Healthcare industry BW

# Research increases hope

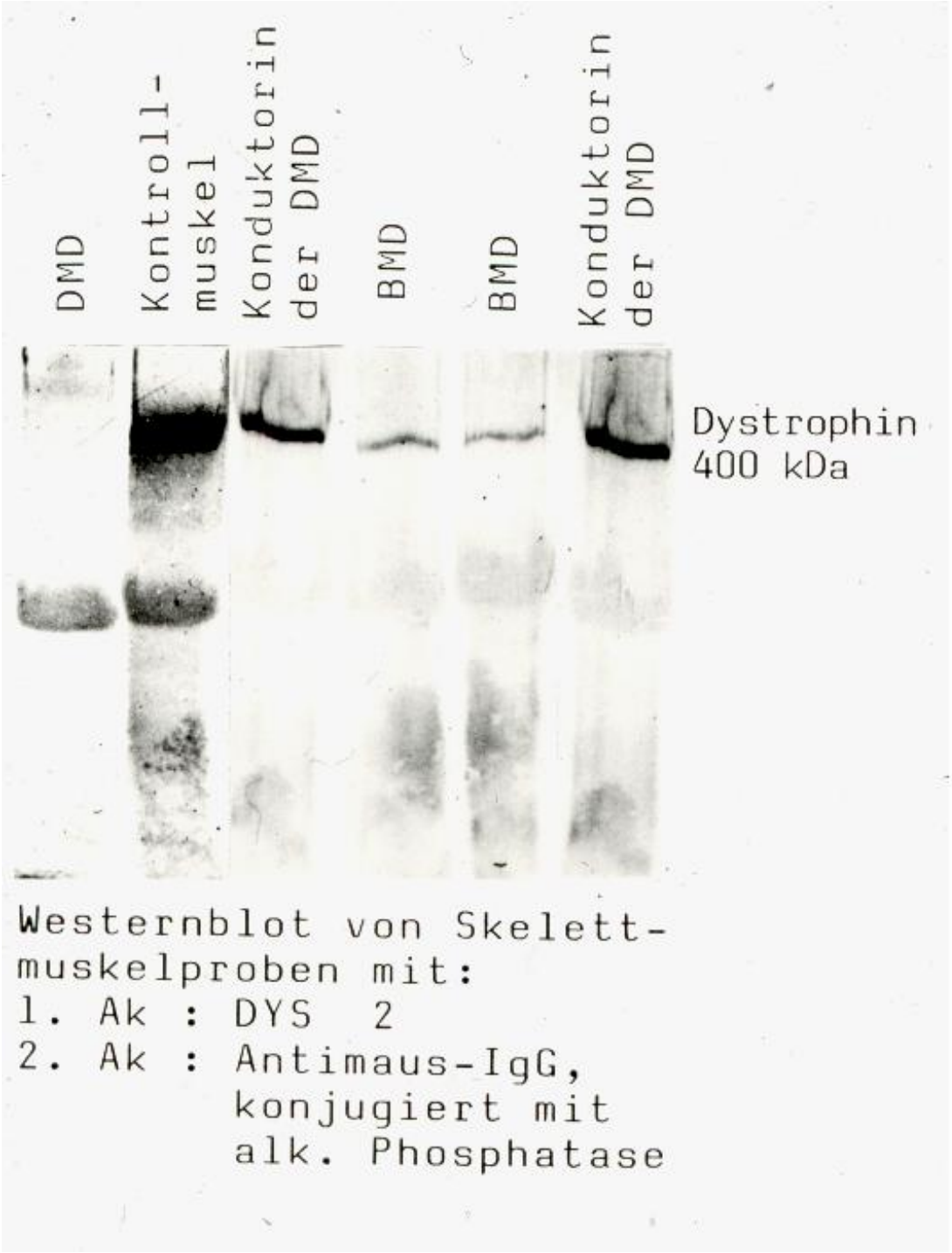
**Duchenne muscular dystrophy (DMD) is a severe disease affecting boys, characterised by rapid progression of muscle degeneration so that boys as young as 10 to 12 years of age have to use a wheelchair, and leading to death in young men. In Germany, about 2500 children and young adults suffer from DMD. Paediatricians assume that one boy in 7000 newborn babies will develop DMD in his first few years of life.**

Being a rare orphan disease, therapeutic treatment for DMD is limited. However, in a large clinical study, planned, coordinated and currently being evaluated at the University Children's Hospital in Freiburg, German, Austrian and Swiss paediatricians are focused on finding a new combination of compounds that is able to delay this deadly disease.

The disease is the result of a mutated gene located on the short arm of the X chromosome. In general, only males are afflicted, but females can carry the disease. As they only have an X and a Y chromosome, boys lack a second intact copy of the defective gene that would be able to compensate for the defect. The majority of the young children lack a big and essential segment of DNA. Geneticists refer to this as a deletion; however, the disease can also result from DNA duplications or point mutations. These modifications alter the DMD gene so that the body is unable to produce the protein dystrophin.

## Agonising hopelessness

The protein dystrophin is an important structural component of the cell membrane that surrounds the muscle fibres, thereby forming a protective network in the membranes. The lack of this structure enables dangerous substances to enter the muscle fibres, damage them and cause them to degenerate, a process known as dystrophy. In addition, the muscle cells lose important substances, including the enzyme creatine kinase, which forms a very important molecule, adenosine triposphate (ATP), which provides the muscles with energy. These processes add up over time and the condition of the sick children gradually deteriorates.

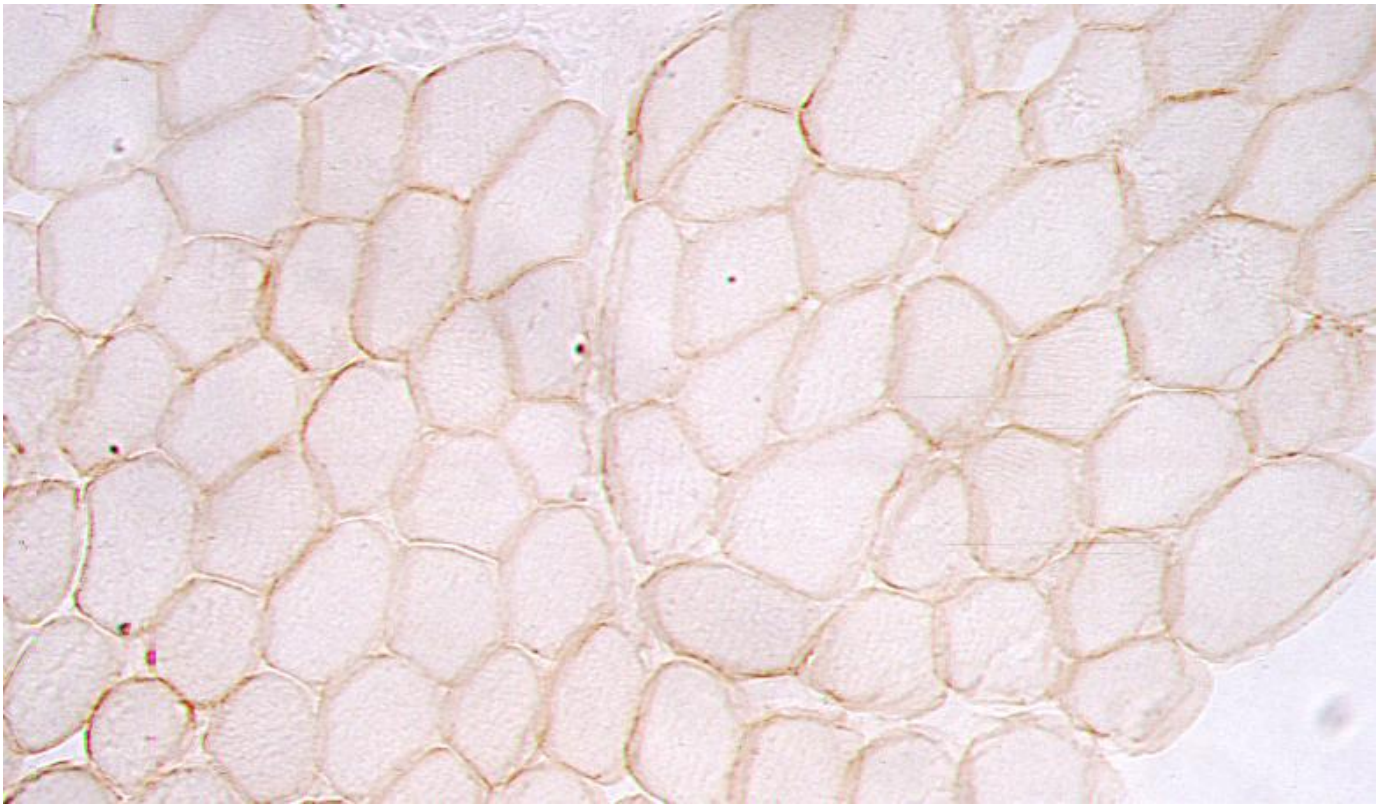



The Western blot clearly shows that patients suffering from Duchenne muscular dystrophy (DMD) lack the protein dystrophin (sample 1). Patients with Becker muscular dystrophy (BMD), with a slower progression of muscular degeneration, are still able to produce small amounts of dystrophin (samples 4 and 5). The carriers of the disease (samples 3 and 6) have less dystrophin in the membranes of the muscle fibres than a healthy human (sample 2). Photo: Korinthenberg

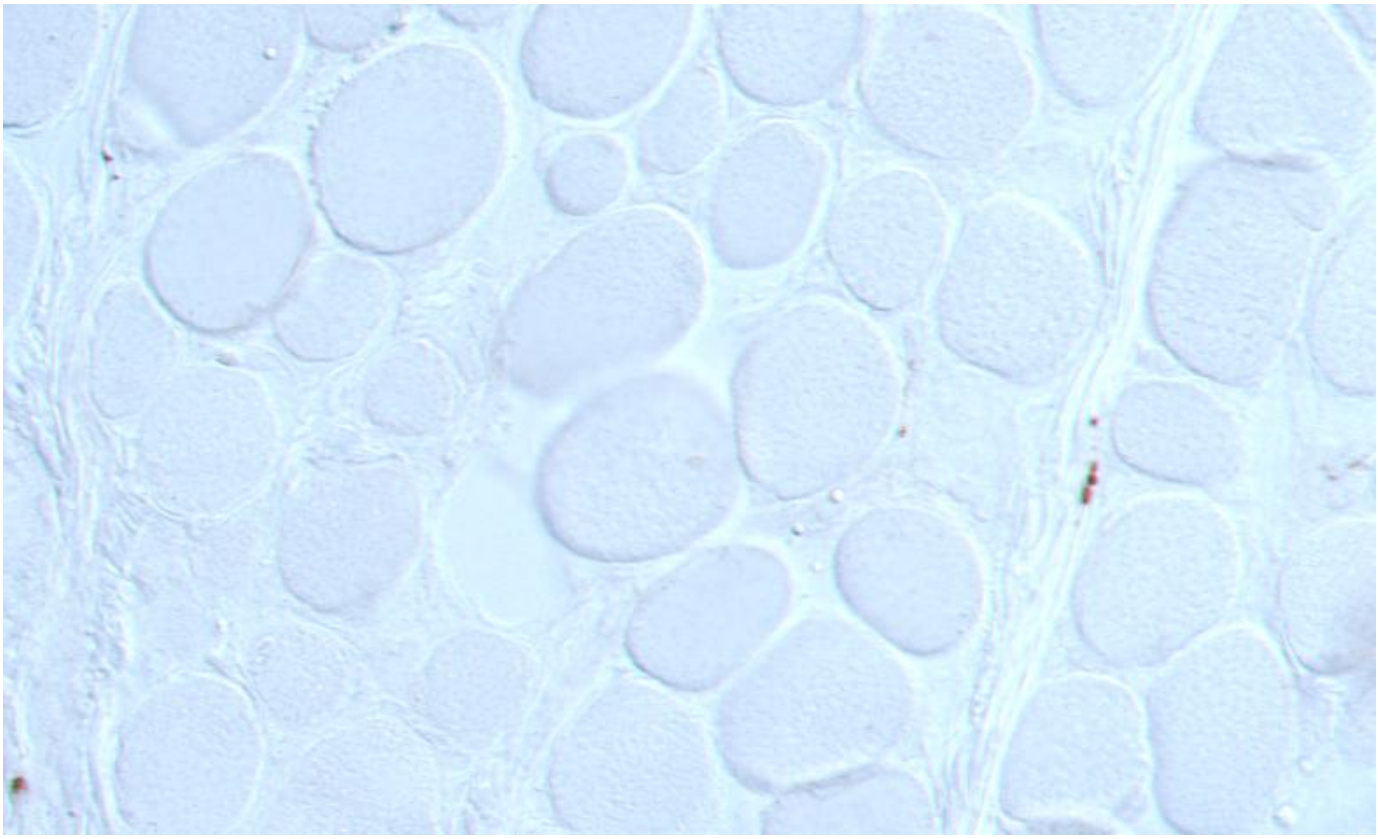
The hopelessness is not the only thing parents and children are faced with. Usually, they have been through a lot of frustration and seen many doctors and hospitals before they are eventually confronted with the shattering diagnosis: DMD. “Something that is rare is also difficult for doctors to diagnose. They lack the experience that is necessary to diagnose the disease at an early stage,” said Prof. Dr. Rudolf Korinthenberg, Medical Director of the Hospital of Neuropaedriatrics and Muscular Diseases at the University Hospital in Freiburg. The Freiburg Hospital is currently looking after 65 children and young adults with DMD, but also patients with other rare diseases. Centres like the one in Freiburg have been established to provide special help for DMD children.

# Considered together, orphan diseases are not so rare at all

In general, the pharmaceutical industry has little interest in developing new drugs for the treatment of rare diseases. The investment costs are high and the profits rather small. In addition, often little is known about the diseases and the processes leading to them. Rudolf Korinthenberg therefore often meets very frustrated parents who have the feeling that their children do not receive the same attention as children suffering from cancer or diabetes. However, Korinthenberg finds that recently, great progress has been made: research into rare diseases is now carried out at different universities and some biotechnology start-up companies have specialised in the development of orphan drugs.



Muscle cells of a healthy child...



... and those of a boy suffering from DMD. The lack of muscle cells and hence the reduction in muscle mass is apparent in the second photo. (Photo: Korinthenberg)

In addition, the German Federal Ministry of Education and Research (BMBF) has realised that it is important to put greater emphasis on the research of orphan diseases, rather than only focusing on common diseases. Considered together, orphan diseases are no rare phenomenon at all. In Germany, several million people suffer from orphan diseases. Since 2003, the German government has been funding ten networks that focus on the research of rare diseases, including the Muscular Dystrophy Network (MD-Net), within which Rudolf Korinthenberg leads a coordination centre for clinical trials. The original proposal written by a team of scientists is still on Korinthenberg's shelf. It is a thick book with as many pages as a doctoral thesis. "We spent many hours working on the proposal," said Korinthenberg recalling the time when they applied for funding, and the success of bringing together German dystrophy experts. Molecular biologists, diagnosticians and clinical doctors from all over Germany are now working together to investigate DMD. One of the projects is a new therapy trial for the treatment of DMD. Working together with the Freiburg Centre for Clinical Studies, Korinthenberg and his team planned the trial, coordinated it and trained study doctors. The treatment of the last of the 150 patients that were enrolled in the study was completed in May 2008. The results of the trial are still being evaluated.

## Looking for an alternative that is better tolerated by patients

The doctors tested a drug that was not specifically developed for the treatment of DMD, something that is quite common when looking for orphan drugs. Korinthenberg and his colleagues focused on a drug that was approved for other indications and combined it with cortisone. "Cortisone is the only drug that has been shown to be effective for the treatment of muscular dystrophy," said Rudolf Korinthenberg. The substance, which is similar to a hormone of the adrenal cortex, reduces the loss of muscular strength and provides the young patients with two extra years of walking and reduced wheelchair use. However, the children pay a high price because cortisone treatment is

associated with many side effects.

“We were looking for an alternative that was associated with as few side effects as possible but also restricted the progression of the disease," said Korinthenberg. New research had shown that immunological processes might be involved in the death of muscle cells lacking dystrophin. Therefore, the Freiburg team chose a treatment strategy that had previously been successful in the treatment of rheumatism. They reduced the amount of cortisone and combined it with an immunosuppressive drug.

## High expectations

In the first phase of the double-blind, randomised study, half of the young patients were treated with the immunosuppressive drug cyclosporin (without cortisone) for three months; the other 50 per cent received a placebo. The investigators hoped to find out whether cyclosporin had an effect on the muscle at all. Neither patients nor doctors knew who received the drug and who received a placebo. In the second phase of the trial, the patients received low doses of prednisone (a man-made cortisone replica) for twelve months, combined with either cyclosporin or a placebo drug. The results of the study, eagerly awaited by patients and doctors, will most likely be available in November.

Nine German hospitals, together with one Austrian and one Swiss partner, participated in the trial. However, the BMBF funds would not have been sufficient to test the therapy. “The BMBF funds financed the posts of 1.5 staff members, but were insufficient for a clinical study,” recalls Korinthenberg who finally decided to contact Novartis executives. Financial support from Novartis, “Benni & Co”, a parent self-help group, and the German Society for Patients with Muscle Disorders (DGM) enabled the trial to go ahead. Novartis provided cyclosporin free of charge and also produced the placebo. “Benni & Co.” and DGM supported the project with research funds and supported the doctors in recruiting the large number of 150 patients, a number that is necessary to obtain a statistically relevant result. It was not difficult to recruit enough children for the study. “Duchenne is a deadly disease and the parents see the health of their children getting worse and worse. A trial like this one offers hope. The parents are keen to do something and see that something is happening,” said Korinthenberg. In order to help the young patients as effectively as possible, a European network for neuromuscular diseases has been established, also involving Dr. Korinthenberg in Freiburg and many of his colleagues across Europe.

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**Further information**

Prof. Dr. Rudolf Korinthenberg
Hospital of Neuropaediatrics and Muscular Diseases
Centre of Paediatrics and Adolescent Medicine
Mathildenstraße
79106 Freiburg
Tel.: +49 (0)761/270-4315

Fax: +49 (0)761/270-434475
E-mail: rudolf.korinthenberg(at)uniklinik-freiburg.de