Developing gene therapy for Duchenne muscular dystrophy

Developing a gene therapy for Duchenne muscular dystrophy Professor George Dickson and his team plan to develop a novel gene therapy approach that is aimed at delivering a functional, full-size dystrophin gene to muscle cells using a harmless virus. So far research has been restricted to delivering smaller mini- or micro-dystrophin genes due to restrictions in the size of the DNA fragment that the virus can accommodate. In this project the researchers will use two or three viruses each carrying a different part of the dystrophin gene. In the muscle cell the different parts assemble to form the blueprint to produce a full size dystrophin protein. If successful this approach could be used to treat people with Duchenne as well as people with Becker muscular dystrophy.

What are the researchers aiming to do?

Duchenne and Becker muscular dystrophies are caused by mutations in the dystrophin gene that contains the instructions for making dystrophin protein. This acts as a shock absorber to prevent damage when the muscle contracts. In people with Duchenne muscular dystrophy the mutation leads to the complete absence of dystrophin protein while in people with Becker muscular dystrophy the mutation leads to the production of a smaller dystrophin protein that retains some of its function. This is why people with Becker muscular dystrophy experience milder symptoms than those seen in people with Duchenne.

Gene therapy approaches offer the possibility of delivering a functional copy of the dystrophin gene to muscle cells where it could restore production of the dystrophin protein. The most promising approach is based on the use of a harmless virus called Adeno-associated virus (AAV) which has been shown to effectively deliver genes to a range of different types of cells and tissues including muscle. The virus triggers a relatively mild immune response which could allow it to be given more than once.

One of the challenges is that the dystrophin gene is too big for the virus to carry - just like an envelope can only hold so many pieces of paper, a virus can only carry a certain amount of DNA. Researchers have made mini- and micro-dystrophin genes

This project is funded by the Duchenne forum - a collaboration established to accelerate progress in the search for treatments and eventually cures.
that have successfully been tested in animal models of Duchenne muscular dystrophy. A phase I clinical trial has also been carried out in the US to test the safety of this approach in a very small number of boys. However, scientists think that using a mini- or micro- dystrophin gene has its limitations as they expect that the severe symptoms of people with Duchenne muscular dystrophy can be only improved to the extent of those seen in people with Becker muscular dystrophy. To address this challenge, transplicing technology has been developed.

Transplicing technology takes advantage of a natural process which lets our cells join different pieces of RNA (the carbon copy of DNA which cells use to carry the genetic messages from the nucleus where genes are kept to the cytoplasm where proteins are made) together to make a single protein.

The dystrophin gene is divided into two, or even three pieces - hence dual- or triple-transplicing - and each piece inserted into an individual virus. If all three viruses infect a single cell, the parts of the dystrophin gene can be joined together to produce a full-length dystrophin protein.

This project is aimed at optimizing transplicing technology - to increase gene delivery to the muscle cells and to make the transplicing process in the cell more efficient. Because viruses delivering a functional copy of the gene could be destroyed by the immune system (which cannot tell the difference between a gene therapy and potential infection) researchers will also work to minimize the chances that the gene therapy virus will be attacked by the immune system. This new technology will first be tested in cells from people with Duchenne muscular dystrophy which can be grown in the laboratory, and then in mouse models of Duchenne muscular dystrophy.

**How will the outcomes of the research benefit patients?**

The main outcome of the project will be the development of an improved gene therapy for Duchenne and Becker muscular dystrophies that will allow production of the full size protein. If this project is successful, further funding will be sought for more pre-clinical work which could lead to clinical trials. As well as benefiting people with Duchenne muscular dystrophy, this project will also be beneficial for people with Becker muscular dystrophy. Furthermore, the improvements in gene therapies could be relevant to other muscular dystrophies and neuromuscular conditions.

**What do the researchers say?**

“*This exciting and important award from MDC will allow us to design, produce and test an advanced gene therapy system for DMD to deliver full-sized fully-functional dystrophin to all the muscles and the heart. Some success is being seen with so-called micro-dystrophin gene therapies, but this new system represents a major advance in concept and design to treat DMD and BMD.*"
Grant information

Project leader: Professor George Dickson
Duration: Three years, starting 2013
Location: Royal Holloway (University of London)
Conditions: Duchenne muscular dystrophy; Becker muscular dystrophy
Total project cost: £ 180,306
Official title: Development of dual/triple transspliced AAV vectors to restore quasi/full length dystrophin variants to muscle.

For further information

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