

The Seeing-Eye Gene

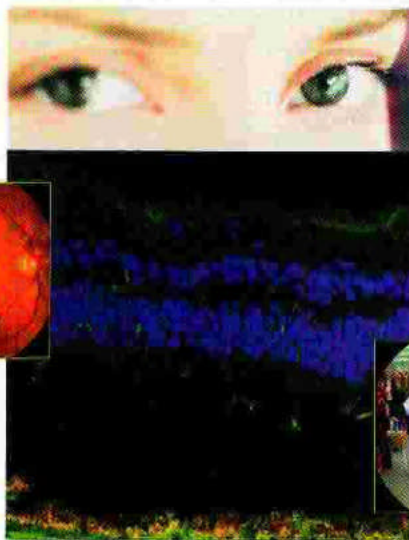
A breakthrough in gene research may offer hope for the millions suffering from macular degeneration | By Emily Schmall

CANDACE COX, A 56-YEAR-OLD management consultant from Scottsdale, Ariz., has watched eight family members go blind, all as a result of age-related macular degeneration, or AMD, which afflicts 9 million people in the U.S. One-third of Americans over age 70 have it. Cox's eyes have signs of early degeneration, but she is determined to outwit her genes. "If it's inevitable, so be it," she says. "I just want to slow down the progression."

AMD comes in two versions, dry and wet. Most people will get only the dry kind, which gradually degrades vision over years. One out of ten dry cases turns into the wet kind, in which leaky blood vessels flood the retina. Wet AMD can completely destroy vision in a matter of weeks or months without regular shots in the eye (up to \$2,000 a month) of cancer drug Avastin or its descendant Lucentis, which dry up the leaky vessels. But the fix is temporary, and it doesn't work for all.

Dry AMD patients have only herbs and quack remedies to choose from. But Candace Cox's doctor, University of Iowa ophthalmologist Gregory Hageman, is at the forefront of research on lasting treatments for dry AMD. Over the past four years Hageman has uncovered how AMD is linked to three variations of the so-called complement factor H gene, which is a crucial player in regulating the immune system. One variation of the gene produces proteins that seem to protect the eye. Those with it enjoy perfect sight well into their 90s. Another variation causes AMD.

Since 2005 a firm in New Haven,



A retina with AMD (left); retinal tissue (center) with lots of factor H protein, in bright green. A protective variant of factor H may yield a drug for deteriorating vision (right).

Conn. called Optheron has been developing Hageman's ideas into a drug to reverse AMD's effects. Animal tests are just getting under way, but in test-tube experiments the protective complement factor H proteins successfully repaired a population of red blood cells damaged by the "bad" variation. Optheron hopes to begin human trials next year.

A half-dozen other biotechs are working on dry AMD, but Optheron controls the patents to Hageman's ideas, has raised the most early-stage venture funding (\$37 million) and is backed by veteran biotech investor David Scheer, who has launched eight companies in 20 years.

Hageman, who is now Optheron's chief scientific officer, began exploring the causes of AMD 20 years ago. When he dissected the blistery deposits, called *drusen* (German for "nodules"), that form on the

surface of retinal cells in patients with AMD, he noticed that they contained a lot of complement factor H protein, about 25% of their mass. Hageman's theory: AMD destroys the eye because flawed factor H genes are signaling immune cells to go after friendly cells in the retina.

In 1993, without much data to support him, Hageman told his theory to an audience at an ophthalmology conference. "They laughed me off the stage," he says. Big Pharma passed on his theories for years. "They either didn't get it or didn't believe it," says Pamela York, director of the University of Iowa's research foundation.

But in 2005 Hageman showed that half of AMD patients had a flawed factor H gene. Later that year he converted more doubters, offering evidence that 85% of AMD cases could be pegged to one of the three complement factor genes. The paper also uncovered the super-vision factor H variation. Optheron is now cloning that gene's protein into a drug. The long bet is that a drug to fix a flawed complement pathway can treat many diseases. "The complement system is involved in everything from asthma to heart disease," says Optheron Chief Executive Colin Foster.

Some ophthalmologists think it's a mistake to depend on a single genetic location for identification and treatment. When Michael Gorin, an ophthalmologist at UCLA, replicated Hageman's 2005 study, he found that 50% of patients carrying a single copy of flawed complement H gene never develop AMD. "You've scared a lot of people, and we don't know whether the disease will ever manifest itself." **F**