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MEDICAL CENTER

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Preventing Blindness from Age-related Macular Degeneration and Stargardt's Disease

Lab Study Shows an Improved Form of Vitamin A May Help

NEW YORK (May 17, 2011) – Slowing down the aggregation or “clumping” of vitamin A in the eye may help prevent vision loss caused by macular degeneration, research from Columbia University Medical Center has found.

Rather than changing the way the eye processes vitamin A, a team of researchers led by Ilyas Washington, a professor in the department of ophthalmology at Columbia's Harkness Eye Institute, decided to focus on changing the structure of vitamin A itself. In turn, Dr. Washington and his lab have taken a novel step toward treating age-related macular degeneration (AMD), a top cause of untreatable blindness – and Stargardt's disease, the most common cause of juvenile macular degeneration.

During the sequence of events that enables vision, vitamin A undergoes a series of chemical transformations in the eye. These processes sometimes allow vitamin A to react with another molecule of vitamin A to form clumpy deposits, or what are known as “vitamin A dimers.” Macular degeneration has long been thought to be associated with the formation of these dimers in the eye.

The concentrations of these dimers are higher in the eyes of the elderly and in those with certain inherited eye diseases. Vitamin A dimers are also found together with insoluble pigment granules called lipofuscin. In eye diseases such as dry-AMD, the accumulation of vitamin A dimers and these granules is thought to happen over decades. But in genetic diseases such as Stargardt's disease, this process can happen much faster, leading to early vision loss as early as age 8.

“Researchers have tried a different approach to preventing the formation of vitamin A dimers by modifying the processing of vitamin A by the eye,” Dr. Washington says. “But these modifications seem to have inhibited vision and caused side effects.”

In animal model studies, Dr. Washington's lab has set about synthesizing a modified vitamin A drug incorporating the hydrogen isotope deuterium rather than protonium (the more abundant isotope of hydrogen) at select positions. Dr. Washington and his lab hypothesized that these modifications would make the bond involved in dimerization harder to break, which would slow dimerization. By feeding this new vitamin A drug to healthy mice, they were able to reduce the amount of vitamin A dimers without any observed side effects, said Dr. Washington, the Michael Jaharis Assistant Professor of Ophthalmic Sciences at Columbia.

When given to mice with the same genetic defect as humans with Stargardt's disease, which usually experience early vision loss, the modified vitamin A resulted in fewer vitamin A dimers, better overall ocular health and improved vision. Importantly, they also observed that the modified vitamin A behaved exactly as normal vitamin A does in all other aspects, making it an attractive potential therapy for preventing blindness in humans.

This work is detailed in a series of articles published recently in the *Journal of Biological Chemistry*, entitled "Deuterium Enrichment of Vitamin A at the C20 Position Slows the Formation of Detrimental Vitamin A Dimers in Wild-type Rodents" and "C20-D3-vitamin A Slows Lipofuscin Accumulation and Electrophysiological Retinal Degeneration in a Mouse Model of Stargardt's Disease."

Dry-AMD affects some 10 million Americans and is the leading cause of blindness in the Western world. Among them, approximately 3 million Americans are at high risk of irreversible vision loss, and 1 million of them are seriously visually impaired due to a late form of dry-AMD. There is currently no treatment for dry-AMD.

Although affecting only 1 in 10,000 individuals, Stargardt's disease is the most common form of inherited macular degeneration and is caused by mutations in a gene responsible for vitamin A processing. Altered vitamin A processing in Stargardt's leads to faster vitamin A dimer formation and subsequently lipofuscin accumulation and to the early onset of visual symptoms, leading to legal blindness in almost all cases. There is no current treatment for Stargardt's disease.

Dr. Washington's lab has been awarded a \$1.25 million grant from the National Eye Institute to further investigate the link between vitamin A dimers and various retinal degenerations. The grant will help further the scientific understanding of how vitamin A dimers, lipofuscin and macular degenerations are related, and could result in new approaches to treat these diseases. Alkeus Pharmaceuticals has licensed from Columbia certain patents relating to Dr. Washington's discoveries and intends to launch clinical trials for Stargardt's disease and dry-AMD.

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