This project is co-funded by Muscular Dystrophy UK and Duchenne Children’s Trust.

**Genome editing to repair duplications in Duchenne muscular dystrophy**

In this project Professor Francesco Muntoni and Dr Francesco Conti are aiming to develop a new gene therapy approach called genome editing to repair mutations in the dystrophin gene caused by duplication of a sequence of DNA. Approximately 10 to 15 percent of people with Duchenne muscular dystrophy have this type of mutation. If successful, this technique could permanently correct the underlying genetic cause of the condition, meaning the therapeutic agent should not need to be administered multiple times.

**What are the researchers aiming to do?**

Duchenne muscular dystrophy is caused by mutations in the dystrophin gene that contains the information to make the dystrophin protein. In approximately 10 to 15 percent of people with Duchenne muscular dystrophy, the condition is caused by the dystrophin gene containing a duplication; this means part of the gene is repeated. The repetition disrupts the message contained in the gene, resulting in no dystrophin protein being made. In the absence of dystrophin protein muscles get damaged at each contraction and waste away over time.

In this study, Professor Muntoni and Dr Conti will use a new gene therapy approach called genome editing (or genome surgery) to remove the repeated section of the gene and therefore restore its readability. Genome editing uses molecular scissors (enzymes called nucleases), to cut the DNA at a desired position. Professor Muntoni and Dr Conti have already designed molecular scissors to target the dystrophin gene where duplication mutations are more frequently found.

In this project the researchers will test these molecular scissors in stored cells from people with Duchenne muscular dystrophy where the underlying genetic cause is a duplication. To do this the scientists will first need to produce harmless viruses (lentivirus), to deliver the information for the molecular scissors to the cells, where they will be made. They will then assess how well the mutation is repaired by measuring the amount of full-length dystrophin protein being made by the cells.

If successful, there are two ways the technique could be applied. It could be used to correct the mutation in the dystrophin gene in muscle stem cells taken from people with Duchenne muscular dystrophy, which would then be transplanted back into the people. This type of cell transplantation has the advantage of not provoking an immune response as it will be using a boy’s own cells. Alternatively, it could be used to directly correct the mutation by
delivering the molecular scissors into a person’s muscle using harmless virus such as adeno-associated virus (AAV). A major advantage of these approaches is that they would not require repeated treatments as the person’s own DNA would be permanently corrected.

In the future, Professor Muntoni and Dr Conti plan to develop new molecular scissors that are targeted to other parts of the dystrophin gene where duplications are found less frequently. The long term aim is to develop molecular scissors for all duplications found in people with Duchenne muscular dystrophy. This will be done in collaboration with other scientists with expertise in this area.

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

This approach has the potential to be developed into treatments for Duchenne muscular dystrophy caused by duplication mutations. The technique could be used to correct the dystrophin gene in muscle stem cells taken from people with Duchenne muscular dystrophy, which could then be transplanted back into the people. Alternatively, the technique could be used to correct the DNA directly in a boy’s muscle. These approaches would have the advantage of not requiring multiple treatments, as the correction of the gene would be permanent.

In the long term, Professor Muntoni and Dr Conti are hoping to generate enough new molecular scissors to correct all duplications in the dystrophin gene which would make this approach suitable for all people with Duchenne muscular dystrophy caused by duplication mutations.

**Grant information**

Project leader: Professor Francesco Muntoni and Dr Francesco Conti  
Location: Institute of Child Health, University College London  
Conditions: Duchenne muscular dystrophy  
Duration: two years, starting 2015  
Total project cost: £118,426  
Official title: Repair of duplications in dystrophin using CRISPR nucleases

**For further information**

Read more about Duchenne muscular dystrophy  
Read more about research we are funding into Duchenne muscular dystrophy  
Read more about genome surgery techniques  
If you would like further details about this research project, please contact:  

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