

Artificial proteins to combat macular degeneration

Glimmer of light for the eye

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Trap-Eye



Sight is the most important of the human senses: 80 percent of what we perceive comes via the eyes. However, this window on the world closes when visual cells in the center of the retina start to die off with old age. One cause is leakage from blood vessels. Now, Bayer HealthCare researchers are carrying out a clinical Phase III study of an active substance which is intended to help patients with wet age-related macular degeneration (AMD) see more clearly again.

The old lady is no longer able to see her grand-daughter's features, nor the faces she pulls to amuse her. This is because all the details in the 73-year-old's field of vision have disappeared, with a large dark spot covering them. Her condition is caused by an insidious disease known as age-related macular degeneration, or AMD for short, in which visual cells die off in a particular tiny area of the retina. There are about eight million such cells on this yellow spot – known in technical terms as the macula – which are responsible for sharp, central vision. The macula measures only about a square millimeter, about the same as a pin head, but if the visual cells in this tiny area are destroyed, humans lose the most important part of their eyesight. Fine vision is lost for ever at this point as the body is unable to regenerate them. Only the area surrounding the macula, which can identify outlines

and light and dark contrasts, prevents those affected from losing their sight completely.

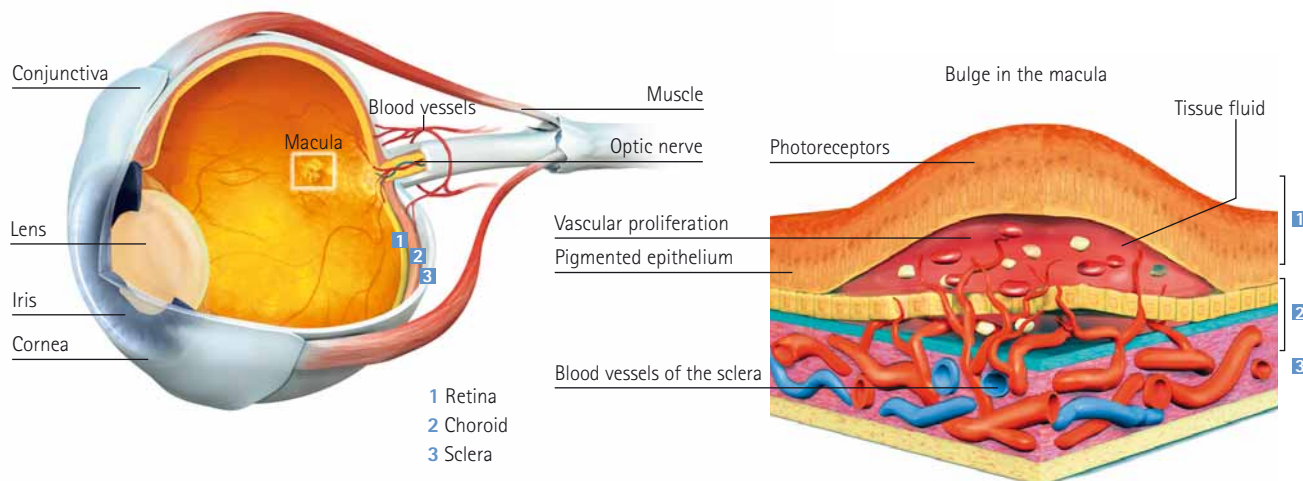
Waste removal in the eye starts to fail

The number of AMD-sufferers is increasing as life expectancy rises. Macular degeneration is primarily an age-related condition: about 15 percent of 61- to 70-year-olds suffer from it, with the figure increasing to as much as 40 percent in the over-eighties. AMD is caused by waste products, which are constantly created in the eye with visualization and are deposited in the yellow spot in the tissue. In younger people they are disposed of correctly, but over the years, the process starts to function less and less efficiently, so that fatty waste products accumulate and destroy the visual cells.

Vision in focus: (large photo from left) Dr. Georg Grötzbach and Dr. Andreas Sachse are working on ways of treating an insidious eye disease called wet age-related macular degeneration (AMD). As the disease progresses, a dark spot appears in the center of the visual field and all the images gradually become blurred.



When blood vessels grow in the eye



The macula is just one square millimeter in size, but it contains around eight million vision cells which confer visual acuity. In wet age-related macular degeneration (AMD), abnormal blood vessels leaking blood and fluid can disrupt the retina and its connections. If the problem is not managed in a timely fashion, sight can be lost irretrievably as the body cannot regenerate these cells and connections. Bayer's scientists are developing a new active substance that possibly stops the growth of blood vessels in the eye. They use a novel fusion protein to fish a special messenger substance out of the vitreous of the eye. The cascade of vascular formation is interrupted and vision is preserved.

A distinction is made between two different types: dry and wet AMD. In the case of wet macular degeneration, the visual cells die off. Initially, the supply of oxygen and nutrients to the eye is blocked. In order to overcome the shortage, the body creates new blood vessels as a way of transporting the substances. "An eminently sensible response, but one which causes more harm than good in this case," says Dr. Andreas Sachse, Global Project Leader at Bayer Health-Care's Bayer Schering Pharma Division. "The new vessels are permeable to tissue fluid, which leaks out and causes edema, or swelling." A cushion of fluid forms beneath or within the retina and causes the retina to become distorted. "The bulging caused by the edema can lead to the layer in this area of the retina becoming about three times thicker than normal," explains Dr. Georg Grötzbach, Senior Director in Global Clinical Development for Specialty Medicine at Bayer Schering Pharma. This fluid can persist and retinal cells can be gradually destroyed. At first, those affected hardly notice it. Decreasing visual acuity and distorted lines are the first signs. If the

eye remains untreated, an irreparable dark spot is slowly and steadily formed in the middle of the visual field. "For the elderly in particular, who may already be hard of hearing or have dementia, this is a very serious impairment," comments Grötzbach. Patients feel themselves cut off from their environment as they are unable to recognize the person facing them, or read, watch television or drive a vehicle, which can often lead to social isolation.

VEGF – the molecule that makes blood vessels grow

Until a few years ago, the only treatment available was photodynamic therapy, which involves injecting the patient with a medication which makes the newly formed blood vessels sensitive to light. The doctor then uses a laser to sclerose them. "However, this only slows down the disease, and is unable to improve the condition. Nor is the treatment suitable for all cases of AMD," explains Professor Bernd Kirchhof of the University of Cologne (see "Interview"). VEGF inhibitors work dif-

ferently. Two products which work on the basis of this new principle and have been granted marketing authorization have already been available for a few years. Now, Bayer scientists may have developed a more effective variant: in order to preserve the eyesight of those affected, they have been concentrating on what causes wet AMD. They want to prevent the inappropriate growth of blood vessels. A signal molecule called VEGF (vascular endothelial growth factor) plays an important part in this. It always occurs in the human body where new arteries are formed – including the eye. If VEGF binds to special binding sites in angiogenic cells, it triggers a cascade of biochemical reactions, allowing tiny new blood vessels to sprout. Since May 2008, Bayer Schering Pharma has been testing a new active substance in a Phase III clinical trial which is designed to interrupt this fatal progression, called VEGF Trap-Eye. With this, the researchers use a new trick to trap the growth molecule: they artificially recreate the most important binding sites for VEGF on the cell surface. They then combine these with elements



Better vision: (from left) Dr. Andreas Sachse and Dr. Georg Grötzbach are developing a new treatment that targets the cause of wet macular degeneration. It stops new blood vessels from growing in the eye. They use the test chart to monitor clinical success in subjects worldwide.

of a human antibody, so that the molecule can be fished out of the vitreous body and the eye tissue before it can cause the growth of blood vessels.

90 percent success rate in clinical studies

The fusion or artificial protein which is used to capture the VEGF molecule was first developed by scientists at the American company Regeneron. Bayer scientists are now further developing this innovative treatment in cooperation with the U.S. scientists. "The trap technology offers great advantages over antibodies, as the new protein binds VEGF particularly efficiently," says Grötzbach. In addition, the immune system has difficulty recognizing it. It can remain active in the eye – the only place where VEGF Trap-Eye is needed to carry out its task – for a long time. This is why the doctor injects the solution directly into the vitreous body of the eye. "VEGF occurs virtually everywhere in the body. This method of administration ensures firstly that the concentration in the eye is sufficiently high, whilst secondly the systemic blood level and thus the risk of potential side effects in the body remain low," explains Sachse.

Study results available to date show that VEGF Trap-Eye can significantly reduce the thickness of the retina and improve visual acuity. "The disease can be halted in nine out of ten patients with VEGF blockers and the visual acuity can even be clearly improved in a relevant number of patients. This means that we have a form of treatment which can be used in the early stage of the disease and can successfully prevent severe visual impairment," says Kirchhof of the new development. The scientific journal *Nature* described VEGF traps as one of the most important advances in medicine in 2006.

The current Phase III study – called VIEW 2 – will include 1,200 patients in cooperation with over 200 centers worldwide. The VIEW 1 study, which is also a Phase III study, is being carried out by Regeneron in North America. If the active substance continues to provide positive results, the prospects for a promising treatment for wet macular degeneration look good. The active substance could also promise a treatment for another patient group – diabetics – in future. After all, diabetic retinopathy is the most common cause of blindness in the 20 to 65 age group in the Western world.

www.augen.de

 This site provides information about the eye, a service for ophthalmologists and the latest news.

Interview



A good perspective

research spoke to Professor Bernd Kirchhof, Head of the Department of Retinal and Vitreous Surgery at Cologne University Ophthalmology Center.

Are there risk factors which favor the development of AMD or influence its course?

The greatest risk is ageing itself, together with a genetic predisposition. Other factors are smoking and high blood pressure or a history of AMD in the family. Existing visual defects such as short- or long-sightedness have no effect on the likelihood of developing AMD.

How can an ophthalmologist recognize AMD?

With the wet form of age-related macular degeneration, tissue fluid leaks from the newly formed vessels. A fluorescent contrast medium is used to visualize the vascular plexus of the retina. If the dye can be seen outside the vessels, this indicates leakage and danger to the eyesight.

How do patients tolerate the injection of the new active substance into the vitreous body?

Despite the unpleasant-sounding treatment, patients are very grateful. Although they have to have at least three to five injections a year, they accept this as the prospects for success are very good. The injection itself is low-risk and to date only one in three thousand patients has suffered inflammation after the treatment.