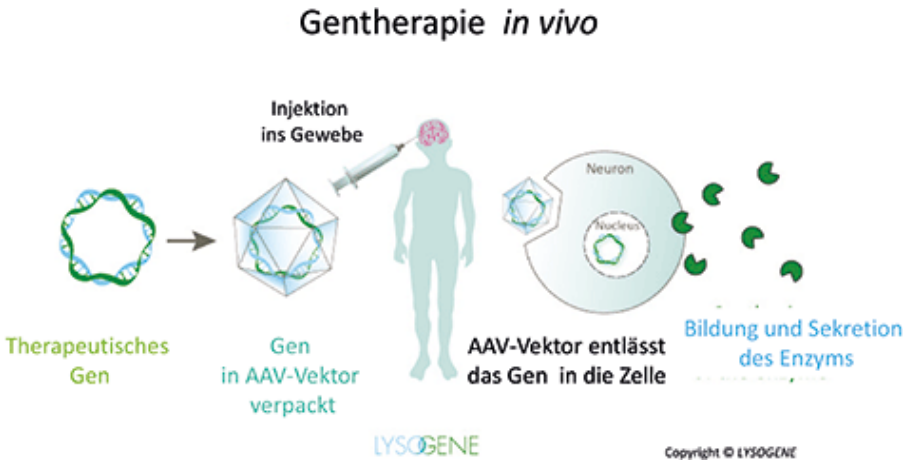
Gene Therapy is Clinical Practice

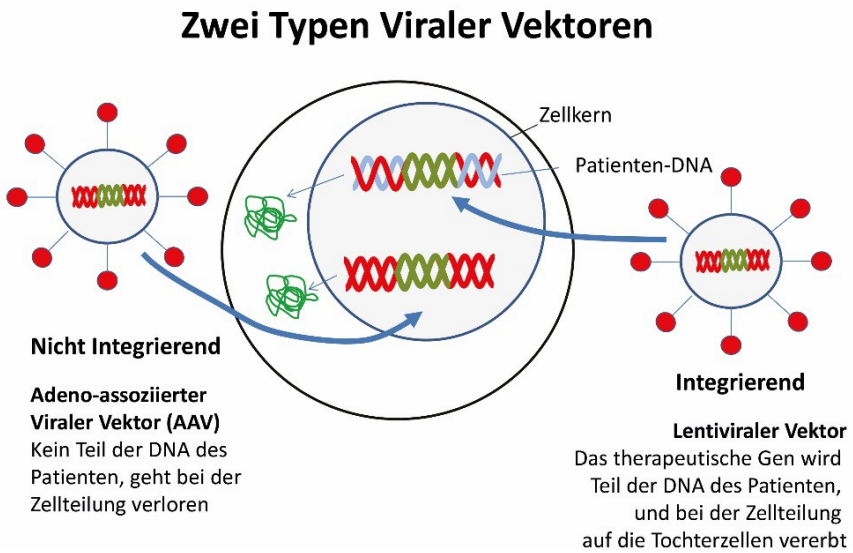
Various known strategies for enzyme replacement therapy (ERT), hematopoetic stem cell therapy (HSCT) and substrate reduction therapy (SRT) have basically proven effective on MPS. None of these methods alone is able to meet all the requirements. Besides several technical improvements, it is to be expected that combinations of all available methods (e.g. HSCZ + ERT or ERT +SRT) will achieve progress and improvement.

Especially through new methods in the fields of gene therapy significant progress could be achieved. Basically, copies of a normal gene have to be integrated into a carrier particle, the vector, in order to guarantee that the therapeutic genes are actually able to eliminate the cause of disease. **There are two different methods, the "in vivo method" and "the ex vivo method".**
In the **"in vivo" therapy, vector** systems are used that have been developed from adenoviruses (adenoassociated viruses, AAV).

They have been modified so that they can enter the cells delivering the therapeutic DNA to the nucleus, but are not able to replicate themselves.



They are especially suitable for long-lived cells with low proliferation, e.g. nerve and muscle cells. The therapeutic gene and not the virus's own genetic material is transported into the patient's DNA.



This means the danger of an inadvertent activation of tumoral growth can be minimized.
However, during cell division the therapeutic gene will be lost.

Such an in vivo - concept is being developed for MPS IIIA by M.Tardieu, Paris and Lysogene – Biotechnology. Pre-clinical trials with MPS IIIA mice demonstrated that the activity of the enzyme in the brain accelerates and the glycosaminoglycan – storage decreases without side effects when injecting the gene for sulfamidase via adenoviral vector.

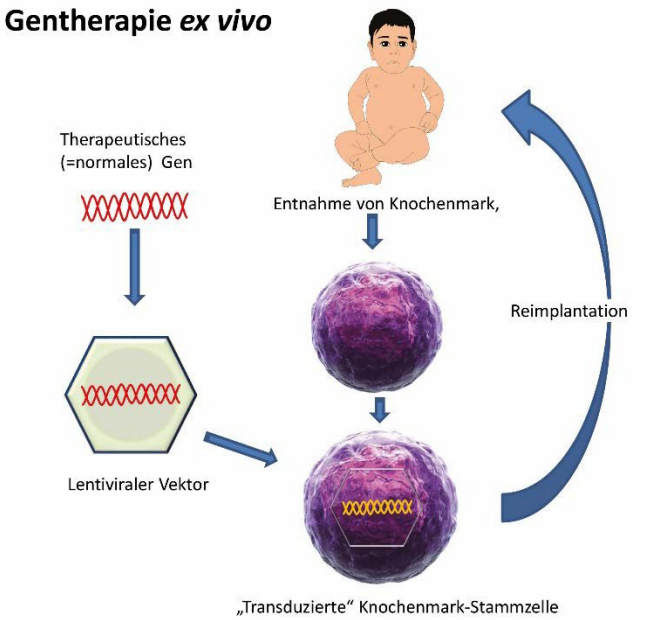
Since 2012 four patients aged between two and six years have been treated by single vector injections into the brain. Treated with agents to prevent rejection (immune-suppressive therapy) all patients showed moderate improvements in neuropsychological tests.

Parents as well reported on improvement in behaviour, sleeping disorder and hyperactivity, a typical symptom of this disease.

A second, improved vector with increased dosage should be tested on twelve patients in a multicentre study in two to three centres in Europe and the US between 2015 and 2017.
A similar gene therapy trial for MPS IIIA should be started in the third quarter of 2015 in Spain.

G. Andria reports a different method for MPS VI, currently undergoing the phase I/II review. He developed an AAV vector, which is desired to deliver the therapeutic gene to the lever. After a single injection, he found a constant, stable rise of the enzyme activity in the liver for at least one year with positive effects on the excretion of glycosaminoglycanes as well as on the function of heart, skeletal muscle and / or bone structure. With similar therapeutic effects, such a use of the liver as “enzyme factory” could drastically reduce the medical costs compared to EET with genetically engineered arylsulfatase B.

In the ex-vivo therapy, stem cells are removed from the patient’s bone marrow and treated in cell culture with a type of vector, which is inserted in the genome of cells (lentiviral vectors).The stem cells are genetically corrected and multiplied in the cell culture and then returned to the patient by infusion.



Compared to conventional stem cell transplantations there is a lower risk of a rejection reaction, since no immunological “foreign” stem cells are used. At the same time much higher doses can be used in genetically modified cells. The higher risk of tumour development when AAV vectors are used, can be minimized by using specially self-inactivating vector types. After the successful application of this method for non – lysosomal diseases e.g. Xadrenoleukodystrophy, this method was used last year in three presymptomatic patients with metachromatic leukodystrophy.

In the span of 7 to 21 months, the patients showed no signs of disease progression compared to siblings. Phase 1 clinical trials with different vectors are planned for MPS I, II and VII.

Therefore, gene therapy is no longer an experimental idea but clinical practice. Its further development must be carried out with great care and with “realistic optimism” (B. Winchester, London).

Prof. Dr. Eduard Paschke
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