Identifying small molecules for Duchenne muscular dystrophy

In this project, Professor Dame Kay Davies and her team will continue their search for new compounds that can increase levels of a protein called utrophin. Urophin is similar to dystrophin and found in small amounts in adult muscle. Increasing its levels might compensate for the lack of dystrophin seen in people with Duchenne muscular dystrophy. Next generation molecules, which have improved drug-like qualities or act through a different mechanism compared to older compounds, are needed to ensure more effective treatments are developed. This approach has the benefit of being applicable to all people with Duchenne or Becker muscular dystrophy, whatever their mutation. This work is funded by the UtroDMD Alliance, of which Muscular Dystrophy UK is a member.

What are the researchers aiming to do?

Duchenne muscular dystrophy is caused by mutations in the dystrophin gene. This gene contains the instructions for making dystrophin protein which acts as a shock absorber to prevent damage when the muscle contracts. The lack of dystrophin in Duchenne muscular dystrophy means that muscle is damaged when it contracts and this leads to wasting of the muscle, with the muscle fibres gradually being replaced by fat and scar tissue.

One way to counteract the effects of dystrophin loss may be to increase the levels of a protein called utrophin in the muscles. Urophin is found in small amounts in adult muscle and is similar to dystrophin in structure and function. Evidence suggests that increasing the levels of utrophin protein is safe and can compensate for lack of dystrophin protein in a mouse model of Duchenne muscular dystrophy, the mdx mouse. The approach is expected to be disease-altering in people with the condition.

Work from Professor Davies and her group has led to the identification of a compound called SMT C1100 that can increase utrophin levels in cells grown in culture and in a mouse model of Duchenne muscular dystrophy. It is now being tested in Phase Ib clinical trials to check its safety, investigate how it moves through the body and see how readily available it is in the bloodstream. Initial results show that it is well tolerated.
However, follow-on compounds are needed to ensure the development of more effective potential therapies. These new molecules will have features that make them better potential drugs than SMT C1100, such as an increased ability to raise utrophin levels, and improved absorption and distribution profiles which make them more readily available in the body. Professor Davies and her team recently published results about one such promising compound, SMT022357, showing the benefits of developing these second- and future-generation compounds.

In this project Professor Davies and her team will continue to evaluate promising new compounds for their ability to increase utrophin levels. They will test compounds similar to SMT C1100, which were also developed by the same pharmaceutical company, Summit Therapeutics, for their ability to increase utrophin protein levels in cells grown in the laboratory. They will use a sensitive cell-based drug screen that was designed specifically for this purpose with funding from Muscular Dystrophy UK.

Additionally, the team will use the cell-based screen to identify other compounds that are unrelated to the SMT C1100 family of molecules, but which can also up-regulate utrophin. These molecules will also be chemically altered to maximise their ability to raise utrophin levels.

All these compounds will then be tested in a mouse model of Duchenne muscular dystrophy, the mdx mouse, and successful candidates will be developed for clinical trials. This work will be done in collaboration with Summit Therapeutics so that potential new drug(s) can be moved into clinical trials as soon as possible.

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

The identification of small molecules that can boost levels of utrophin protein is the main outcome of this project. These molecules will be next-generation, meaning they will be more effective than the existing lead compound, SMT C1100 at increasing utrophin levels and preventing the muscle damage seen in Duchenne muscular dystrophy. The compounds will be developed for clinical trials. As the approach is not dependent on the mutation in the dystrophin gene, the small molecules could potentially be of benefit to all people with Duchenne muscular dystrophy or Becker muscular dystrophy.

Professor Kay Davies said: “We are delighted that MDUK have awarded us funding so that they can continue to be active members of the UtroDMD Alliance for the development of a therapy applicable to all DMD patients irrespective of their mutation. We are at a very exciting stage with preclinical data showing the proof principle of utrophin modulation and this funding will greatly facilitate our progress.”

**About the UtroDMD Alliance**

The UtroDMD Alliance is a multi-year strategic collaboration that combines the extensive biology, chemistry and drug development expertise of the University of
Oxford, Summit Therapeutics, supported by the Medical Research Council, Muscular Dystrophy USA and Muscular Dystrophy UK, with the sole aim to accelerate the development of first, second and subsequent generation utrophin modulator therapies for all Duchenne muscular dystrophy patients.

**Grant information**

Project leader: Professor Kay Davies  
Location: University of Oxford  
Duration: three years, starting 2015  
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**For further information**

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