First achromatopsia gene therapy clinical trial in Germany is going well

Achromatopsia is a heterogeneous inherited disease that affects around 3000 people in Germany. People with the disease are born without the ability to differentiate colours and with severely reduced visual acuity measured at only ten percent of normal values. Achromatopsia sufferers also experience other problems, including high sensitivity to light and glare. They can only go outside if they are wearing heavily tinted glasses. Sufferers are unable to perform many everyday activities like driving a car. Children with the disease need special assistance at school including appropriately filtered eyewear or classrooms equipped with tinted windows, to name but two examples. This severe visual impairment is due to total loss of function of the colour receptors in the retina, i.e. the cone cells responsible for visual acuity and colour vision. The disease is the result of an inherited defect caused by mutations in one of the genes that encode for a protein found in the cone cells. Any one of several gene variants can separately create the condition.

A gene defect causes the severe eye disease

Prof. Dr. Bernd Wissinger and his team from the Department of Ophthalmology at the University Hospital of Tübingen have been exploring the molecular causes of achromatopsia for many years. Back in the 1990s, the research group managed to identify one of the genes that lead to the disease and found that mutations in the CNGA3 gene cause achromatopsia in around a third of sufferers. In cooperation with researchers from the University of Munich, the scientists from Tübingen developed a mouse model (knock-out mice) in which they switched off the CNGA3 gene. “We found that the mouse model represented the human situation very well, and knocking off the gene made all cones non-functional,” said Wissinger. The researchers used the model to demonstrate that the severe eye disease was in fact caused by the genetic defect. They then began working on the development of a gene therapy to treat the defect in humans.
Around five years ago, the Tübingen scientists and their colleagues from Munich used the approach to successfully treat the disease in the mouse model. “We were able to show that injecting viral vectors with intact CNGA3 sequences into the eyes of the mice restored cone function in the animals,” said Wissinger. The success of the treatment was demonstrated with objective measurements and behavioural experiments. “We saw a major difference in the ability to recognise colours between mice that were delivered a normal gene copy to the cone cells and mice...
that were not,” said Wissinger, who is professor of molecular genetics of sensory systems at Tübingen University Hospital.

Gene therapy preparations have existed since 2012

The scientists also used histological methods to find out whether the gene product had reached the target tissue. The gene therapy approach requires part of the retina to be lifted up, an invasive procedure that an experienced retinal surgeon can perform relatively easily. As only part of the retina is lifted up, the therapy only reaches this particular retinal region rather than the entire retina. Using histological methods, the researchers from Tübingen were able to show which cells came into contact with the viruses and where the gene was expressed, thus demonstrating that the gene therapeutic approach can successfully correct achromatopsia.

After obtaining positive results with mouse models, the researchers went on to optimise the approach for application in humans: the mouse vectors were adapted to the human organism, i.e. humanised, produced under GMP conditions and once again thoroughly tested. “The viruses need to be tested in the animal model again to find out how they are distributed in the body and how many are excreted. This procedure is the same as that applied to other pharmaceuticals,” said Wissinger.

In addition to developing the drug, the scientists had to find suitable patients for the planned clinical trial. “It is relatively difficult to identify achromatopsia sufferers. However, we are an
achromatopsia centre and are therefore in the fortunate position to have collected several hundred blood samples from achromatopsia sufferers,” said Wissinger. “We identified several dozen sufferers with the genetic defect that we were looking for and we also used state-of-the-art methods to substantiate initial findings at different points in time.”

The search for sufferers came up with completely new findings

The complex patient tests have also led to other important results. Wissinger comments: “We found that the clinical picture is not as static as previously thought, but very much subject to change. We found that the number of cells that died increased as sufferers got older.” This finding was extremely important for Wissinger and his team as gene therapies can only be applied to cells that are alive and still able to respond to treatment. “Dead cells cannot be treated,” says Wissinger.

“We did not expect this at all and were somewhat concerned. The likelihood of a positive treatment outcome is generally higher the younger the patients are. That said, of course, the situation differs from case to case. This finding demonstrates that gene therapy only has a therapeutic effect when the disease is diagnosed as early as possible. And that's the problem. It's the same with many other rare diseases. It usually takes several years before people are referred to specialist centres and diagnosed with the disease,” said Wissinger.

Ongoing clinical trial comes up with rather promising results

In autumn 2015, the scientists got the go-ahead from the relevant German authority and the ethics committee to commence the clinical trial. A few weeks later, the first achromatopsia patient underwent gene therapeutic treatment at the University Eye Hospital in Tübingen. The trial is designed as a dose escalation study that establishes the dose of drugs for Phase II trials and involves three patients per dose level. Treatment starts with subtherapeutic doses that are gradually increased. An adequate period of time is allowed between individual dose levels so that potential adverse effects can be dealt with. In addition, an external evaluation team performs an ethics and safety evaluation on the patient data. “It goes without saying that such trials take a long time,” Wissinger says. “We expect to treat the final patient group, i.e. the patient group that is given the highest drug dose, by the end of the year. In addition to assessing the safety of the application, the ongoing clinical trial is predominantly focused on the therapeutic benefit.”

As far as the results are concerned, the scientists expect the lowest dose level group to experience no notable effect. “We need to determine the therapeutic dose, so we are starting with a very low dose that is gradually increased,” says Wissinger. Nevertheless, patients who received the lowest virus doses reported that treatment has made them less sensitive to light. Objective tests carried out by doctors substantiated the patient observations. “And as far as adverse effects of the viral vector are concerned, we can conclude with certainty that treatment has not led to problems in the six patients we have treated so far. The only complaints about adverse effects could be attributed to cortisone that was taken to prevent inflammatory reactions.” Whether the first gene therapy approach for treating achromatopsia and the first eye disease gene therapy in Germany is successful can only be determined after the trial has been completed. However, Wissinger believes that initial findings point to a positive outcome for both scientists and patients.