New drug candidate is promising therapeutic option for angiogenic retinal diseases

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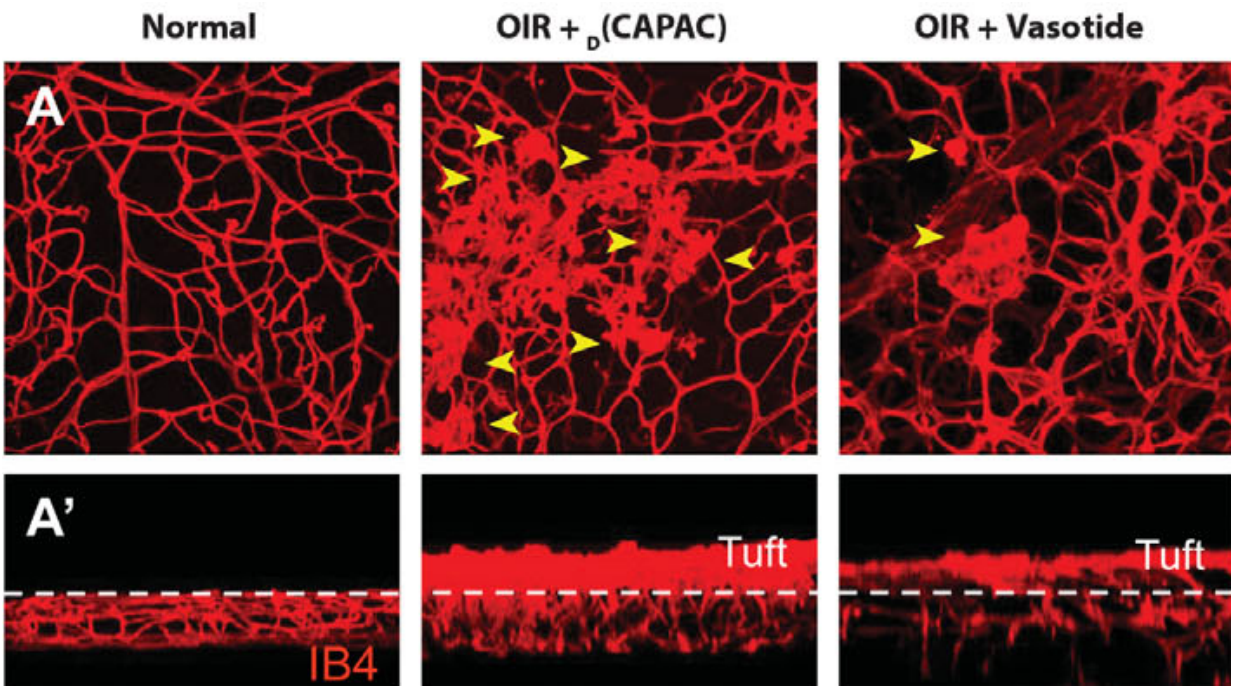

IB4-stained branched vessels and tufts in horizontal retinal scans in normal wildtype mice and mice with oxygen-induced retinopathy treated with a control peptide, D(CAPAC), or the drug Vasotide. Credit: Sidman et al., Science Translational Medicine (2015)

A research team led by scientists at Beth Israel Deaconess Medical Center (BIDMC) and the University of New Mexico School of Medicine has identified a small molecule that treats animal models of aged

macular degeneration (AMD) and retinopathy of prematurity (ROP) by preventing the overgrowth of blood vessels that are characteristic of these two retinal diseases.

The new findings, described in today's issue of the journal *Science Translational Medicine*, show that this molecule, named Vasotide in this paper, can be delivered in the form of eye drops, a discovery that offers a promising alternative to current therapies for these retinal diseases, which require monthly injections of large molecules directly into the eyeball.

"Angiogenesis, the abnormal overgrowth of blood vessels, underlies many severe diseases, and when angiogenesis develops in the eye's retina it causes decreased vision and can even lead to blindness," said the study's corresponding author Richard L. Sidman, MD, an investigator in the Department of Neurology at BIDMC and Bullard Professor of Neuropathology (Neuroscience), Emeritus, at Harvard Medical School. Sidman is a leader in the field of mammalian brain development whose studies have focused on disease mechanisms in mouse neuro-genetic disorders, including disorders of the retina, the light-sensitive layer of brain tissue at the inner surface of the back of the eye that transmits image information to other parts of the brain via the optic nerve.

AMD develops in approximately 14 million older individuals throughout the U.S. This overgrowth of blood vessels damages the photoreceptor cells near the center of the eye's retina, resulting in the loss of central vision so that individuals can no longer see objects directly in front of them. Retinopathy of prematurity (ROP) occurs in premature infants, who develop a similar retinal disease as a side effect of high-level oxygen treatments used until their lungs develop sufficiently to handle the much lower oxygen levels in room air.

In previous investigations, the study's co-senior authors Renata

Pasqualini, PhD, and Wadih Arap, MD, PhD, of the University of New Mexico, had developed a laboratory screening technique called in vivo phage display and used it to identify an early version of this peptide. (A peptide is a short chain of linked amino acids, a small version of a protein.)

In this new study, Sidman and his coauthors tested Vasotide in three separate animal models - two forms of AMD and one form of ROP. Their results showed that Vasotide led to decreased blood vessel growth in all three models when the agent was administered by either systemic injection, or through eye drops.

"Under normal circumstances, a protein called vascular endothelial growth factor [VEGF] binds to pertinent endothelial cell receptors lining the blood vessels, causing these cells to multiply, migrate, and form new blood vessels," he noted. "Vasotide is the only external agent that uniquely blocks VEGF from binding to two different endothelial receptor molecules—VEGF receptor-1 and neuropilin-1—to keep excessive blood vessels from forming."

Although a few other anti-VEGF drugs have been approved for therapy of AMD, they must be delivered directly into the eye through monthly intravitreal injections. "These treatments are costly, require highly skilled professional execution, and, in rare cases, can cause bleeding or infection in the eye," said Sidman. Furthermore, he added, not all patients respond to these agents and, for many patients, responsiveness decreases after about six months.

"In addition to future clinical trials on AMD and ROP, we think that diabetic retinopathy and certain forms of cancer may also prove to be responsive to Vasotide," said Sidman.

"This is a very exciting development in that it has the potential to allow

the self-administration of a sight-saving drug to patients with AMD," said Harold F. Dvorak, MD, Mallinckrodt Distinguished Professor of Pathology at HMS and BIDMC, whose laboratory first identified the VEGF signaling protein nearly 30 years ago.

More information: The peptidomimetic Vasotide targets two retinal VEGF receptors and reduces pathological angiogenesis in murine and nonhuman primate models of retinal disease, stm.sciencemag.org/lookup/doi/ … scitranslmed.aac4882

Provided by Beth Israel Deaconess Medical Center