Dear Friends and Colleagues,

I’d like to introduce you to a new newsletter that will supplement our larger publication, Advances in Ophthalmology. We want to share with you, on a more frequent basis, news of research and clinical advances at the University of Michigan Kellogg Eye Center.

This is an exciting time for research in ophthalmology and vision science. During a period of rapid growth in the field of genetics, Kellogg scientists are making good progress in their search for genes associated with glaucoma, age-related macular degeneration, and other hereditary eye diseases. In Kellogg labs, scientists are also searching for ways to prevent vision loss caused by diabetes; other researchers are studying mechanisms related to retinal regeneration, abnormal cell growth, and cell signaling—all factors that underlie eye disorders and pave the way for potential new therapies.

In recent months several new research scientists have joined Kellogg. In this issue you’ll read about the work of David Zacks, M.D., Ph.D., and Howard Petty, Ph.D., two of our newest faculty members.

We take pride in the breadth, depth, and excellence of our research. I hope you enjoy this brief review of Kellogg’s efforts to bring research advances to serve our patients and, ultimately, to stop blinding eye disease.

Paul R. Lichter, M.D.
Director, University of Michigan W.K. Kellogg Eye Center
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In the search for AMD genes, answers may be buried in the data

Kellogg scientists have made impressive gains in the search for genes associated with age-related macular degeneration (AMD). But the newest research techniques generate such vast quantities of data that it is often difficult to see the patterns buried within.

Now, thanks to a grant from the Elmer and Sylvia Sramek Charitable Foundation, our researchers are developing a sophisticated data management and analysis system—consisting of six interactive, integrated databases—to help them extract meaningful information from two major lines of research. They will bring together data from genetic studies of specific families affected by AMD, and genomic studies that seek to identify changes in the expression of “eye” genes during aging and as the disease progresses.

Anand Swaroop, Ph.D., checks the microarray robot that speeds the search for AMD genes.

Anand Swaroop, Ph.D., Professor of Ophthalmology and Visual Sciences and of Human Genetics, will direct the study. Using Kellogg’s microarray facility, Dr. Swaroop’s researchers will scan some 20,000 eye-related genes to identify possible candidates for susceptibility to AMD. In the first phase of the study, researchers will look for changes in gene expression that occur during normal aging, and as the retinal disease progresses.

At the same time, Dr. Swaroop and his colleagues are collecting data—demographics, age, risk factors—from families affected by AMD. Some 1800 individuals, including 1050 families with AMD, have volunteered for this ongoing Kellogg study.

The genetic underpinnings of AMD are quite complex—the disease is probably caused by the interaction of multiple genes and environmental risk factors.

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Cornea implants have restored vision for thousands of people. But some who cannot tolerate that procedure—perhaps due to dry eyes or other complications—may benefit from an implant that creates a transparent window in the cornea. The device, called a keratoprosthesis, is a plastic disc placed in corneal tissue. Surgeons can insert the disc into a cornea that has been rendered opaque due to scarring or disease.

A keratoprosthesis may improve vision when cornea transplants don’t succeed.

**Cornea implant creates a window for clear vision**

Kellogg cornea specialist Shahzad I. Mian, M.D., performed the procedure during his fellowship at Massachusetts Eye and Ear Infirmary at Harvard Medical School. Dr. Mian says that the procedure had limited success in its earliest years; between 1965 and 1975 surgeons at Massachusetts Eye and Ear implanted only 36 devices. With design modifications, the success rates have improved, and since 1990 approximately 200 devices have been implanted. The FDA approved the Dohlman-Doane keratoprosthesis in 1992.

The device has been most successful for people who have had repeated corneal graft failures. Success rates are lower, but steadily improving, for patients who suffer from corneal injury due to chemical burns or inflammatory diseases such as Stevens-Johnson syndrome and pemphigoid. Dr. Mian notes that complications include infection, inflammation and melting of surrounding corneal tissue, but advances in technology and availability of better antibiotics have minimized the risk of these complications. Many patients who are candidates for a keratoprosthesis can develop glaucoma before or as a result of the surgery, requiring medications or additional surgery.

The Kellogg Eye Center is participating in a multi-center trial comparing the keratoprosthesis to repeat corneal transplantation in patients with previously failed corneal transplants. Dr. Mian says the procedure can benefit a select group of patients, and for the right candidate, the results are dramatic. “To see a patient who was blind emerge from the surgery with 20/20 vision is a remarkable experience,” he says.

### Looking at common factors in AMD & HEART disease

After analyzing a number of studies on age-related macular degeneration (AMD), Andrew K. Vine, M.D., has observed that the risk factors for AMD have much in common with those for cardiovascular disease. Though some of the findings vary, the risk factors for AMD most often cited include smoking, advanced age, obesity, atherosclerosis, and decreased antioxidant status. That list, says Dr. Vine, represents a cardiovascular risk profile. Dr. Vine, senior retina specialist for the Kellogg Eye Center, has designed a pilot study to determine whether some of the same underlying mechanisms are at the root of both diseases.

The study will test individuals with AMD for two substances that have been linked to cardiovascular disease: C-reactive protein and homocysteine. C-reactive protein, a blood protein which indicates underlying inflammation, is of interest because inflammation is a reliable predictor of cardiovascular disease, even among apparently healthy men and women. Elevated homocysteine, an amino acid in the blood, has been shown to correlate with increased cardiovascular disease.

Dr. Vine wants to know whether these substances are elevated in patients with AMD, and, if so, what role they may have in triggering the disease.

These disease indicators go hand in hand with Kellogg’s genetic research. When we combine knowledge of specific genes that may trigger or exacerbate AMD with information about the risk factors expressed through proteins, we will develop a more complete picture of the causes and progression of the disease.

Dr. Vine says that results of the pilot study, which is supported by the UM Office of the Vice President for Research, will be part of a future grant proposal to assess other inflammatory factors and specific genes associated with this progressive blinding eye disease.

buried in the data

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Says Dr. Swaroop, “The interplay of genes and risk factors makes the task of integrating divergent genetic and gene expression data sets even more crucial.”

Dr. Swaroop is Director of the Sensory Gene Microarray Node and Coordinator/ Director of the Center for Retinal and Macular Degeneration at the Kellogg Eye Center.

The Elmer and Sylvia Sramek Charitable Foundation, based in Chicago, was established in 1995 to support a broad range of charitable and educational projects that focus on visual impairment in the elderly and on the prevention, treatment and cure of cancer.
Thanks to a new four-year grant, Kellogg scientists will study the process by which certain retinal cells die during retinal detachment, a condition that can cause individuals to become blind or lose a significant portion of vision. David N. Zacks, M.D., Ph.D., will direct the research under a Career Development grant totaling $200,000 from Research to Prevent Blindness (RPB).

Dr. Zacks, a retina specialist who has recently joined Kellogg, will study the mechanisms underlying the death of photoreceptors, the light-sensitive cells that are essential for vision. In previous studies of retinal detachments in rodents, Dr. Zacks collected data suggesting that apoptosis, or programmed cell death, is the primary mechanism in the death of photoreceptors. The grant will allow Dr. Zacks to go a step further—to explore the molecular and cellular processes that trigger the cascade of ever-greater cell loss. His ultimate goal is to develop neuroprotective therapies to treat retinal detachments and related diseases.

Retinal detachment occurs when the retina is pulled away from its normal position in the back of the eye. Because the retina sends visual images to the brain through the optic nerve, a detached retina will blur the vision and can cause blindness if it is not treated. The condition is more prevalent as we age, but it can also occur in younger individuals.

If a tear in the retina is found early, surgeons can treat patients on an outpatient basis, using lasers or a freezing technique to seal the damage. When the disease progresses and the retina detaches from the back of the eye, patients must undergo more complex surgical procedures. Dr. Zacks notes that about one in 10,000 people in this country are affected by retinal detachments each year. He hopes that one day his research will lead to treatments that will improve the visual outcome for patients with this debilitating disease.

RPB is the world’s leading voluntary organization supporting eye research. Since it was founded in 1960, RPB has channeled hundreds of millions of dollars to medical institutions throughout the United States for research into all blinding eye diseases. Dr. Zacks’ grant marks the fourth time the Department of Ophthalmology and Visual Sciences has received a Career Development Award.
Shining the light on PULSING immune cells

Kellogg’s newest senior scientist, Howard R. Petty, Ph.D., is using high-speed imaging to provide fascinating new details about the way immune cells fight off invading bacteria or disease cells. He has recorded the wave-like action of the immune cells, called neutrophils, as they move toward the foreign substance.

Dr. Petty, who comes to Kellogg from Wayne State University, published the results of his studies in collaboration with colleague and fellow biophysicist Andrei Kindzelskii, M.D., Ph.D. Together they showed that as neutrophils move toward their target they create reactive oxidizing toxins that carry out the attack. Dr. Petty explains that the cell has its own metabolism, which generates a wave-like action. He detected the waves by shining a light on NAD(P)H, a chemical compound within the neutrophils that is naturally fluorescent.

Dr. Petty compares the oscillating action to that of a chemical clock within each cell. The purpose of the clock, he explains, is to help cells coordinate multiple chemical reactions and, consequently, cell functions.

The discovery of chemical wave motion in cells surprised the scientific community because it contradicts a fundamental law of thermodynamics. Until the ’60s, it was believed that a chemical reaction would move in one direction until it weakened and reached a stable state. A Russian chemist was first to show the oscillating inorganic chemical reactions. Now Dr. Petty brings the focus to a single cell, showing that as long as they are fed, the waves of NAD(P)H can move back and forth indefinitely.

Dr. Petty’s research has given us a whole new level of understanding about the biochemistry of living cells. One of his most significant findings is that neutrophils play a key role in inflammatory responses in autoimmune diseases. His research has major implications for understanding diseases such as arthritis, the eye condition uveitis, and multiple sclerosis.