Visum sees the light

By Chris Cain, Staff Writer

Researchers at **Case Western Reserve University** have identified 16 approved drugs that could help treat Stargardt's disease and dry age-related macular degeneration by preventing the toxic buildup of visual cycle byproducts.[1] **Visum Therapeutics Inc.** has licensed the findings and has variants of the drugs in preclinical development.

The visual cycle is a metabolic process in the retina required for vision, but aberrant accumulation of toxic byproducts produced by the cycle can cause cellular damage. Stargardt's disease is a heritable genetic disorder of the visual cycle that affects about 1 in 10,000 people. Patients are highly susceptible to light and glare and develop severely impaired vision and blindness as they age.

The orphan disease is primarily caused by mutations in *ATP-binding cassette sub-family A member 4* (*ABCA4*; *ABCR*), which is expressed in the eye and is required to properly localize *N*-retinylidenephosphatidylethanolamine (*N*-ret-PE), an intermediate of the visual cycle. When *N*-ret-PE is not localized properly in the eye, it can react with free all-*trans*-retinal, one of the metabolites of the visual cycle, to form *N*-retinylidene-*N*-retinylethanolamine (A2E). A2E is a toxic compound that induces apoptosis in retinal pigment epithelial cells. High levels of A2E also are associated with the development of dry age-related macular degeneration (AMD).

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—William Harte, Visum Therapeutics Inc.

A team at Case Western hypothesized that lowering the level of free all-*trans*-retinal in the eye could decrease the buildup of A2E and improve visual function.

"The fundamental idea is to temporarily lower levels of all-*trans*-retinal," said William Harte, CEO of Visum. "You need all-*trans*-retinal to generate 11-*cis*-retinal for normal vision, but what we are doing is temporarily sequestering any excess all-*trans*-retinal so it does not generate toxic byproducts."

To temporarily lower all-*trans*-retinal levels, the team reasoned that drugs containing a primary amine group would chemically react with and reversibly convert free all-*trans*-retinal into an inactive form.

"We narrowed it down to 24 compounds with primary amine groups that could be applied at a relatively high dose and were likely to penetrate the CNS," said Krzysztof Palczewski, chair of the Department of Pharmacology at Case Western and CSO of Visum.

To test the compounds, the group used a mouse model of Stargardt's disease that is driven in part by the deletion of *Abca4*. In the model, which was previously developed by Palczewski's lab, 16 of 24 drugs tested significantly lowered retinal degeneration compared with vehicle controls.

The researchers also suggested that the primary targets of the drugs were not responsible for the protective effects on the retina. In one study, for example, the researchers looked at *R*- and *S*-stereoisomers of Lyrica pregabalin, a γ-aminobutyric acid receptor (GABAR) agonist from **Pfizer Inc.** that is approved to treat pain and other neurological indications. The isomers had similar efficacy in the mouse model, even though the *R*-stereoisomer has much weaker affinity for GABAR.

To nail down how the drugs were working *in vivo*, Palczewski performed mass spectrometry analysis of all-*trans*-retinal and related retinoids extracted from the eyes of treated animals. Specific chemical signatures in the eyes indicated a primary amine group had reacted with all-*trans*-retinal and converted it to an inactive form that could no longer generate toxic byproducts.

Results were published in *Nature Chemical Biology*. Palczewski was the paper's senior author.

"This is a very elegant approach to preventing the accumulation of A2E," said Jay Lichter, a partner at **Avalon Ventures** and president and CEO of **ReVision Therapeutics Inc.** "Palczewski has shown you can administer a compound and get it to the eye in sufficient quantities to prevent A2E accumulation, and that is a significant breakthrough. An added benefit of this approach is that it is not targeting the visual cycle, but a toxic byproduct. Inhibition of the visual cycle can often cause side effects including a delay in dark adaptation."

ReVision's fenretinide (RT-101) has completed Phase IIb testing in patients with geographic atrophy, an advanced form of dry AMD. The compound acts in part as a visual cycle modulator that inhibits retinol binding protein, which leads to decreased levels of retinol in the eye and lower A2E production. Lichter added that RV-101 also has anti-inflammatory properties because it inhibits the production of ceramide.

Lichter said the company decided not to run a Phase III trial in dry AMD because the cost was prohibitive. Unrelated to the current paper, ReVision plans to start a short Phase II trial in patients with Stargardt's disease this summer.

Another company targeting the visual cycle is **Acucela Inc.** ACU-4429, a small molecule that targets retinal pigment epithelium-specific protein 65 kDa (RPE65), another component of the visual cycle, is in Phase II testing with partner **Otsuka Pharmaceutical Co. Ltd.** to treat dry AMD. Acucela declined to comment. Palczewski was formerly on the company's scientific advisory board.

Seeing the money

Harte and Palczewski cofounded Visum, which has exclusively licensed a patent from Case Western covering the findings. The company is fundraising and conducting additional preclinical work on a lead candidate to treat Stargardt's disease.

"The challenge with using these FDA-approved drugs is removing the 'on mechanism' approved pharmacological effect of the agent. We were able to modify one of the drugs, demonstrate retinal protection in this model and are now performing IND-enabling studies," said Harte. He would not disclose which drug is being modified.

Whichever drug is chosen as a starting point, Lichter said the key will be developing a distinct new chemical entity.

"It would be a serious uphill battle to get patent protection that is meaningful," he said. "Say you get a method-of-use patent for using pregabalin to treat Stargardt's disease. That's great, but once the drug becomes generic, how are you going to make any money?" Lyrica loses patent protection in 2018.

Harte said Visum has a pending patent that broadly covers the use of primary amine-containing compounds to treat ophthalmic disease.

Visum plans to measure A2E levels as a biomarker of disease progression during the clinical development of its lead candidate. The company noted that A2E is a highly fluorescent molecule and can be noninvasively measured.

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COMPANIES AND INSTITUTIONS MENTIONED

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