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Can the ticking Huntington clock be stopped?

An early phase clinical study involving thirty-six Huntington's disease (HD) patients is currently underway to investigate whether a method called gene silencing can cure the disease. If the gene that causes the disease can be turned off, it would be the first step towards a treatment that not only fights symptoms but actually treats the causes of HD, hence providing a cure. Prof. Dr. G. Bernhard Landwehrmeyer, a neurologist from Ulm who is heading up the German contribution to the international clinical trial, not only sees light at the end of the tunnel for patients suffering from this particular fatal neurodegenerative disease.

If the phase Ib study is successful, and there are many indications that it will be, the new approach could also potentially be used with other active substances for treating other diseases caused by a single faulty gene (the World Health Organisation estimates that there are more than 10,000 single-gene disorders). But before this can happen, further larger studies will have to be carried out to substantiate initial findings.

First trial that targets the root of the disease

The approach being taken at the University Hospitals of Ulm and Bochum, as well as at hospitals in Great Britain and Canada, uses small chemically modified nucleic acids (antisense oligonucleotides, ASOs) that prevent the expression of harmful gene products. The therapeutic principle of gene silencing involves switching off the expression of the gene that leads to HD by introducing short, single-chain ASOs. These ASOs stick to the messenger RNA, and stop the huntingtin protein from developing. The ongoing phase Ib study is the first to investigate the therapeutic silencing of a disease-causing gene in HD patients. Similar early phase clinical trials have focused on other neurodegenerative diseases (Chiriboga 2016; Miller 2013).

Huntington's disease is one of the most common neurodegenerative hereditary diseases in the world. In Germany alone, an estimated 8,000 people have the disease and around 30,000 people might carry a mutant form of the huntingtin gene (also called Huntington's disease gene). The huntingtin gene is located on the short arm of chromosome 4 and is linked to the development of HD. As a young scientist, Landwehrmeyer spent some time in a laboratory in Boston which was instrumental in the discovery of the huntingtin gene in 1993. Despite intensive research, no cure is yet available for the devastating disease, which is characterised by motor and psychological disorders and progressively impairs cognitive abilities. It is also associated with life-threatening complications. HD is caused by an extra-long stretch of CAG triplets within the huntingtin gene that code for the amino acid glutamine. Healthy individuals carry between 11 and 34 repeats of the

Prof. Dr. G. Bernhard Landwehrmeyer, HD expert and head of the German contribution to the clinical trial.
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base triplet CAG, HD patients have between 42 and around 150 CAG repeats.

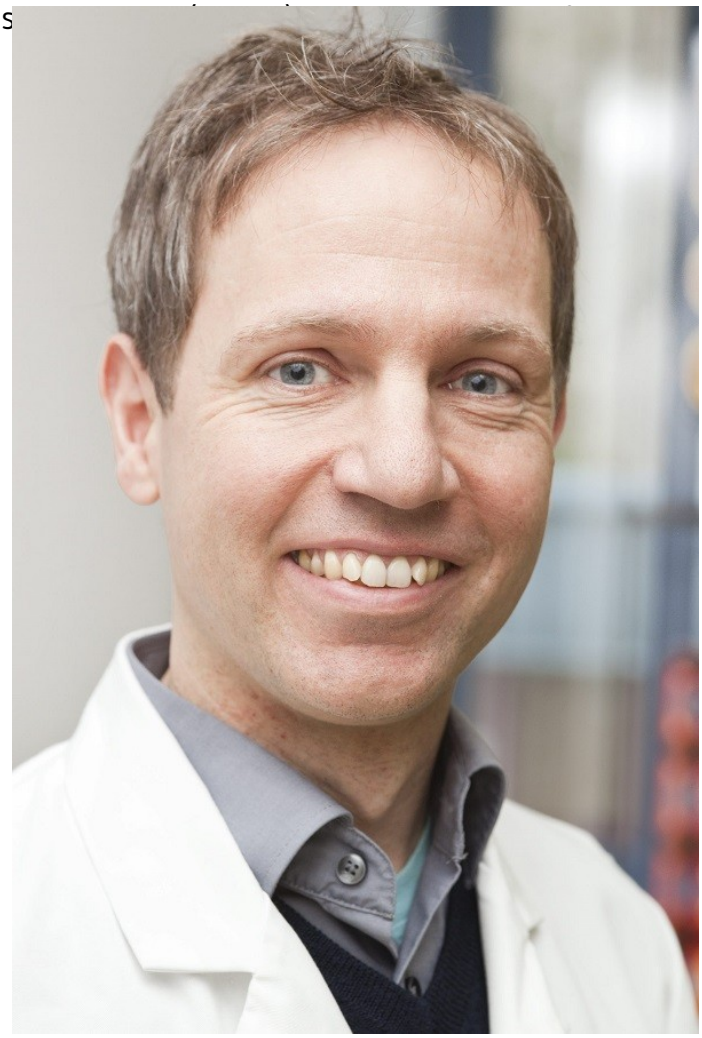
Safety and tolerability first

The ongoing, double-blind phase Ib study is aimed at evaluating the safety and tolerability of ASOs. A small group of patients is being treated with different amounts of ASOs, starting with a low amount that is gradually increased to help find the optimal dose and determine whether the drug has adverse side effects. The study participants – patients in early stages of HD who are still able to make complex risk-benefit assessments – are aware that the trial is not in any way aimed at influencing the progression of HD. This type of trial only lasts six months (including a two-month observation period) and is too short to influence disease progression.

As ASOs cannot cross the blood-brain barrier, they must be delivered directly to the central nervous system (CNS). To get them into the brain, they are administered by way of a needle inserted into the fluid-filled space below the lower spinal cord. The advantage of this is that it distributes the ASOs widely across the CNS, thus reducing the quantity of huntingtin mRNA and hence mutant huntingtin protein in the brain and spinal cord tissue (Miller, 2013, p. 436). However, injecting the drug into the fluid-filled space does not necessarily reach all brain cells. The rationale of the study is clear: the researchers want to find out which adverse effects can be attributed to epidural drug delivery and which to the drug under investigation.

How necessary are healthy huntingtin gene products?

The substance tested reduces the quantity of mes
production of both healthy and defective huntingtin proteins. The neurologists hope that a therapeutic effect can be achieved despite the lower concentration of healthy proteins. Landwehrmeyer explains that all animal experiments carried out so far have demonstrated that the number and quantity of pathological alleles or their products are crucial for the formation of the pathological phenotype. Animal experiments suggest that a reduction in pathogenic huntingtin gene products over a prolonged period of time will reach a sufficiently high number of cells to have a positive effect on clinically measurable disease symptoms or at least slow down disease progression.



PD Patrick Weydt and his colleagues are evaluating the drugs.
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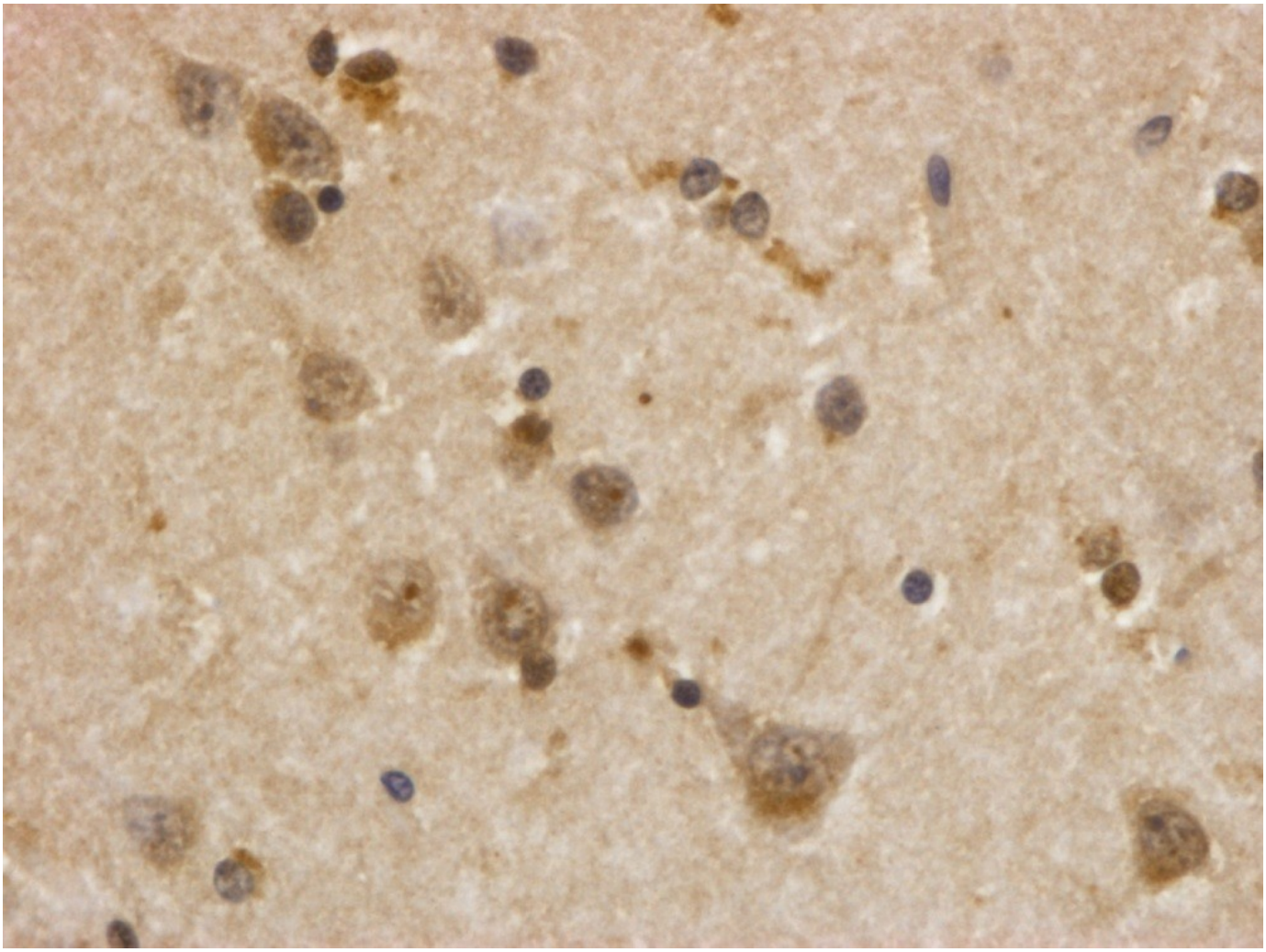
The targeted reduction (of up to 50%) of huntingtin gene expression level entails a certain number of risks, but the researchers believe that the risk level is relatively low. In concrete terms, there is a risk of allergy (immune system response to a synthetic nucleic acid) and of the level of healthy huntingtin protein, which is required for normal development before birth, becoming too low. The neurologist from Ulm is therefore pleased that the clinical trial is using a compound that is excreted after three months, thus increasing gene expression to the pre-treatment level. The most unfavourable outcome the researchers can imagine is when, for a limited period of time, the amount of unaltered huntingtin gene product falls to amounts as low as 50 percent.

Therapy starts at the roots of the disease

Although the pathogenesis of HD is not understood in every detail, the neurologists are relatively unconcerned about this as their approach targets the primary disease cause rather than intermediate steps. “We do not need to understand all the ramifications in detail, at least not for the moment. However, we believe that intermediary pathways might be excellent targets for future treatment approaches and interventions,” say the researchers.

It is known that mutant huntingtin protein is toxic for the striatum. However, it is also known from animal experiments that the targeted expression of mutant huntingtin genes in the neurons of the striatum alone is not sufficient to cause either HD-related deficits in the motor system or neuropathologies.

Normal huntingtin protein, which is produced throughout the body, but mainly in the brain, is required for one or several development steps prior to birth. Animal experiments have provided evidence to back the hypothesis that there is a therapeutic window for the safe and effective



Huntingtin protein aggregates (red-brown deposits) in the brain are the cause of HD and the new therapeutic approach is the first time they have ever been targeted directly.
© Katrin Lindenberg, Neurology, Ulm University Hospital

temporary suppression of huntingtin gene expression using a non-allele-specific ASO approach (Kordasiewich 2012, p. 1041).

Reaching as many brain regions as possible

According to the current state of research, the development and progression of the disease depends on the expression of mutant huntingtin protein in different cell types of the striatum and the cortex. As the striatum makes up only 1% of brain volume and advanced stage HD patients have lost around 30% of brain mass, the researchers conclude that HD also affects other brain areas. It is therefore assumed that totally effective HD treatment has to target several brain regions (Kordasiewicz, 2012; p. 1031).

What will be the best-case scenario? Researchers might be able to apply the therapy over a prolonged period of time and investigate the effect that relieving the body of mutant huntingtin protein has. If the results of the phase I trials are positive, additional trials, and in particular phase 3 clinical trials with an increasingly large number of patients will need to demonstrate that silencing the huntingtin gene will improve the symptoms of HD.

First positive signals

Although the researchers from Ulm do not yet have results from cohorts one and two, the independent safety committee has given the go-ahead for the third cohort, based on previous results. The researchers can thus assume that the doses used in the investigation are safe and well tolerated by the patients. The researchers are aware, and the HD patients have been told, that this is only the first, but potentially also decisive step towards developing a curative treatment for HD. The researchers are carrying out the current trial to find out which brain cells and regions the ASOs can reach. This will determine how noticeable the clinical benefits of this approach are for patients.

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Article

02-Aug-2016

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- HD Outpatient Clinic in Ulm

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