Daily pill for Duchenne muscular dystrophy

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A new drug for the muscle-wasting disease Duchenne muscular dystrophy has shown significant benefits in mice, opening the door for clinical trials.

The promising results indicate that a simple, daily pill to treat all patients with Duchenne muscular dystrophy should be possible, whether or not this specific drug formulation makes it all the way through clinical trials without further development.

The study, led by researchers at Oxford University, the University of Bari in Italy and Summit plc with funding from the Muscular Dystrophy Campaign and the Medical Research Council, is published in the journal PLoS ONE.

‘We’ve shown that the drug can dramatically reduce muscle weakness in mice.

These results give us everything we need to go forward into initial clinical trials in humans,’ says Professor Dame Kay Davies of the Department of Physiology, Anatomy and Genetics at Oxford University, who led the research.

Duchenne muscular dystrophy affects about 100 boys born in the UK each year, or around 1 in every 3,500 male births.

The disease involves a progressive muscle weakness, with the first signs of difficulty in walking seen between the ages of 1 and 3. Boys with the condition are likely to be in a wheelchair by age 12 and live into their twenties or thirties.

The condition is caused by problems in a gene on the X chromosome for a protein called dystrophin that’s found in muscle fibres.

The result is that muscle cells break down and the muscle fibres themselves are gradually lost.

There are no effective treatments for the disease.

Steroids and growth hormones are used to manage the condition.

Novel genetics-based approaches to correct readout of the dystrophin gene are in clinical trials. But depending on each patient’s particular genetic changes, any one treatment is only likely to be effective for perhaps 15% of patients.

The current study reports a significant step in the search for a simple, conventional oral pill to be taken daily that would be effective for all patients.

Rather than concentrate on the problems in dystrophin, this alternative approach focuses on a related protein called utrophin.

Previous work by Professor Kay Davies’ group in Oxford showed that increasing the amount of utrophin in muscle cells could help compensate for the lack of a functioning dystrophin protein in a proof-of-principle study in mice.

The Oxford team then developed a lab test that could detect increased production of utrophin in human muscle cells.

This allowed a UK-based biotechnology company, Summit plc, to use the test to screen a huge number of drug compounds for any that could increase levels of utrophin.

They have now identified the most promising of these compounds, currently named SMT C1100.

The new publication reports the work of three independent groups – in Oxford, Italy and the US – to determine the effectiveness of the drug in mouse models of Duchenne muscular dystrophy.

The three groups all found that daily doses of the drug had a protective effect against the progressive muscle weakness that is characteristic of the disease.

The mouse models for the disease receiving the drug could run 50% further in exercise tasks similar to the six-minute-walk test used as a standard measure in human patients.

In combination with a steroid, the mice showed no fatigue in these tests at all.

‘These are the most stringent tests we have and mean that there is more chance of achieving the same benefits in humans,’ says Professor Davies.

These results have seen the drug SMT C1100 move into early-stage clinical trials in humans.

Preliminary results from a phase I trial among a small number of healthy volunteers suggest that the drug in its current formulation is not consistently present at high enough levels in the blood.

However, most drug candidates need reformulating and optimising after initial discovery, and the intention is to pursue this with SMT C1100.

‘The results are sufficiently exciting to do further human trials with improved formulations of SMT C1100 and to look for follow-on compounds that could prove superior in the long term,’ says Professor Davies.

Dr Marita Pohlschmidt, Director of Research at the Muscular Dystrophy Campaign, says: ‘The Muscular Dystrophy Campaign has supported this line of research in Professor Davies’ lab from the start and it is fantastic that it is now coming to fruition. Many of the treatments currently being developed are very personalised and can only be used for a subset of patients.

However, this approach of raising the activity of the utrophin gene could potentially be of significant benefit to all individuals with Duchenne and Becker muscular dystrophy.

This would be a huge advantage and we look forward to hearing how well an improved formulation of the SMT C1100 drug does in the next clinical trial.’

Professor Max Parmar, Director of the Medical Research Council's Clinical Trials Unit, says: ‘This is a great example of Medical Research Council support for basic research, which could soon lead to a real public health benefit.

This study, without necessarily providing us with the final solution, does give us an important platform from which to move forward and really make a serious progression through clinical trials. This is a vital part of the drug discovery process.

**Notes for editors**

* The paper ‘Daily treatment with SMTC1100, a novel small molecule utrophin upregulator, dramatically reduces the dystrophic symptoms in the mdx mouse’ is to be published in the journal PLoS ONE.
* The research was funded by the Medical Research Council, Muscular Dystrophy Campaign, Muscular Dystrophy Association USA, the Association Francaise contre les Myopathies and Telethon-Italy.
* **The Muscular Dystrophy Campaign** is the leading UK charity focusing on muscle-wasting disease. It has pioneered the search for treatments and cures for more than 50 years, and is dedicated to improving the lives of all children and adults affected by muscle disease.  
  We fund world-class research to find effective treatments and cures; provide practical information, advice and emotional support for individuals, their families and carers; campaign to raise awareness and bring about change; award grants towards the cost of specialist equipment; and provide specialist education and development for health professionals.
* For almost 100 years the **Medical Research Council** has improved the health of people in the UK and around the world by supporting the highest quality science. The MRC invests in world-class scientists. It has produced 29 Nobel Prize winners and sustains a flourishing environment for internationally recognised research. The MRC focuses on making an impact and provides the financial muscle and scientific expertise behind medical breakthroughs, including one of the first antibiotics penicillin, the structure of DNA and the lethal link between smoking and cancer. Today MRC funded scientists tackle research into the major health challenges of the 21st century. [www.mrc.ac.uk](http://www.mrc.ac.uk)
* **Oxford University’s Medical Sciences Division** is recognized internationally for its outstanding research and teaching, attracting the brightest minds from all over the world  
    
  It is one of the largest biomedical research centres in Europe, with over 2,500 people involved in research and more than 2,800 students, and brings in around two-thirds of Oxford University’s external research income. Listed by itself, that would make it the fifth largest university in the UK in terms of research grants and contracts.  
    
  Oxford is home to the UK’s top-ranked medical school, and partnerships with the local NHS Trusts enable patients to benefit from the close links between medical research and healthcare delivery.  
    
  14 winners of the Nobel Prize for Physiology or Medicine worked or were educated at Oxford, and the division is home to 29 Fellows of the Royal Society and 68 Fellows of the Academy of Medical Sciences.  
    
  Past successes include the development of penicillin, which ushered in the modern age of antibiotics, and the confirmation of the link between smoking and cancer, which has prevented many millions of deaths. Oxford continues to be at the forefront of medical research, whether it’s the genetic and molecular basis of disease, the latest advances in neuroscience, or clinical studies in cancer, diabetes, heart disease and stroke. Oxford has one of the largest clinical trial portfolios in the UK and great expertise in taking discoveries from the lab into the clinic.  
    
  A major strength of Oxford medicine is its long-standing network of clinical research units in Asia and Africa, enabling world-leading research on the most pressing global health challenges such as malaria, TB, HIV/AIDS and flu. Oxford is also renowned for its large-scale studies into the causes and treatment of cancer, heart disease, diabetes and other common conditions.
* **Summit plc** is an Oxford, UK based drug discovery company with a portfolio of drug programme assets and an innovative technology platform called Seglins for the discovery of new medicines.  
    
  Summit’s programme portfolio consists of a number of drug programmes targeting high-value areas of unmet medical need including Duchenne Muscular Dystrophy and C. difficile infection. Seglin™ technology is using new chemistry to access biological drug targets that cannot be exploited by conventional drug discovery approaches and Summit’s internal research is currently focussed in high-value therapy areas.  
    
  Summit is listed on the AIM market of the London Stock Exchange and trades under the ticker symbol SUMM.  Further information is available at [www.summitplc.com](http://www.summitplc.com).