Effects of IGF-I and IL-15 gene transfer on the structure and function of skeletal muscles of *mdx* dystrophic mice

J.D. Schertzer and G.S. Lynch, Basic and Clinical Myology Laboratory, Department of Physiology, The University of Melbourne, VIC 3010, Australia.

Until corrective genetic strategies overcome several major obstacles, other ways to ameliorate the pathophysiology of muscular dystrophies are required. We used an electroporation-assisted plasmid based gene transfer protocol in tibialis anterior (TA) muscles of *mdx* dystrophic mice to test the efficacy of over-expressing two proteins that have shown potential for improving the dystrophic pathology. We hypothesized that administration of insulin-like growth factor-I (IGF-I) and Interleukin-15 (IL-15) to muscles of *mdx* mice would have synergistic effects by simultaneously promoting muscle fibre growth and reducing fibrosis, thereby improving dystrophic muscle function. Mice were anaesthetised with pentobarbital sodium (60 mg/kg, i.p) and the right TA muscle surgically exposed and injected with the appropriate plasmid DNA (or their combination) using a 29 gauge needle, and electroporated (75-100 V/cm). After 4 weeks, the animals were anaesthetised (pentobarbital sodium, 60 mg/kg, i.p.) and muscle function determined *in situ*. Anaesthetised mice were killed by cardiac excision. Non-viral gene transfer of IGF-I caused skeletal muscle fibre hypertrophy in *mdx* mice, but did not improve the functional properties of TA muscles. IL-15 delivery had minimal effects on muscle structure or function in *mdx* mice and did not enhance (or negate) the effects of IGF-I when co-administered. Functional characteristics are critical end-points for assessing the potential of such therapies in dystrophic muscle and our findings highlight the limitations of delivering IGF-I post-natally *via* plasmid-based gene transfer for improving the dystrophic phenotype and show that IL-15 and IGF-I do not act synergistically in dystrophic skeletal muscle *in vivo* when delivered this way.

Supported by the Muscular Dystrophy Association (USA).