Point of View
THE EYE RESEARCH INSTITUTE UNIVERSITY OF WISCONSIN–MADISON
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Come Fly With Me

Imagine walking into a hangar filled with 6 million airplane parts. Properly assembled, the pieces will form a Boeing 747. Much in the same way, the human genetic "hangar" contains 3 billion pairs of DNA building blocks strung together in specific combinations to make our genes. Our human genetic makeup can be compared to the 747's list of parts. Just as putting all the parts out on the runway and cataloging them will not tell you how the plane flies, simply identifying the parts of the human genome does not tell scientists everything they need to know about how humans function and the underlying causes of blinding diseases.

"The pursuit of genetic mutations that cause retinal degenerations is not unlike assembling an airplane," says Nansi Colley, associate professor of Ophthalmology and Visual Sciences and Genetics, and member of the UW Eye Research Institute. "In some diseases, genetic mutations remain unknown. In others, the mutations are known but how they cause disease is not. Unraveling the underlying mechanism of disease is complex because, unfortunately, we don't have the 'assembly plans' for humans."

Originally trained as a marine biologist and geneticist, Dr. Colley investigates a creature far removed from sea life — *Drosophila*, the common fruit fly. Just as the Cessna is a miniature relative of a 747, the fruit fly serves as a small-scale model to provide clues about how the human visual system works in health and disease. In Dr. Colley's lab, the flies are the cornerstones of work on understanding blinding diseases such as macular degeneration and retinitis pigmentosa.

"*Drosophila* are ideal organisms for unraveling the genetic basis of a disease," says Dr. Colley. "A single mating produces 150 offspring that are genetically identical. Fruit flies have a two-month lifespan, so we can study the onset and progression of an age-related disease in a very short time. And, best of all, we already have the parts list — the entire genetic makeup of the fruit fly is well known. We can therefore identify the genetic mutations and study the mechanisms leading to vision loss."

Nansi J. Colley, PhD, investigates genes and mutations impacting the health of photoreceptor cells, the cells responsible for converting light into electrical impulses the brain translates into sight.

Diseases like age-related macular degeneration (AMD) and retinitis pigmentosa (RP) are *genetically diverse*, meaning that different families likely have varying genetic causes for the disease. (For more information on these diseases, see inset on the back.) This variability makes it challenging for the ophthalmologist to diagnose any one individual's disease. Dr. Colley's lab is focused on gathering information about the genetics of AMD and RP through the eye of the fly. Information gathered through the fruit fly model will help physicians treat these difficult conditions in their patients.

Her task began with a screening of 12,000 different sets of fruit flies that had been exposed to a chemical causing genetic mutations. Of that group, over 900 were observed to undergo retinal degenerations; each of these 900 mutations holds the potential for inroads to therapeutic treatments. But how to choose which to pursue first?

Dr. Colley's lab further characterized the pathology and underlying cell biology and biochemistry of these degenerations and set out to map the genes defined by the mutations. She focused first on a major visual pigment in the retina, known as rhodopsin. A key cause of vision loss in RP is due to mutations in rhodopsin; in fact, over 100 mutations in the rhodopsin molecule have already been identified in human patients with blinding disease.

Retinal degenerations can be triggered by defects in almost every protein involved in the light-converting pathways

Studies of* Drosophila*, the common fruit fly, are providing insights into mechanisms of retinal degeneration in human diseases such as macular degeneration and retinitis pigmentosa.

of the eye, and two common mechanisms involve protein folding defects and unregulated calcium levels.

"Many mutations interfere with the manufacturing of rhodopsin and cause the protein to fold incorrectly," explains Dr. Colley. "For proteins like rhodopsin to become functionally active, they must fold into a precise three-dimensional structure and then successfully navigate to their final destination in the light-sensing cells of the eye, the photoreceptors. If the rhodopsin doesn't get there, the photoreceptors can't function, retinal degeneration occurs, and the eye doesn't see."

In addition to rhodopsin, Dr. Colley's investigations have pinpointed gene mutations in calnexin. Her lab has shown that calnexin is a protein with two functions — one is assisting with rhodopsin folding, and the other is in binding calcium. Precise regulation of calcium is critical for cell survival, with sustained, elevated levels of calcium causing cell death. Calnexin can be thought of as a sponge within cells that soaks up surplus calcium.

Mutations causing retinal degenerations found so far affected either protein folding or calcium levels, but Dr. Colley's work is the first to show that calnexin is a culprit involved in *both* of these mechanisms, and is therefore a strong target for further research.

Dr. Colley notes, "While mapping genetic mutations in fruit flies may seem a bit far removed from an individual's diagnosis of AMD or RP, the similarities are more striking than one might think. The first Genome Project mapped all the genes of the fruit fly. Comparing the fly genome to the human genome, the calnexin in flies and the calnexin in humans are 49% identical. This is a good indication that mutations identified in the fly may be clinically relevant to hereditary human retinal degenerations."

Utilizing a network of worldwide collaborators, Dr. Colley's findings serve as a foundation for genetic studies in different models by a multidisciplinary team of scientists. Dr. Marek Michalak, professor and Chair of Biochemistry at the University of Alberta in Edmonton, applies this information in his studies of calnexin in his mouse models of retinal degeneration, comparing what is known in the fruit fly to a mammalian model. Dr. Ed Stone, professor of Ophthalmology at the University of Iowa, has a database of human families with retinal degenerations, and he is able to cross-reference Dr. Colley's fly data with the information on his families.

Dr. Colley explains, "These collaborations move us from the fly to the mammal (mouse) to the human, and allow the identification of genetic culprits in human disease." While much more information is needed before new treatments for AMD or RP are developed, Dr. Colley's discoveries in the fruit fly are key to understanding the genetic framework for blinding diseases.

Otto Lilienthal, 19th century inventor of the glider, remarked, "To invent an airplane is nothing. To build one is something. To fly is everything." The goal of vision scientists like Dr. Colley is much the same:

To understand the genetics of the fly, mouse, or human is significant. To use that understanding to develop treatments is critical. To help a person see is everything.

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Age-related macular degeneration (AMD)

is a disease that blurs the sharp, central vision needed for "straight-ahead" activities such as reading, sewing, and driving. AMD affects the macula, the part of the eye that sees fine detail. In some cases, AMD advances so slowly that people notice little change in their vision. In others, the disease progresses faster and may lead to a loss of central vision in both eyes. AMD is a leading cause of vision loss in Americans 60 years of age and older.

Retinitis pigmentosa (RP)

is a group of inherited retinal diseases affecting about 1 in 4,000 people. Those with the disease typically report night blindness in adolescence and notice a loss in side vision due to progressive loss of photoreceptor cells in the retina. Most of these people have reductions in central vision by age 50 to 80 years, but the pattern and degree of visual loss are variable.