Developing gene therapy treatments for spinal muscular atrophy

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Project background

Spinal muscular atrophy (SMA) is the most common childhood form of motor neuron disease (MND). The most prevalent form of SMA is very aggressive and children born with this condition usually die before the age of two. In contrast to amyotrophic lateral sclerosis, the common adult-onset form of MND, the genetic cause of SMA is well established: defects in the survival motor neuron 1 gene (SMN1) in SMA patients leads to progressive breakdown and loss of motor neurons as well as significant muscle wasting. Although the genetic cause of SMA is well known, no approved treatments for SMA are currently available.

Recent breakthrough research from the University of Edinburgh has identified a key pathway that is disrupted as a result of defects in the SMN1 gene, leading to a build-up of defective proteins that are detrimental to motor neurons and muscles. One particularly important protein involved in this pathway is called UBA1. Levels of UBA1 are dramatically decreased in SMA, and we have shown that this decrease is responsible for many of the major symptoms of SMA. Excitingly, pilot experiments in our lab have shown that increasing UBA1 levels using a technique known as ‘gene therapy’ may be potentially beneficial for SMA. Importantly, UBA1 gene therapy also appears to be safe and well-tolerated in the long term. We now need to undertake a detailed investigation of UBA1 gene therapy in SMA models to determine whether it is a novel therapeutic approach for treating SMA.

Aim

To develop UBA1 gene therapy as a treatment for SMA.

Details

We will use a type of gene therapy where recombinant adeno-associated (AAV) viruses are used to safely deliver UBA1 throughout the body in SMA models. Common challenges in gene-therapy studies are potential differences between different batches of produced virus and optimal delivery to ‘difficult’ regions of the body (including the brain and spinal cord). We therefore plan to test a range of different types of AAV viruses to establish which one gives us the quickest and best increase in UBA1 levels across a range of different sites in the body. The generation of these viruses on a large scale will minimise the risk of batch differences between experiments, which is a big problem for developing and testing gene therapy approaches. In our SMA models, we will then examine the impact of AAV-UBA1 gene therapy on the breakdown of motor neurons and muscle to establish suitable parameters that can subsequently be used to move forward towards clinical trials in human SMA patients.
Budget
The total £5,000 budget for this project will be allocated as following:

- purchase of AAV7- and AAV9-UBA1 expression constructs £1,250
- purchase of AAV7- and AAV9-GFP matched control expression construct £1,250
- purchase of large volumes (4-5ml) of high-titer virus supernatant for each of the above expression constructs £1,500
  **Subtotal:** £4,000
- purchase of small items of consumables/equipment to facilitate the delivery of gene therapy £1,000

**Total:** £5,000

Expected outcomes
Our early pilot data indicates that UBA1-targeted gene therapy is safe and potentially beneficial in a model of SMA. Receiving this EMC Ice Bucket Award will allow us to generate a large volume of highly concentrated UBA1 virus stock in order to optimise the efficiency of delivery and robustly assess therapeutic potential. Upon completion of this project we will have established whether UBA1-targeted gene therapy is an effective novel treatment approach for SMA, and established optimal parameters to move forward with further pre-clinical studies.