

Phase I trials

Potential dry AMD treatment slows visual cycle to prolong eye health

Orally delivered modulation therapies selectively target cells within the retina to protect visual acuity

By Jennifer A. Webb

Reviewed by Ryo Kubota, MD, PhD

Bothell, WA—The “dry” form of age-related macular degeneration (AMD) affects 90% of the 29 million people worldwide with AMD. Although the dry form can progress to “wet” and lead to central vision loss, little can be done to save patients’ vision.



Dr. Kubota

Just as the number of people with AMD is expected to double over the next 20 years, work under way here is leading to what researchers hope will be a treatment to halt progression of the disease.

Ryo Kubota, MD, PhD, and a team of researchers at Acucela Inc. are working to develop orally delivered visual cycle modulation therapies that selectively target cells within the retina to protect visual acuity. By modulating the visual cycle, they believe they can protect the retina from light damage, improve retinal vasculature, and reduce the accumulation of toxic by-products, including A2E (pyridinium bis-retinoid).

Modulating the eyes’ rods

Dr. Kubota explained that the research centers on the idea that we don’t fully utilize our eyes’ rods, which are responsible for our night vision, but little else. They col-

Take-Home Message

A team of researchers is working to develop orally delivered visual cycle modulation therapies to halt the progression of age-related macular degeneration.

lect information and feed it to our brain, which does not fully process it. This activity causes the rods to slowly deteriorate as we age, and as the rods cease to support cone cells, vision suffers. The deterioration causes a build-up of toxic by-products (lipofuscin) associated with the pathological mechanisms that lead to dry AMD and other degenerative retinal diseases, including Stargardt’s disease.

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Ryo Kubota, MD, PhD

“We are modulating rods, which are responsible for generating 90% of toxic by-products in the eye to prevent progression of AMD,” said Dr. Kubota, Acucela’s

chairman, president and chief executive officer.

The visual cycle modulators under development by Dr. Kubota’s team slows the visual cycle, thereby protecting rod cells from deterioration, allowing the rods to support cone cells longer, and reducing the build-up of lipofuscin.

It all would happen via a daily pill, which is easier and more convenient than the injections currently proving effective at treating the wet form of AMD.

“We think this is changing the paradigm in how ocular diseases are treated,” he said.

Early trials show a “significant decrease in the incidence of conversion to wet AMD” when administered doses of the Acucela product in development, which the company is calling ACU-4429, Dr. Kubota said. “We show in pre-clinical models we can get rid of neovascularization. It’s huge.”

Dr. Kubota discovered the glaucoma gene, myocilin, while performing ocular research at Keio University, Tokyo, in 1997. He continued his research at the University of Washington, Seattle, and later joined the faculty as an assistant professor. His work today on ACU-4429 is building on the visual cycle modulation he helped to pioneer more than 10 years ago. However, the work needed the backing of large, multi-disciplinary team to come up with a drug as a safe and potent molecule, and he licensed his findings from the university

and founded Acucela in 2002.

Impact of vitamin A

While vitamin A plays an important role in helping our eyes adjust to light changes and has been hailed for its antioxidant properties, Dr. Kubota said it also contributes to the decline of the rods. "Rods require vitamin A to fire upon light hits," he explained. "In the current light environment, rods are constantly being bleached." By reducing a specific form of vitamin A in the eye, researchers can slow the activity of the rods, and prolong their lifespan.

Dr. Kubota doesn't suggest patients reduce vitamin A in their diets, because it is a vital nutrient elsewhere in the body. "We're coming in with a very fine, pinpoint approach," he said.

Phase I trials have so far shown Acuce-

la's product to be effective with no adverse events. In pre-clinical models, ACU-4429 reduced the accumulation of A2E (the toxic byproduct) and provided protection in pre-clinical light damage models. The company presented a poster about its findings at the Association for Research in Vision and Ophthalmology annual meeting last May.

In that single-center, randomized, double-masked, placebo-controlled, dose-escalating study, each cohort of six healthy volunteers aged 55 to 80 were given oral doses of ACU-4429 up to 60 mg or a placebo. Full-field electroretinography images were recorded following dark adaptation and at 10-minute intervals after exposure to a bleaching light. Subjects demonstrated a marked slowing of the b-wave amplitude recovery time following the bleach.

Slowing the visual cycle could hold a key to treating dry AMD and other retinal degenerative disorders, including diabetic retinopathy and retinopathy of prematurity, Dr. Kubota said.

"I think this is addressing a fundamental pathology of multiple retinal diseases," he said. "Too much light and using too much energy in the eye is really bad and accelerates the aging process in the eye for no good reason, because you don't get any information from the rods." **OP**

FYI

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