabetes and other systemic diseases are also risk factors. Among Hispanics, glaucoma is the most common cause of blindness.

“Treating glaucoma is a forte of Bascom Palmer Eye Institute,” says Parrish. The Institute’s first glaucoma specialist, Douglas R. Anderson, M.D., professor of ophthalmology and the Douglas R. Anderson Chair in Ophthalmology, has been at the forefront of glaucoma research for more than 50 years. He discovered that elevated intraocular pressure impairs axonal transport in the optic nerve and is affected by glaucoma. Paul F. Palmberg M.D., Ph.D., professor of ophthalmology, coined the term “target pressure” and helped to clarify the relationship between the level of pressure in the eye and how well a glaucoma patient retains peripheral vision.

Today, clinicians have found that most types of glaucoma respond well to medication if diagnosed at an early stage, says David S. Greenfield, M.D., professor of ophthalmology. Greenfield has a particular interest in the treatment of patients with open-
WHAT IS GLAUCOMA?

Glucoma is a leading cause of blindness in the United States, especially for older people. But loss of sight from glaucoma can often be prevented with early treatment.

RISK FACTORS FOR GLAUCOMA

- FAMILY HISTORY OF GLAUCOMA
- AGE 60+
- ABNORMALLY HIGH INTRAOCULAR PRESSURE
- AFRICAN DESCENT, AGE 40+
- PAST EYE INJURIES
- DIABETES
- PRESSURE FOR GLAUCOMA RISK FACTORS

Dr. Richard Parrish

visual field loss in patients with uncontrolled glaucoma,“ Greenfield says. His recent work in collaboration with Tracy M. Wright, M.D., assistant professor of clinical ophthalmology, has shown that in some patients, the visual field can actually improve following surgery for glaucoma. “This indicates that lowering of IOP not only prevents visual field degradation, but can actually enhance visual sensitivity in areas of the visual field that have been depressed by glaucoma damage,” Greenfield says.

One of the major questions for ophthalmologists has been what type of glaucoma surgery produces the best long-term results. Steven J. Gedde, M.D., professor of ophthalmology and the John G. Clarkson Chair in Ophthalmology, was the lead investigator of the international “Tube Versus Trabeculectomy (TVT) Study,” a five-year (and ongoing) multicenter clinical trial that evaluates these two types of surgical procedures for patients with a failed prior eye surgery. “Similar degrees of pressure reduction were observed with both groups, but there was a higher success rate in the tube shunt group,” Gedde says. “That group had a much lower rate of follow-up surgeries, while the trabeculectomy patients needed additional surgery to control pressure.”

Gedde says this landmark clinical trial has supported a shift in practice patterns, as Medicare data and surveys of AGS members show that tube shunts are increasingly being utilized as an alternative to trabeculectomy. The TVT study also prompted another multicenter clinical trial, also led by Gedde, the “Primary Tube Versus Trabeculectomy Study (PVTY)” involving patients without previous ocular surgery. “We expect that the PVTY study will provide valuable information to guide patient care,” Gedde says.

Helene Kornmann, M.D., Ph.D., assistant professor of clinical ophthalmology, is leading a prospective randomized clinical trial evaluating the use of topical nonsteroidal anti-inflammatory drugs (NSAID) after tube shunt implantation. “A topical NSAID may beneficially affect the healing process following tube shunt surgery and further enhance the success of the procedure,” says Kornmann.

Bascom Palmer is also a leader in minimally invasive glaucoma surgery. Alana Grajewski, M.D., professor of clinical ophthalmology, and Ta Chen P. Chang, M.D., assistant professor of clinical ophthalmology, are among the first surgeons in Florida performing gonioscopy-assisted transluminal trabeculotomy (GATT) on adults.

Bascom Palmer’s bioengineering team has also spent more than two decades developing an innovative microdrainage shunt to keep the drainage system open without inflaming nearby tissues. Jean-Marie Parel, Ing ETS-G, Ph.D., research associate professor of ophthalmology, Henri and Flore Lesieur Chair in Ophthalmology, and director of Bascom Palmer’s Ophthalmic Biophysics Center, began discussing a potential microshunt with Parrish in the 1980s and continued working with the late Francisco E. Fantes, M.D., professor of clinical ophthalmology, in the 1990s. “Francisco wanted something simple and easy to implant that would last forever,” says Parel. “But it wasn’t until Leonard Pinchuk, Ph.D., D.Sc. developed a synthetic biomaterial that Francisco’s dream could become a reality.” Pinchuk is a polymer chemist and entrepreneur, as well as a distinguished research professor of biomedical engineering at the University of Miami.

Bascom Palmer researchers are collaborating with the Laser Center in the Dominican Republic to conduct clinical trials using the microshunt. Their research was presented at Bascom Palmer’s 2014 educational program, CURSO Interamericano.

Using sophisticated imaging

Luis E. Vazquez, M.D., Ph.D., assistant professor of clinical ophthalmology, is using sensitive optical coherence tomography (OCT) instruments and analyses to better understand the structural changes in the retinal ganglion cells and the bundle of fibers in the optic nerve—the key pathway for visual signals traveling from the eye to the brain. This is important because early detection of glaucoma and disease progression translates to timely treatment and prevention of vision loss.

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Improving monitoring and screening

“Previously, glaucoma monitoring consisted of periodic IOP measurements and annual visual field testing to detect changes,” says Greenfield. “Now, the standard of care includes sophisticated digital imaging of the optic nerve and surrounding retinal nerve fiber layer as an adjunct to visual field testing. In many patients this has remarkably enhanced our ability to identify optic nerve damage years before vision loss has occurred.”

Since glaucoma is a chronic, progressive “theft of vision,” ophthalmologists need the best possible monitoring and screening tools, says Parrish. “A typical screening looks only at elevated IOP,” he adds. “However, as many as one-third of glaucoma patients have a normal eye pressure and may not be diagnosed until they have suffered a significant loss of vision.”

Screening is particularly important for high-risk populations, such as African-Americans, Afro-Caribbeanans and Hispanics. “Haitian-Americans have some of the highest rates of glaucoma in the world,” says Lee. “There is clearly a genetic link.”

Lee collaborated with Parrish in a recent study, “Glaucoma Screening in the Haitian Afro-Caribbean Population of South Florida.” The study found that many Haitian-Americans under age 40 have early warning signs such as high eye pressures and suspicious changes to the optic disc.

Lee is also medical director of ophthalmology for Project Access, a University of Miami Miller School of Medicine initiative to improve healthcare in Haiti. “We initiated a laser therapy program to reduce the IOP in glaucoma patients, helping to save their vision since many of these glaucoma patients have no access or economic resources to pay for glaucoma medications,” he says. Lee is also the medical director for community ophthalmology where he leads groups of medical students from the Ophthalmology Interest Club along with ophthalmology residents and fellows from Bascom Palmer, to screen patients for glaucoma, especially in economically challenged and high-risk populations.

Lee and neuro-ophthalmologist Byron L. Lam, M.D., professor of ophthalmology and the Robert Z. & Nancy J. Greene Chair in Ophthalmology, are analyzing the results of these vision screenings to develop approaches for better detection and more efficient screening of patients for glaucoma.

Searching for potential causes

While high IOP has long been known to lead to glaucoma, Bascom Palmer’s researchers are trying to identify other potential causes that could result in better treatments. For instance, Lee is an investigator in two NIH-funded studies — one on the genetics of pseudoexfoliation glaucoma and another on the genetics of open angle glaucoma. These international studies involving institutions in Europe, Asia and the United States have already produced a number of important and high profile findings on genetic risk factors for glaucoma.

Parrish notes that while many glaucoma patients benefit from pressure lowering, a sizeable percent does not improve. “So, we have to look beyond the obvious IOP for other risk factors,” he adds.

Parrish says there are a number of potential culprits, such as sleep apnea. “Some people don’t breathe normally when asleep, and that can result in a low level of oxygen that may starve the optic nerve,” says Parrish, who is studying the issue with researchers at the University of Miami Sleep Center, located within Bascom Palmer’s Miami eye center.

With support from the National Institutes of Health (NIH), Porciatti has been using noninvasive electrophysiology tools to track 600 adult patients with a family history of glaucoma, elevated IOP or another high-risk indicator. “We want to see what happens with the retinal ganglion cells in patients that develop glaucoma,” Porciatti says. He is also tracking the physiological response of retinal ganglion cells under stress to identify susceptible subjects upon head-down body posture, which temporarily increases intracocular pressure.

“We need a better way to identify whether a patient who is at risk for glaucoma is a good candidate for treatment before prescribing expensive eye drops for the next 20 or more years,” he says. “Our studies may point clinicians in the right direction.”

The role of lipids

Currently, Sanjoy K. Bhattacharya, Ph.D., M.Tech., professor of ophthalmology, is studying the role of lipids in glaucoma. Long known for their role in heart disease — both positive and negative — lipids are hydrophobic compounds that are also found in the eye. For more than a decade, Bhattacharya has been seeking to identify endogenous non-prostanoid lipids that could be potentially used for treatment of glaucoma without causing inflammation. Currently prostanooids are the only class of lipids that are used for glaucoma treatment. Prostanooids were originally discovered in 1965 in the iris, and became the first commercial glaucoma medication in 1997. No other class of lipids has ever been investigated for glaucoma therapy, which was a key motivating factor for Bhattacharya’s research.

About four years ago, Bhattacharya and Lee began looking at the lipid differences between aqueous humor fluid and anterior chamber tissues of normal eyes and those of glaucoma patients. “We felt that if there were missing lipids with the disease, restoring those lipids to the eye could potentially help stop the progression of glaucoma,” he says.

In addition to his ongoing funded research, Bhattacharya recently received a three-year, $999,998 grant from the U.S. Department of Defense to study the use of lipids to help patients who have suffered a traumatic injury to the eye resulting in glaucoma.

Focusing on neuroprotection

Several Bascom Palmer researchers are focusing on neuroprotective strategies to keep retinal ganglion cells alive and healthy. “We may be able to make these nerve cells more tolerant of high pressures,” says Vazquez. “If we can increase the stability and health of the fibers that make up the optic nerve,
Treating Pediatric Glaucoma

Bascom Palmer is one of the few institutions with deep expertise in treating pediatric glaucoma. “You need to address the child's visual development as well as the glaucoma,” says Ta Chen P. Chang, M.D. “Our care team does both” he says. “We also put an emphasis on helping children and parents understand how to deal with the disease.”

Alana Grajewski, M.D., says Bascom Palmer's integrated approach to pediatric glaucoma includes genetic testing services and low-vision specialists who can help maximize a child’s available eyesight.

Instead, Lee is looking at cellular and molecular ways to use stem cells to provide nutrients and other support for the endangered retinal ganglion cells to keep them healthy and transmitting to the brain. "All cells have to work closely with their neighbors, so implanting stem cells can help improve the functioning of retinal ganglion cells," Lee and Bhattacharya call their innovative approach “neuro-rejuvenation.” They have recently created a novel approach to stimulating the function of retinal ganglion cells that preserves the cell connections to the brain after ocular trauma.

Lee and Bhattacharya are also testing a new class of molecules that lower IOP in the eye in experimental models. Lee adds that the University of Miami is obtaining patent protection for their collaborative new drug discovery, and the next step will be clinical trials.

New research directions

Valery I. Shestopalov, Ph.D., professor of ophthalmology, is using a combination of high-throughput technologies with molecular and transgenic approaches to find potential targets for glaucoma medications. "Existing glaucoma therapies are all based on lowering IOP," he says. "We need to develop different strategies and identify new targets to improve treatment. When we understand the molecular mechanisms that cause neurons to die, we can block one or several components of this pathway and this will become a major step forward toward improved preservation of vision."

Shestopalov's project started in 2004 with reconstructing a disease-disrupted network of cellular interactions between neurons and glial cells and building a bioinformatics model of glaucoma. "This approach proved to be very effective for identification of pathogenic molecules, which are the new targets for therapeutic interventions in glaucoma," he adds.

Recently, Shestopalov found that the cell communication channel Pannexin1 (Panx1) is the "Achilles' heel" of injured retinal neurons. Teaming with colleagues at Cornell University, Scripps Research Institute, and institutes in Canada and Europe, Shestopalov found that the Panx1-mediated mechanisms actively contribute to several disorders, such as glaucoma, retinal ischemia and ischemic optic nerve stroke.

“Our leading hypothesis states that uncontrolled activation of these molecular channels triggers a death spiral in retinal ganglion cells," he says. "This suggests the Panx1 pathway as a novel target for therapy in these blinding pathologies."

Since the only Panx1-blocking drug, probenecid, is nearly a century old and is not truly specific, Shestopalov is developing a more specific drug to be tested in these diseases. In 2013 he started screening for new inhibitors and established a new collaboration with a life sciences company to develop a new generation glaucoma drug.

Reflecting on Bascom Palmer's ability to deliver leading-edge patient care while advancing medical knowledge, Shestopalov says, "This is an exciting time for all of us in glaucoma research. We are continuing to make solid progress in the worldwide struggle against this blinding disease."