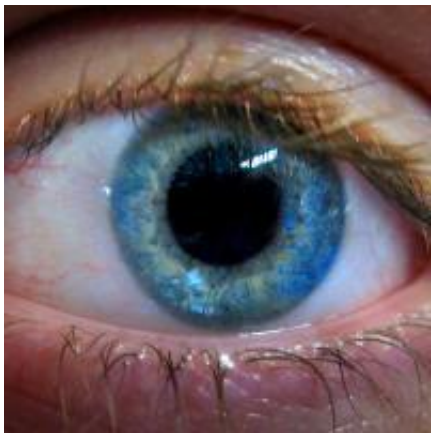
New eye treatment effective in laboratory tests

23 October 2013



A promising technique for treating human eye disease has proven effective in preclinical studies and may lead to new treatments to prevent blindness, according to experiments conducted at The Scripps Research Institute (TSRI) in La Jolla, California.

The studies involved controlling the actions of microRNAs, tiny pieces of RNA that were once considered to be "junk" but are now known to fine-tune gene activation and expression. The researchers showed that treating mice with short RNA strands that precisely target and inhibit microRNAs ("antimicroRNAs") can stop the aberrant growth of blood vessels ("neovascularization").

It is this abnormal proliferation of vessels that exacerbates vision loss in neovascular eye diseases like "wet" macular degeneration and diabetic retinopathy, two of the leading causes of blindness.

Described in the cover story of the November issue of the *Journal of Clinical Investigation*, the microRNA treatments blocked aberrant vessel growth without damaging existing vasculature or neurons in three separate models of neovascular eye disease—a proof-of-principle that suggests future treatment based on the same approach may be effective in humans.

"We believe that targeting and inhibiting the action of microRNAs involved could represent a novel and effective way to treat a broad range of neovascular eye diseases such as diabetic retinopathy, macular degeneration and macular telangiectasia," said TSRI Professor Martin Friedlander, MD, PhD, who was senior author of the study. "We are excited about this approach to halting abnormal blood vessel growth without inducing off-target side effects."

The work is the first published result of a five-year, $10.2 million grant awarded last year by the National Eye Institute of the National Institutes of Health. The grant aims to harness the potential of microRNAs to stop abnormal blood vessel sprouting in the back of the eye and prevent blindness.

Friedlander said that the researchers hope to advance this approach with clinical trials; a potential pharmaceutical partner is interested in partnering with them once the therapy is optimized for human use. Clinical trials may take several years, and any such treatment would have to prove safe and effective before it would be routinely available.

"Are we ready to go to the clinic tomorrow?—no," said Friedlander. "But is this class of therapeutics 'druggable'—the answer is 'yes.'"

Diseases Tied to Protein Called VEGF

Many types of blindness can be tied directly to the abnormal growth of blood vessels in the back of the eye—the retina, a soft tissue already rich with vasculature and crowded with light-sensing cells

that capture visual cues and send signals to the brain.

In diseases like "wet" macular degeneration and diabetic retinopathy, abnormal blood vessels proliferate under or on top of the retina, respectively, presumably in response to hypoxia, or low oxygen levels. While the precise cause of the hypoxia is not clear, in the case of macular degeneration it may be due to deposits of abnormal molecules leading to inflammation and neovascularization. In diabetic retinopathy, scientists believe that the vessels themselves function abnormally, leaking fluid and bleeding, leading to loss of vision and the growth of additional abnormal vessels.

For many years, scientists have sought to address vision loss by stemming this sort of aberrant growth of blood vessels. In the last decade, much of the focus has been on a molecule found in the human body called VEGF (vascular endothelial growth factor).

VEGF is central to many types of aberrant blood vessel growth. When the body senses too little oxygen, it produces VEGF, and when vessels in the eye sense the elevated levels of that molecule, they sprout new shoots. VEGF and other molecules that promote blood vessel growth activate Ras, a gene that has to be activated for blood vessel sprouting to occur. Stopping VEGF, scientists have thought, would be a viable way to prevent blindness in many people.

The pharmaceutical industry has been hotly pursuing ways to block the action of VEGF in people at risk of blindness and for other diseases as well, including cancer. Tumors often overproduce VEGF to stimulate blood vessel growth within tumors so that their fast-dividing cells are kept supplied with oxygen and other nutrients. Several anti-VEGF drugs (such as Lucentis® (ranibizumab), Macugen (pegaptanib), Eylea® (aflibercept) and Avastin® (bevacizumab)) are already in use, and dozens more are in clinical trials against cancers and common eye disorders such as wet macular degeneration.

Blocking VEGF in eye diseases has proved to be complicated, however. In addition to stimulating the growth of new blood vessels and mediating vascular permeability, the molecule also plays a critical function in maintaining the health of nerve cells and blood vessels in the retina, so disabling it too much can create unintended consequences within the eye's delicate tissues.

A New Approach

Last year, in another paper published in the *Journal of Clinical Investigation*, Friedlander and his colleagues showed that VEGF is critically important for maintaining healthy vision as well and that blocking it completely can kill the eye's light-sensing cells, actually causing severe vision loss. (Friedlander's lab has investigated a number of other, non-VEGF angiogenic pathways and has shown that combining antagonists of these pathways along with a VEGF antagonist can actually enhance anti-angiogenic activity when used as combination therapy.)

"Our collaborator, David Cheresh, and his lab observed that microRNAs could be used to target neovascularization at a point in the pathway 'downstream' of VEGF," said Peter Westenskow, PhD, a postdoctoral fellow at TSRI and first author of the new study. "We have now shown that microRNAs can inhibit the actions of multiple pro-angiogenic compounds including, but not limited to, VEGF. Blocking these 'downstream' targets would stop the aberrant blood vessel sprouting while maintaining the health of the normal blood vessels in the eye."

In the new study, the team focused on microRNA-132, blocking it in the eye and preventing Ras activation using a tiny 22-base anti-microRNA. This work was the first to test its effect for neovascular eye diseases, showing that the new approach inhibited angiogenesis in three different models of neovascular eye disease.

The researchers believe this work is especially promising, as other anti-microRNA-based therapies for different diseases are already in clinical trials.

More information: The article, "Ras pathway inhibition prevents neovascularization by repressing

endothelial cell sprouting," by Peter D. Westenskow, Toshihide Kurihara, Edith Aguilar, Elizabeth L. Scheppke, Stacey K. Moreno, Valentina Marchetti, Iacovos P. Michael, Sudarshan Anand, Andras Nagy, David Cheresh and Martin Friedlander appears in the *Journal of Clinical Investigation*. See: www.jci.org/articles/view/70230

Provided by The Scripps Research Institute