

Gene therapy shows promise against agerelated macular degeneration

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A gene therapy approach using a protein called CD59, or protectin, shows promise in slowing the signs of age-related macular degeneration (AMD), according to a new in vivo study by researchers at Tufts University School of Medicine. Led by senior author Rajendra Kumar-Singh, PhD, the researchers demonstrated for the first time that CD59 delivered by a gene therapy approach significantly reduced the uncontrolled blood vessel growth and cell death typical of AMD, the most common cause of blindness in the elderly. The study was published on April 28 in *PLoS ONE*.

Activation of the complement system, a part of the immune system, is responsible for slowly killing cells in the back of the eye, leading to AMD. Activation of this system leads to the generation of pores or holes known as 'membrane attack complex' or MAC in cell membranes. CD59 is known to block the formation of MAC.

"CD59 is unstable and hence previous studies using CD59 have had limited success. The <u>gene therapy</u> approach that we developed continuously produces CD59 in the eye and overcomes these barriers, giving us renewed hope that it can be used to fight the progression of AMD and potentially other diseases," said Kumar-Singh.

Kumar-Singh is associate professor in the department of ophthalmology at Tufts University School of Medicine (TUSM) and member of the genetics; neuroscience; and cell, molecular, and developmental biology program faculties at the Sackler School of Graduate Biomedical



Sciences at Tufts.

Kumar-Singh and colleagues delivered CD59 to the eye using a deactivated virus similar to one previously shown to be safe in humans. Using an established <u>mouse model</u> of age-related <u>macular degeneration</u>, they found that eyes treated with CD59 had 62 percent less uncontrolled <u>blood vessel growth</u> and 52 percent less MAC than controls.

"Treatment was effective when administered at a very specific location beneath the <u>retina</u>, but importantly, also when it was administered to the center of the eye. This finding is especially encouraging because it would allow for a safer and more convenient route of administration of treatment," said co-first author Siobhan Cashman, PhD, assistant professor in the department of ophthalmology at Tufts University School of Medicine and member of Kumar-Singh's lab.

The current standard treatment for some forms of AMD requires an injection directly into the eye approximately every four weeks. According to Kumar-Singh, gene therapy approaches to treat AMD are especially attractive because they will allow patients to be treated less frequently, reducing patient discomfort and lowering chances of infection and other side effects associated with frequent injections into the eye.

The researchers, including co-first author Kasmir Ramo, BS, research technician, believe that while CD59 has significant potential as a treatment for AMD, the gene therapy approach lends itself for application also in other eye and systemic disorders where low-level activation of complement has been implicated.

"Prior to initiating human clinical trials, we will need to perform extensive preclinical toxicology studies. In order to advance this study to Phase I clinical trials, we have formed a partnership with Hemera



Biosciences Inc. to raise private venture capital," said Kumar-Singh.

AMD, which results in a loss of sharp, central vision, is the number one cause of visual impairment among Americans age 60 and older. While treatments are available for wet AMD, they do not prevent the progression of dry AMD, the form that affects 90 percent of AMD patients. Kumar-Singh noted, however, that the current study in combination with a previously published study from his laboratory suggests that CD59 may be useful for the treatment of both the dry and wet forms of AMD.

More information: Cashman SM, Ramo K, Kumar-Singh R. PLoS ONE. "A Non Membrane-Targeted Human Soluble CD59 Attenuates Choroidal Neovascularization in a Model of Age Related Macular Degeneration." Published online April 28, 2011, doi:10.1371/journal.pone.0019078

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