

## **MDA Scientists Find Two Chemicals That May Slow Wasting in Muscular Dystrophy**

VANCOUVER, Canada, July 12, 2002 – Scientists funded by MDA have identified two chemicals that, when systemically given to mice with Duchenne muscular dystrophy, can partially compensate for the genetic defect underlying the disease.

These are the first "hits" in a long search for chemicals able to stimulate the production of a muscle protein called utrophin, which is a close cousin to dystrophin — the protein missing in Duchenne MD. Two groups presented the findings Thursday at the 10th International Congress on Neuromuscular Diseases in Vancouver, partly sponsored by MDA.

One group, led by Sabine de la Porte of the Centre National de la Recherche Scientifique in Gif-sur-Yvette, France, found that the small compound L-arginine can increase utrophin levels in mice with Duchenne MD. Another group, led by Tejvir Khurana at the University of Pennsylvania in Philadelphia, found that a small protein called heregulin has a similar effect.

When injected into the abdominal cavities of mice with Duchenne MD, each chemical partly protects against the muscle wasting associated with the disease.

DMD is caused by mutations in the X chromosome gene encoding dystrophin, and almost exclusively affects boys. It causes progressive muscle wasting beginning in early childhood, and typically leads to death from respiratory failure in the 20s.

"This is a very gratifying advance, one we've been striving toward," MDA Research Development Director Sharon Hesterlee said. "Further research into the effects of these chemicals could prove one of the most promising avenues yet for treating children with Duchenne muscular dystrophy."

Since its discovery in 1989, scientists have considered utrophin a prime target for treating Duchenne MD. While some scientists hope to treat Duchenne MD by using gene or cell therapy to correct the absence of dystrophin, others believe that boosting the small amounts of utrophin already present is less likely to provoke adverse reactions from the immune system.

De la Porte decided to investigate the effects of L-arginine because it's a source of "fuel" for nitric oxide synthase (NOS), a protein that generates the small signaling compound nitric oxide. NOS is closely linked to utrophin at the muscle membrane, so de la Porte suspected that increasing NOS activity might have a comparable effect on utrophin levels.

After several months of L-arginine, given once daily for five days a week, the limb and respiratory (breathing) muscles of mice showed fewer signs of degeneration, and their respiratory muscles showed improved strength, compared to those of untreated mice.

Treated mice also had lower blood levels of creatine kinase (CK), a protein that leaks out of damaged muscle cells.

Through years spent studying the gene that encodes utrophin, Khurana and his group learned the gene could be "turned on" by heregulin, a type of protein that nerves release to stimulate muscle development. The limb muscles of Duchenne mice that were given twice-weekly heregulin injections over a three-month period showed less degeneration and improved resistance to contraction-induced damage compared to those of untreated mice.

The two groups presented their results with cautious optimism. De la Porte acknowledged that, because nitric oxide controls many processes in the body, including blood vessel dilation and cell metabolism, it becomes toxic with increasing dosage. The potential toxicity of heregulin at high doses hasn't yet been addressed.

Kay Davies of the University of Oxford in Great Britain, who discovered utrophin with support from MDA and first conceived the idea of utrophin "upregulation," said her studies suggest it may take a 10-fold increase of utrophin to protect muscles completely against Duchenne MD. In de la Porte's work, L-arginine increased utrophin levels by about two-and-a-half-fold, and in Khurana's work, heregulin had a nearly threefold effect.