Emerging pharmaceutical platform may pose risks to retinal health

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According to new research by University of Kentucky investigators, an emerging pharmaceutical platform used in treating a variety of diseases may produce unintended and undesirable effects on eye function. The paper, "Short-interfering RNAs Induce Retinal Degeneration via TLR3 and IRF3", appears in the current online edition of the journal *Molecular Therapy,* a publication of the Nature Publishing Group and the American Society of Gene and Cell Therapy.

"Short-interfering RNA (siRNA) technology has been regarded as one of the most exciting emerging platforms for new pharmaceuticals, said Dr. Jayakrishna Ambati, professor of physiology, and professor and vice chair of ophthalmology and visual sciences at UK.

To this point, siRNA drugs have been the subject of clinical trials past and present for a variety of disorders including: cancers, viral respiratory infections, hypercholesterolemia, macular degeneration, diabetic retinopathy and glaucoma. Major obstacles to realizing the therapeutic potential of siRNAs include delivery of the drug into cells and a generic suppression of blood vessel growth through immune activation, as shown by a 2008 paper from the Ambati group in the journal Nature.

"We now show a new undesirable effect of siRNAs that are 21 nucleotides or longer in length: these siRNAs, regardless of their sequence or target, can cause retinal toxicity. By activating a new immune pathway consisting of the molecules TLR3 and IRF3, these siRNAs damage a critical layer of the retina called the retinal pigmented

epithelium (RPE). Damage to the RPE cells by siRNAs can also lead to secondary damage to the rods and cones, which are light-sensing cells in the retina," said Ambati.

The scientists' findings indicate that caution should be applied when designing or using siRNAs intended for either direct application to the eye, or intended for use in a way that may allow the drug to access the eye.

"Another novel aspect of this research is that the RPE degeneration caused by siRNAs resembles the pathology seen in the advanced form of age-related macular degeneration called geographic atrophy, said Ambati. "As there are few models of geographic atrophy, which affects millions of people worldwide, this paper provides an important advance for research in developing new treatments for this disease."

Because the research shows that siRNAs shorter than 21 nucleotides in length can evade the TLR3-IRF3 off-target immune response, it may be possible to achieve therapeutic effects without retinal damage by designing shorter siRNAs.

Provided by University of Kentucky