Gene Therapy for Rare Disease

An interview with Dr Piter Bosma and Dr Sem Aronson

By Ingrid Lutke Schipholt

Crigler-Najjar is a liver condition which results in jaundice. Patients need to lie under blue light for hours every day to break down the yellow pigmentation. If they don't, they die. Piter Bosma and Sem Aronson have high hopes for gene therapy.

In April, Molecular Biologist Piter Bosma and doctor Sem Aronson reached a milestone in their search for a treatment that will cure the liver disease Crigler-Najjar. They will start a trial where patients are given gene therapy: a vector (a virus from which the harmful DNA is taken out and to which a curing gene is added) administered intravenously.
Crigler-Najjar (CN) is rare and affects one in a million people. "The liver is unable to produce a specific enzyme necessary to clear bilirubin, a yellow coloured pigment, from the body"

says Sem Aronson. “Patients turn yellow and need to sleep under blue light for many hours a day their entire lives. The blue light makes sure that bilirubin can be converted and cleared from the body. Adults sometimes need to lie under blue light for 10 to 12 hours every twenty-four hours for it to have sufficient effect on the conversion of bilirubin.”
Bosma explains how the trial works: “Before patients receive the gene therapy we monitor them for three months to determine how high the bilirubin level is during blue light treatment. After that we administer the vector. The virus finds its own way to the liver and does its work there.” ”The patients are in fact their own control group”, Aronson adds. “That is because there are only a limited number of patients: in the Netherlands approximately six patients will participate”.
The Amsterdam UMC and the Erasmus MC in Rotterdam are in this study together. The other eleven to fourteen patients are from France, Italy and Germany.
“The trial is only for adults and adolescents because the liver of a child is not mature enough for this form of gene therapy”, Aronson goes on to say. “The cells in the liver of small children multiply which means the effect of the treatment is temporary.”

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The bed with the blue light patients sleep under during the trial was made by the father of a young CN patient. He designed the bed so that his child could continue blue light treatment during holidays as well. This model enables you to adjust intensity and operating time of the light. This means that researchers can now simulate the patient’s home situation at the hospital. Other light beds do not allow this.
Bosma emphasises that the gene therapy is not a dangerous treatment. “Everything that could be harmful is taken out of the vector. No virus material is present anymore. We only use the empty shell. So the vector cannot multiply. As yet, a patient can only receive this therapy once because the body will make antibodies against the foreign vector. If we repeat the therapy at a later moment, the patient will have antibodies against this vector meaning it will not reach the liver. It has been very successful in rats so we have good hopes that it will be successful in people as well. Salient detail is that the disease was discovered in rats long before it was discovered in people.”
According to Aronson, the production of the vector was the reason the trial was delayed for several years. “We had a model but British research among haemophilia patients told us that the dose we had chosen was too low. It was necessary to increase the efficiency of the production to make enough vector for a higher dose. The production has now been completed. As soon as we have all the permissions we will start. After the trial we will begin procedures to get the therapy registered officially at the European Registration Office EMA.”
Because of the joint registration and in order to involve as many patients as possible in the trial, a consortium was formed with France, Germany and Italy. All researchers involved met at the Tytgat Institute in April to prepare the start of the trial.

Piter Bosma has worked as a Molecular Biologist at Amsterdam UMC since 1991. He obtained his doctorate in Leiden and is connected to the Tytgat Institute. Bosma leads the clinical study on gene therapy for inherited hyperbilirubinemia.

Sem Aronson is a doctor and has done research into gene therapy for Crigler-Najjar syndrome as a PhD student at Amsterdam UMC since 2014. His promotor is Hepatologist Prof Ulrich Beuers.

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From left to right: Piter Bosma with the designer of the bed Jack Janssen, Ulrich Beuers and Sem Aronson
Photo: Marieke de Lorijn/Marsprine