Scientists develop active substance for fatal muscle wasting in male children

February 3 2015

Duchenne muscular dystrophy is a congenital disease which causes muscle degeneration and eventual death in teenagers. Recently, researchers from Bern developed an active substance, which they together with an international team tested successfully.

Duchenne muscular dystrophy (DMD) is a relatively rare congenital disease which only affects boys and which leads to irreversible muscle wasting. Around 1 in 3500 newborns is affected. At approx. 10 years old, Duchenne patients are dependent on a wheelchair and in increasing need for care. Patients are not expected to make it to their late 20s and often die from heart or respiratory failure. There is no current cure for DMD but recently researchers from Bern, France, England and Sweden tested a promising active substance. The corresponding trial was published in the journal *Nature Medicine*.

Genetic defect leads to muscle failure

In recent years, it was possible to find the genetic origin of the disease which lies in a defect of the gene responsible for the production of dystrophin. Dystrophin is an important protein for a normal muscular function. An absence of dystrophin means that one single muscle cell cannot function with the others anymore leading to a failure of the entire muscle. The mutation of the gene subsequently leads to the fact that dystrophin is not produced or only a non-functional variant of it.

A promising therapy approach, which has been performed since recently, is to correct the defect in the production of dystrophin with short segments of a chemically modified DNA, so-called antisense oligonucleotides (AO). A significant curative effect with the tested active substances had not been achieved until now. That is because the corresponding active substances are not yet active enough and do not reach vital muscles such as the heart.

First tests were successful

The Department for Chemistry and Biochemistry of the University of Bern with the financial support of the Swiss National Foundation (SNF) and the Association Monégasque contre les Myopathies (AMM) now developed an oligonucleotide, the so-called tricyclo-DNA, which shows substantial benefits in comparison to the already known active substances. Experiments in mice show evidence that the agent leads to an improved dystrophin production in all muscles including the heart and the lungs and subsequently leads to an improved mobility and an increased life expectancy in mice.

Surprisingly it was also observed that the dystrophin production in the brain was corrected as well. It was thus shown for the first time that an oligonucleotide can pass the blood-brain barrier and become active there. Such discovery should be particularly significant for other neuromuscular diseases, such as spinal atrophy or Huntington's disease.

The next step of the clinical trial is to test tricyclo-DNA in humans. The trial is coordinated by the spin-off enterprise Synthena AG of the University of Bern founded in 2012. The enterprise manufactures tricyclo-DNA and advances the development of a medication for Duchenne patients. Shareholders of the enterprise are the University of Bern, the inventors of the technology and the two charitable patient organisations Duchenne Project France (DPPF) and AMM.

More information: "Functional correction in mouse models of muscular dystrophy using splice-switching tricyclo-DNA oligomers," *Nature Medicine*, 2015, DOI: 10.1038/nm.3765

Provided by University of Bern