UCLA researchers make real progress against one of the leading causes of blindness at the End of the Tunnel

BY MICHAEL GOUGIS

AFTER YEARS OF STRUGGLE AGAINST ONE OF THE leading causes of blindness, UCLA researchers are at the dawn of a new era in the treatment and prevention of macular degeneration.

In the journey from theory to therapy—research, clinical trials, epidemiological studies—researchers at the David Geffen School of Medicine at UCLA and UCLA’s Jules Stein Eye Institute have played key roles in advancing the field of knowledge about the disease.

And now, they are watching as that knowledge translates into new treatments and even prevention strategies against a multi-faceted disease that inevitably leads to a patient slowly losing his or her eyesight.

“We are entering an incredibly exciting time in our field: the pharmacotherapy era for macular degeneration,” says Dr. Steven D. Schwartz, Chief of the Retina Division at UCLA’s Jules Stein Eye Institute.

“At the Institute, we have led translational research from the laboratory bench to the bedside, and that research is about to make available drugs that successfully treat all forms of ‘wet’ macular degeneration. It is an immensely satisfying time for us; we’re on the verge of making an enormous impact in the fight to preserve vision,” Schwartz says.

Macular degeneration is a disease that damages or destroys the center of the retina, the portion of the eye known as the macula. Macular degeneration destroys a person’s vision through the center of the retina, leaving only peripheral vision unaffected; a person can walk across a room, yet be unable to read a book or drive.

Smoking, diet, and genetic factors all play a role in the onset and development of the disease. While some forms attack the young, macular degeneration hits the elderly the hardest; 30 percent of people over 75 have some form of age-related macular degeneration. Among those 65 and older, between 15 percent and 20 percent has some form of the disease, and it is the leading cause of blindness in those 55 and older.

“If this were caused by a pathogen, you’d consider this a raging epidemic,” says Dr. Dean Bok, a professor of neurobiology and Dolly Green professor of ophthalmology at UCLA’s Jules Stein Eye Institute. “Our baby boomers are going to be burdened with a massive economic responsibility if we don’t come up with effective treatments.”

Age-related macular degeneration is typically found in two forms. Wet (neovascular) macular degeneration is a malfunction of the blood vessels under the retina; the dry (atrophic) version is an atrophy or degeneration of the tissues themselves. The wet form, by some accounts, is responsible for 90 percent of all cases of blindness in macular degeneration patients. Current treatment options have significant drawbacks. One treatment, an injected drug called Visudyne® (verteporfin) that is activated by a laser, attempts to cauterize the leaking blood vessels without collateral damage. But it can damage the retina’s blood supply or the retina itself, resulting in permanent loss of vision.

The dry form has proven particularly vexing to researchers—to date, there is no effective treatment known. Dry macular degeneration progresses at a slower rate than the wet form, and typically progresses over a decade.

VICTIMS OF MACULAR DEGENERATION, LIKE OTHER forms of blindness, pay a heavy toll in their quality of life; simple, daily activities become difficult, if not impossible.

Alice Remer, 97, a Santa Monica resident, has led a life worthy of a novel—a childhood in Austria, a harrowing escape by her family from the Nazi occupation of that country. Remer’s life has actually been the subject of two novels, both penned by her. When she was first diagnosed with macular degeneration, she was still writing, taking classes, hoping for the best when it came to her eyesight.

“In the beginning, I could read if I had a good light. When I attended a class to prepare the autobiography, I would bring a very strong light from home. Gradually, I could not read or use a computer,” she says.

“Now, it’s very foggy, everything. Any light is blinding, and it’s still getting worse. I cannot watch television, go to a movie, do anything that people do. I try to dictate my stories now, but it’s not the same. I cannot describe things in the same way. It becomes more of a report than a story from the heart, you know? It is too much for me. It makes you dependent. It takes everything.”

At its core, this is what UCLA researchers have been striving for—successful, effective treatments that improve the quality of life for these people.

Dr. Anne L. Coleman, professor of ophthalmology at UCLA, and Dr. Carol M. Mangione, professor of medicine at UCLA, are studying macular degeneration in approximately 5,000 older women. “We’ve found a high rate of macular degeneration in these older women. We started this research in 1997 to determine the impact of macular degeneration on falling and hip fractures, but along the way we’ve collected information about diet and quality of life, among
other lifestyle factors,” Coleman says. Their research now encompasses quality-of-life issues, incidence of macular degeneration, impact of nutrition on the disease, candidate genes for macular degeneration, and falls and fractures secondary to macular degeneration.

The complex causes of age-related macular degeneration have been the focus of Bok’s research. For example, while age-related macular degeneration has a genetic component, it involves more than one gene and sometimes results from a combination of mutations that interact to form the disease.

In addition to the genetics, environmental triggers can cause the disease to progress and worsen. Many studies have demonstrated that the incidence of macular degeneration is five times higher among smokers than among non-smokers. And the rate of visual loss is four to eight times higher among tobacco users.

Genetic treatments have shown promise in the treatment of some genetic causes of blindness. Experiments on animals have proven to be high-profile successes. For example, two dogs—Lancelot and Guinevere—who were born blind were treated with a modified adeno-associated virus designed to promote the production of 11-cis retinaldehyde, a derivative of vitamin A that the dogs were missing, causing their blindness. As Bok says, “They took the guts out of this virus and put in a gene that is absolutely essential for the production of 11-cis retinaldehyde. You create a virus with cargo capacity, and you put in a gene that is therapeutic.” Lancelot and Guinevere are now no longer blind and have appeared on Capitol Hill to demonstrate the potential for genetic therapies. Indeed, the 11-cis retinaldehyde protein turned out to be intricately linked to one key form of macular degeneration.

Future treatments, Bok

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says, may involve genetic therapy that introduces into the eye the cytokine or CNTF molecule, via an engineered virus ("a Trojan Horse," Bok says). Or treatments could involve an engineered cell that manufactures the CNTF molecule that is implanted into the eye and “drips” the medicine into the damaged eye.

**Pushing the Frontiers of Genetic Therapies** is the goal of Dr. Anurag Gupta, ULCA assistant professor of ophthalmology and a researcher at the Institute. Gupta is principal investigator of a study that uses manipulated genetic material injected into the eye via a non-active virus to provoke the retina to generate pigment epithelial-derived growth factor (PEDF), known to combat the growth of the blood vessels that cause wet macular degeneration.

“We just finished phase I trials, and we’re excited because we’ve found that it is remarkably safe as an injection. We’re formulating phase II trials now,” Gupta says.

“Medicines are moving toward genetic-based treatments. It may be a better approach to rebalance naturally occurring cytokines in the attempt to block new blood vessel growth,” Gupta says.

Molecular treatments under investigation include attacking the wet form of age-related macular degeneration with biological rather than destructive approaches. In the wet form of the disease, new blood vessels begin to grow—rapidly—beneath the macula and frequently leak, destroying the retina’s ability to convert light into a neural signal. The growth in the blood vessels is due to a molecule known as VEGF (vascular endothelial growth factor); one treatment approach is to introduce an aptamer (a synthetic oligonucleotide) that binds to the VEGF molecule, preventing it from damaging the eye.

Gupta is principal investigator of a clinical trial using anecortave acetate, a modified steroid, to prevent dry macular degeneration from turning into the wet form—particularly in patients who have wet macular degeneration in one eye and the dry form in the other. The disease can attack each eye in different forms, and can progress at different rates.

**Three Macular Degeneration Studies at the Institute**

Instituting treatments designed to halt the progression of—or reverse—the wet form of the disease are being conducted by Dr. Christine Gonzales, UCLA assistant professor of ophthalmology. Her trials have involved an anti-VEGF agent known as Macugen® (pegaptanib sodium injection), which is injected into the diseased eye every six weeks. She conducted phase I/II safety trials and subsequently led recruitment in the pivotal phase III trials, which were designed to determine if the treatment could slow the rate of visual loss from the wet form of macular degeneration.

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**Dr. Christine Gonzales, UCLA assistant professor of ophthalmology**

It did. Researchers found that among the patients given a placebo, 45 percent had lost three lines of vision—a measurement of their ability to see—over the period of a year. Among the patients given Macugen, only 30 percent had lost the same amount of vision.

Equally as impressive was the safety and efficiency rates demonstrated in the trial. Among the 1,200 patients in the study, more than 7,500 injections were delivered with “very few serious ocular or systemic side effects,” Gonzales says. The lowest of the three doses tested worked equally as well as the highest dose. And the treatment worked on all three sub-types of wet macular degeneration.

“These results show that Macugen will fill an enormous unmet medical need, because prior to this study, we had no proven treatment for more than 75 percent of the population with wet macular degeneration. It (Macugen) is a phenomenal new treatment for patients who have no options,” Gonzales says.

Her other two trials are, in essence, extensions of the first; one aims to determine how long the medication remains in circulation; the other is designed to determine whether or
not the injections have an impact on macular thickness.

Gonzales says the Food and Drug Administration put the treatment on fast track for approval, and it has been approved for usage beginning February 2005.

"It's going to have a huge impact on the way we manage macular degeneration," Gonzales says. "We're turning away from physically destructive treatments to biological treatments that address the root cause of the condition. In a substantial number of patients, we will see an improvement in their eyesight."

Dr. Gabriel Travis, professor of ophthalmology and professor of biological chemistry at UCLA, has been researching the causes of one of the most heartbreaking manifestations of macular degeneration—Stargardt's disease, which attacks the vision of the young. "As Stargardt's develops, only peripheral vision remains. You can imagine how terrible it is. We wanted to understand what this disease was doing and come up with a solution," Travis says. "The light-sensitive chromophore in our retinas can be likened to a mouse trap," Travis explains. "Absorption of a photon 'trips' the mouse trap. Before light sensitivity can be restored, the chromophore must be re-made by an enzyme pathway called the visual cycle. The gene affected in Stargardt's disease, ABCA4, encodes a component enzyme in this pathway."

To study the function of this enzyme, Travis generated mice with a "knockout" mutation in the ABCA4 gene, similar to the defect in humans with Stargardt's. "We discovered that when the ABCA4 gene is 'broken' in the knockout mice, mimicking the Stargardt's condition, levels of all-trans-retinaldehyde increase. This leads to the build-up of toxic pigments called lipofuscin. If lipofuscin accumulates unchecked, it ultimately kills the rods and cones, causing blindness," Travis explains. "We wondered if there was some way to 'detune' the visual cycle, to reduce the levels of all-trans-retinaldehyde, and thus inhibit accumulation of lipofuscin."

The basis for this therapeutic strategy is rooted in our evolutionary past, when the ability to see in dim light could make the difference between escaping from a predator or not. Rods evolved, permitting humans and other animals to see by starlight. Yet with the advent of artificial lighting, rods have become less useful to modern man, who spends most of the time under light conditions in which rod response is saturated and vision is mediated entirely by cones. "Although our rods contribute nothing to useful vision in bright light, they still churn through chromophore. The visual cycle must work overtime due to our prolonged exposure to light, which contributes to the formation of lipofuscin pigments, especially in patients with Stargardt's defect. Inhibiting the visual cycle pharmacologically potentially could alleviate the biochemical defect in Stargardt's patients," Travis explains.

People with severe acne are often treated with a drug that has a side effect of reduced vision in dim light due to the inhibition of the visual cycle. "We decided to exploit this side effect by treating Stargardt's mice with the drug," explains Travis. "It worked better than we expected in the mice; it completely blocked formation of toxic lipofuscin pigments, and also blocked formation of the toxic lipofuscin degradation products. This treatment strategy amounts to a trade-off in visual function; by giving up the ability to see well in dim light, Stargardt's patients may delay the onset of blindness due to their disease."

This particular drug has other undesirable effects that render it unsuitable for long-term treatment, but Travis and colleagues are working to identify safer drugs to slow the visual cycle and thus prevent accumulation of toxic pigments.

Whatever the approach to curing the disease, UCLA's Jules Stein Eye Institute remains at the center of the search.

"We've been involved in most major multi-center clinical trials investigating new treatments for macular degeneration," Gonzales says. "Dr. Schwartz has done a wonderful job in bringing these to the Institute so that we can participate in cutting-edge research during what is, really, a very exciting time in which we are making important breakthroughs in the treatment of this disease."

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