

Dear Friends and Colleagues,

Kellogg maintains its position at the forefront of vision research, in part, because our researchers have developed a wide array of strategies for tackling eye disease. In this issue, you'll read about one lab's progress in defining the chromosomal regions where we are most likely to find genes related to age-related macular degeneration (AMD).

At the same time, Kellogg scientists are looking for more immediate solutions for our patients. One clinical trial assesses a new drug that shows promise for treating the wet form of AMD. While that is the less common form of the disease, it is the type that is more likely to cause severe vision loss.

In the broader area of retinal degeneration, we are pleased to have an internationally-known ophthalmologist join our faculty. **John R. Heckenlively, M.D.**, will continue his groundbreaking research on retinal dystrophies, in particular retinitis pigmentosa. We are delighted that he is here. He tells us that this eye center is unique in having both excellent resources and an environment that fosters collaboration. We will keep you posted on his research.

Finally, we have recently installed a laser system that is the direct result of Kellogg research. The IntraLase system, which grew out of our work on the femtosecond laser, has attracted many patients interested in its use for LASIK surgery. Back in the laboratories, Kellogg researchers are examining how this ultrafast laser could improve other forms of eye surgery.



Paul R. Lichter, M.D.  
Director, University of Michigan  
W.K. Kellogg Eye Center

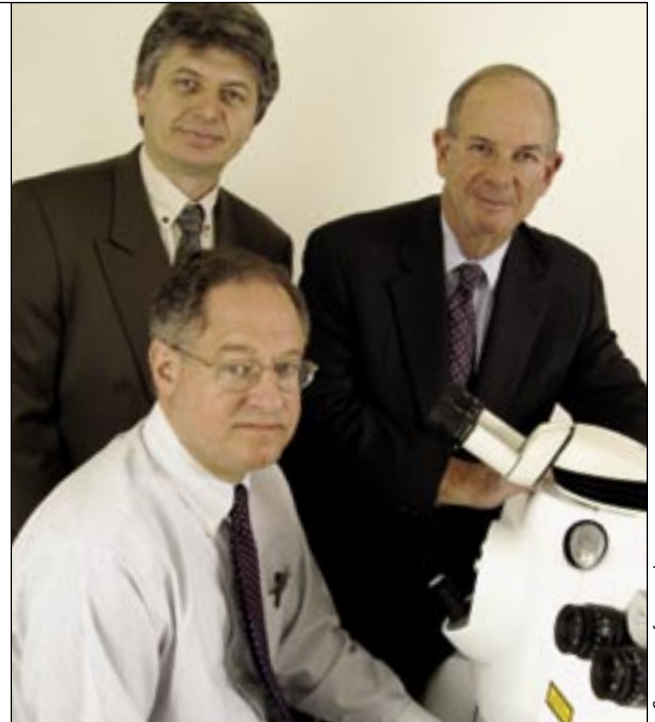
## Ultrafast laser developed at MICHIGAN

Some ten years ago, when Kellogg ophthalmology resident Ron Kurtz, M.D., learned that researchers at the College of Engineering were testing the ultrafast or femtosecond laser for industrial use, it occurred to him that the same laser could be a powerful tool for eye surgery. Dr. Kurtz pursued the idea, and by 1997, he and UM physicist Tibor Juhasz, Ph.D., had developed the concept sufficiently to form a company to commercialize the ultrafast laser for LASIK surgery.

Today, Kellogg surgeons perform refractive surgery with the IntraLase FS laser, and Michigan physicians are again investigating new surgical uses, this time for corneal transplants and glaucoma surgery. In each case the laser performs a procedure that traditionally requires a surgical blade or knife.

Alan Sugar, M.D., senior ophthalmologist in Kellogg's Cornea Service, explains that the laser's speed and precision make it a formidable tool for refractive surgery and other cornea procedures. In LASIK surgery, the femtosecond laser is now used in place of a microkeratome blade to make a flap in the cornea. The laser creates an incision using rapid pulses that focus on a spot of only 3 microns. The speed is measured in femtoseconds, equal to one quadrillionth of a second.

Dr. Sugar says that most of his patients now choose the IntraLase option



Tibor Juhasz, Ph.D., Paul R. Lichter, M.D., and, in front, Alan Sugar, M.D., worked on the original research project.

photo by Lin Goings

because it has been proven to reduce complications. Surgeons expect that the femtosecond laser will eventually be the standard of care, though the investment in the equipment brings added costs to ophthalmologists and their patients.

According to IntraLase, Inc., over 100,000 IntraLase LASIK surgeries have been performed since 1997.

### *Simplifying cornea transplants*

Other Kellogg researchers, including cornea specialist H. Kaz Soong, M.D., are investigating the femtosecond laser for a type of cornea transplant that surgeons consider to be extremely difficult. Under an NIH grant, Dr. Soong is working with Dr. Juhasz and Shahzad I. Mian, M.D., to investigate the use of the femtosecond laser for replacing the back (posterior) part of the cornea in a procedure known as posterior lamellar keratoplasty.

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## Narrowing the search for AMD genes

Kellogg scientists, working with colleagues in the School of Public Health, have significantly narrowed the range of chromosomal locations where they expect to find genes associated with age-related macular degeneration (AMD).

In a paper published in the *American Journal of Human Genetics*, Kellogg's Anand Swaroop, Ph.D., and his research team have used genetic scanning techniques to identify regions on five chromosomes where AMD genes are likely to reside. They have identified two new locations (on chromosomes 2 and 22) and have confirmed three locations (on chromosomes 1, 5, and 9) previously suggested by other researchers.

Dr. Swaroop explains that cross-validation is important for complex diseases such as AMD. "Our researchers have been able to build on past studies—our own and a handful of others," he says. "We have identified specific regions of the genome where we can intensify our research efforts."

Kellogg researchers narrowed the search for AMD-related genes by performing a high-resolution genome scan of all 23 pairs of participants' chromosomes. They used over 700 DNA markers, placed in relatively close proximity, to define smaller regions where they will continue their search for susceptibility genes.

Markers are commonly used in genetic research. They are known DNA segments that help define locations and regions on chromosomes.

Patients were recruited from the Kellogg Eye Center's clinical practice. Most had late-stage AMD. Each individual was paired with a sibling or other relative to create a greater likelihood of gathering subjects with similar genetic profiles.

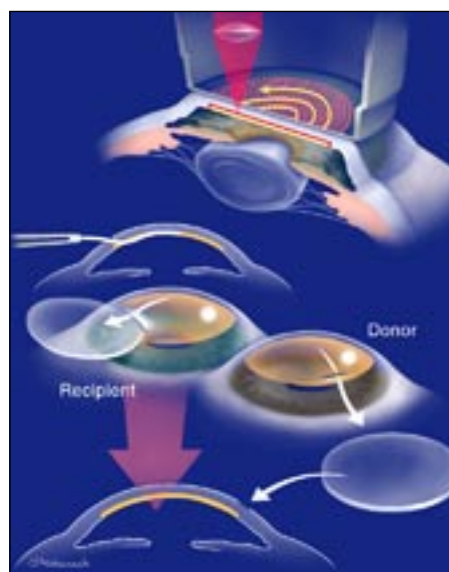
The next step for Kellogg researchers is to identify candidate genes within the newly defined regions, says Dr. Swaroop. "The next few years should be very exciting," he adds.

## developed at Michigan

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Cornea transplants restore vision for some 40,000 individuals each year. In the standard penetrating keratoplasty, surgeons remove the entire cornea in "cookie cutter" fashion and replace it with a similarly shaped cornea from a donor. "The problem with this method is obvious," says Dr. Soong. "Why replace the full-thickness cornea in cases where the disease affects just the innermost layer?"

In 1997 a Dutch ophthalmologist devised a surgical method of removing the back portion of the cornea. Despite several advantages, the procedure was very complex and few cornea surgeons opted to perform it.



*After the laser cuts the cornea, the back portion is removed through the side slit and the donor tissue implanted.*

Dr. Soong believes the femtosecond laser will eventually offer a simpler and safer means of removing the posterior side of the cornea. The surgeon will use the femtosecond laser to make side cuts of a remarkably precise depth—about 300 microns (the cornea itself is 500-600 microns thick) and then use the laser to split the cornea's thickness. Next the surgeon, almost miraculously, pulls the posterior portion of the cornea through the side slit and inserts the corresponding donor tissue.

One of the chief advantages is that the laser process leaves the top layer of the cornea intact. There is no need for sutures because the top layer holds the new posterior layer in place. A practiced surgeon, Dr. Soong says, "I'm impressed by the potential of this laser. It's like magic."

The resulting strength of the cornea after surgery is another benefit. "If you are hit in the eye, the graft-junction holds—it doesn't tear apart," says Dr. Soong, who sees patients each year with torn corneas, even years after the initial full-thickness transplant. When the investigation advances to clinical testing, perhaps by year's end, Dr. Soong expects that vision will improve within a month after surgery, as compared to 6-12 months for full-thickness cornea transplants.

## Improving glaucoma surgery

Studies are underway using the femtosecond laser to create channels beneath the eye's surface to allow the fluid inside the eye to drain more easily. This lowers the pressure inside the eye, which is the objective in treating glaucoma with either eye drops or surgery.

Paul R. Lichter, M.D., director of the Eye Center and a glaucoma specialist, explains that in conventional glaucoma surgery, the healing response, in part related to the damage of tissues at the incision site, may result in scarring and subsequent closure of the drainage channel. However, the very short and powerful energy of the femtosecond laser allows the surgeon to make channels beneath the surface of the eye, while leaving overlying tissues intact. This approach aims to avoid the healing process associated with conventional glaucoma surgery, thus preserving the flow of the eye's fluid through the newly created channel.

In addition to Dr. Lichter, the research team includes, from Kellogg: Maya Eibschitz, M.D., and Victor M. Elnor, M.D., Ph.D.; and from the UM Center for Ultrafast Optical Science: Hsiao-hua Liu, Ph.D., Marcelle Mourou, B.S., and Gerard A. Mourou, Ph.D. Tibor Juhasz, Ph.D., has a joint appointment in Ophthalmology and in Bioengineering.



*Dr. Johnson talks with Ruth Fry, a participant in the clinical trial.*

## New treatments for wet AMD

Kellogg is testing a drug that shows promise for treating the wet form of age-related macular degeneration (AMD). Retina specialist Mark W. Johnson, M.D., is principal investigator for two clinical trials designed to assess rhuFabV2, which appears to inhibit the growth of abnormal blood vessels in the less common, wet form of AMD.

According to Dr. Johnson, wet AMD accounts for less than 20% of all AMD cases, but is responsible for 80-90% of vision loss associated with the disease. Although more people suffer from dry AMD, a disease in which one gradually loses central vision, there are no known treatments. Only a few treatments exist for wet AMD.

Preliminary studies on rhuFabV2 produced some very positive findings. "About a third of patients with wet AMD showed improved vision, a rare occurrence for macular degeneration," said Dr. Johnson. "Current treatments either stabilize vision or slow the progression of the disease."

Now Dr. Johnson and others will treat selected patients with rhuFabV2 and evaluate their progress over the next two years. A second clinical trial will compare rhuFabV2 with photodynamic therapy (PDT).

In wet AMD, abnormal blood vessels grow under the retina. If these vessels rupture and leak, they can cause scarring of the macula, the center of the retina. The result is sudden and severe vision loss.

Growth of the abnormal vessels is driven by a protein called vascular endothelial growth factor (VEGF). It appears that rhuFabV2 inhibits VEGF, and therefore, the growth of these vessels.

Dr. Johnson observes that current treatments help only half the people with wet AMD. One of these, laser photocoagulation, destroys or seals blood vessels, which stops the leakage. But the laser also burns tissue and causes scarring, and cannot be used for patients with abnormal vessels in the macula, where it would destroy fine vision.

Another treatment, PDT, has fewer side effects and helps more patients; it will be compared to rhuFabV2 in one of the clinical trials. In PDT, a patient receives an injection of the drug Visudyne, and then has a "cool" laser light directed at his/her eyes. The laser sets off a chemical reaction that destroys the abnormal blood vessels. While this treatment can stop vision loss, Dr. Johnson notes that it seldom improves sight.

If rhuFabV2 fulfills its promise, retina specialists will have a drug that treats most forms of wet AMD, explains Dr. Johnson. "We hope rhuFabV2 will prove both more effective and work for a wider range of patients than current treatment options."

Dr. Johnson cautions that rhuFabV2 is most useful for patients in the early phase of AMD. It cannot reverse vision loss for those who have already experienced scarring of the macula. He believes rhuFabV2 will eventually be tested for treating diabetic retinopathy and retinal vein occlusion.

## Advances in Research

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## IMPROVING eye surgery for patients with Graves Disease

Plastic surgeons at the Kellogg Eye Center have perfected a surgical technique to help patients with eye-related complications associated with Graves disease, an autoimmune disease that affects more than 3 million people in the United States and Europe. About half of these people develop eye manifestations, such as protruding eyes and retracted eyelids.

The new technique, graded anterior blepharotomy, is a simple, rapid, and predictable procedure that corrects the retracted eyelid, enabling it to close completely over the eye.

Kellogg's Victor M. Elner, M.D., Ph.D., and Bartley R. Frueh, M.D., developed the technique based on the

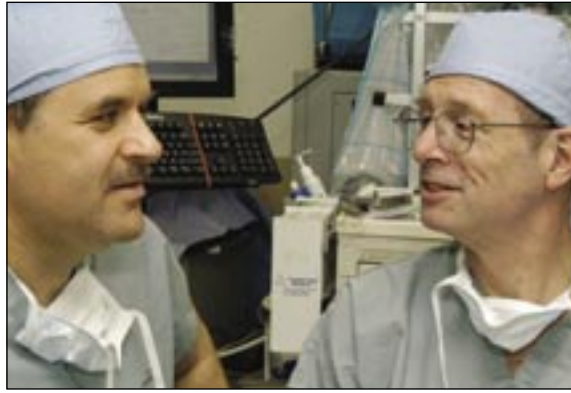


photo by Robert Prusak

*Drs. Elner and Frueh discuss the new surgical technique.*

work of Leo Koornneef, M.D., who conceived of this new approach in the early 1990s, and presented his findings at the Kellogg Eye Center in 1999.

According to Dr. Elner, patients with eyelid retraction, which leaves part of the eye exposed, must deal with significant physical discomfort and a range of risks to the cornea, including dry eyes, blurred vision, increased tearing, risk of corneal damage, and heightened glare. "Then too," he says, "they face embarrassment from

the obvious cosmetic deformity which, at times, can be severe."

Over the past 50 years numerous procedures have been proposed to deal with this debilitating problem. Not only were these complex and time-consuming, none of them have been particularly successful. "A vexing problem," says Dr. Elner.

The new technique requires minimal surgical dissection, an advantage over earlier procedures. A related benefit is that it does not need permanent sutures or the implantation of foreign material. The result is a simpler, more reliable technique that, even in the most severe cases, has been predictable and effective.

At last year's American Ophthalmological Society meeting Drs. Elner and Frueh reported that 93% of their patients' medical and cosmetic eye symptoms have resolved or been improved by this technique. The Kellogg surgeons describe the procedure in the January issue of *Archives of Ophthalmology*.



**In this issue, read about Kellogg research:** Ultrafast laser developed at Michigan, the search for AMD genes, new treatments for wet AMD, and eye surgery for Graves.

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