

# Finding strength

## Reinforced hope for DMD boys



**Urs T. Ruegg, PhD, Professor of Pharmacology at the University of Geneva, will conduct a trial this winter in Berlin with 150 patients on the effects of antioxidant polyphenols in green tea extracts to relieve oxidative stress that contributes to muscle tissue degradation in DMD**

One in 3,500 boys from infancy have difficulty sitting, walking and talking, and tire easily. Their leg muscles become so weak that often by age 12 they must use wheelchairs. Heart and respiratory conditions develop in their teen years, usually killing these young men by their 20s or early 30s.

Named for the pioneering 19<sup>th</sup> century French neurologist Guillaume Benjamin Amand Duchenne who discovered the disease, these boys suffer from Duchenne muscular dystrophy (DMD), the most common form of childhood muscular dystrophy. Presently incurable, women carriers transmit it to half of their newborn sons on average.

DMD is caused by mutations in the dystrophin gene preventing the assembly of dystrophin protein. Without dystrophin, excessive calcium enters muscle fibres killing cells and causing muscle wasting. One molecule of dystrophin protein is only 0.000125 mm long, but missing this protein has devastating repercussions throughout the entire body.

### Light at the end of the tunnel

Currently, steroids are the only drug treatment proven to maintain muscles for a limited time. A recent outpouring of research promises much, though. Dutch Prosensa Therapeutics BV and American AVI BioPharma, companies that specialize in RNA-based therapeutics, have developed a new treatment called exon skipping. Prosensa's PRO051 and AVI's AVI4658 remove an unwanted faulty section of gene product allowing a form of dystrophin to be created. The latest clinical trial results are not yet available, but due to positive results in animal trials both companies are confident that their "smart drugs" cause systemic dystrophin expression.

PTC Therapeutics has developed a similar drug, Ataluren, that enables the synthesis of functioning dystrophin in patients. Ataluren resolves the problem that develops from one type of mutation in the gene code, a nonsense mutation. A Phase 2b >>>>



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clinical trial to test improved muscle function and strength is running with 165 patients in 37 centres around the world (3 children from Switzerland are participating thanks to the Swiss Registry). Excitingly, Ataluren has the potential to treat any genetic disorder caused by nonsense mutations. The despair that existed even five years ago in the DMD community has turned to hope.

**The push against odds**

Despite the present optimism, much still needs to be done to translate

research into commercial products and improve Duchenne boys’ lives. Although symptoms are similar, many different types of mutations to the dystrophin gene cause DMD. Ataluren only targets one type of mutation. The exon skipping drugs correct the most prevalent mutation, but this still only affects 5–10% of the DMD population. Clearly, each drug will have to be specialized and, thus, extremely expensive. Treatments correcting more complex mutations need further research. The rarity of the disease and expense of drugs reduces interest and

support from the public and large pharmaceutical companies. To counteract this, the focus needs to remain on the science, on the hard work of individuals and groups.

Switzerland has great talent and resources to capitalize on in the fight against DMD. One of the few pharmaceuticals companies to invest in rare diseases, Santhera Pharmaceuticals, a Swiss specialty company focusing on small molecule products for orphan neuromuscular diseases, has headquarters in Liestal. Clinical trials to test whether their product, Cantena,

improves or slows decline in cardiac function are successfully underway.

Innovative researchers are also based in Switzerland, such as Urs Ruegg, PhD, head of the Laboratory of Pharmacology, Universities of Geneva and Lausanne. In tests with mice, he has successfully shown how antioxidant polyphenols in green tea extracts relieve oxidative stress that contributes to muscle tissue degradation in DMD. This winter he will begin a trial with 150 patients at Berlin Hospital, which has better access to a higher number of patients than facilities in Switzerland.

Dr Pierre-Yves Jeannet at the Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne hopes to make it easier for researchers to locate Swiss patients with specific clinical criteria. In January 2008 he started the Swiss registry for DMD and spinal muscular atrophy (SMA). The registry concludes that about 200 paediatric DMD and SMA children reside in Switzerland. This small number makes it hard for clinical trials to be held in Switzerland but the diagnostically complete registry is still very beneficial because it improves the chances Swiss boys have of being included in other countries' trials. To date, two boys have participated in trials in France and one boy in Italy.

#### Collaboration for a cure

The Swiss registry contributes to the global registry created by Treat-NMD, a pre-eminent European network bringing together patients, scientists, healthcare professionals and the pharmaceutical industry to advance research and treatment. The global registry standardized DMD registration, beautifully illustrating the type of collaboration necessary to effectively turn possibility into reality.

The World Muscle Society to be held this September in Geneva, with Urs Ruegg leading the Organizing Committee, also promotes creating the type of dense network that will most benefit patients.

Within Switzerland, Progena Foundation, a Swiss research promotion organization and support group that co-



**As the initiator and investigator in charge of the Swiss registry, Dr Pierre-Yves Jeannet of the Paediatric Neuromuscular Centre at CHUV in Lausanne is making it easier for researchers to locate Swiss patients with specific clinical data**

sponsors the Swiss registry and the green tea polyphenols trial in Berlin, attempts to create a more cohesive Swiss network. With several sophisticated hospitals and research centres actively involved in DMD and three official languages, Switzerland can be fragmented in its front against DMD. For a small country with few patients, more progress can come with unity.

Robert Palm, the co-founder of Progena, says he is "excited but frustrated". With promising new therapies and the growth of the registry, long-term treatment is tantalizingly

close. But it can be exasperating to be so close and yet still need more research, work and funding.

Now is the time for a big push. The innovation and commitment from individuals and organizations are as crucial to a cure as the drugs themselves. <<<<<

For more information on DMD research, clinical trials and organizations visit [www.treat-nmd.eu](http://www.treat-nmd.eu), e-mail [info@treat-nmd.eu](mailto:info@treat-nmd.eu) or call +44-(0)191 241 8605. For information about the Progena Foundation, visit [www.progena.ch](http://www.progena.ch).