Using gene transfer technology to study muscle diseases

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Many of the world's most serious medical conditions are caused or exacerbated by the loss of striated muscle function, or resultant metabolic disturbance (Booth & Lees, 2007). The prevention and treatment of muscle-related illness could significantly improve human health, but requires a more complete understanding of the mechanisms that govern muscle adaptation in health and disease. To this end, the advent of gene delivery technology is poised to revolutionize the study of muscle, and accelerate the development of innovative therapeutic interventions for muscle-related disease (Gregorevic *et al*., 2004a). As an example, recombinant viral vectors derived from non-pathogenic adeno-associated viruses (rAAV vectors) offer a means of readily delivering "gene expression cassettes" and transcription-regulating elements to mammalian striated muscle, to achieve sustained, highly-specific transgene expression (Blankinship *et al.*, 2004). For research, these vectors offer the opportunity to dissect the intracellular mechanisms underlying the phenotypic adaptation of muscle *in vivo* with a level of precision and speed otherwise unachievable. Local intramuscular administration of vectors can elicit robust gene expression within days of treatment, and the ensuing gene expression can be maintained for years without further interventions if desired. Furthermore, modes of vector administration can be utilized to transduce musculature body-wide (especially in murine models) *via* intravascular administration (Gregorevic *et al.*, 2004b).

As a prospective medicine, vector-mediated gene modulation heralds the means with which to correctively restore the expression of defective genes, or drive compensatory expression of other genes for therapeutic gain. Various modes of rAAV-mediated gene delivery have already established proof of "therapeutic concept" in models of disease (Gregorevic *et al*. 2004b, 2006) and in some instances have commenced transition to clinical trials. As an example of muscle-focused gene therapy showing promise for therapeutic application, administration of rAAV6 vectors carrying an engineered dystrophin-based construct can restore organisation of sarcolemmal protein structures throughout the muscles of mice that model a severe form of muscular dystrophy, to achieve whole body amelioration of pathology, increasing muscle function and resulting in extended lifespan (Gregorevic *et al.*, 2004b, 2006). Work is underway to evaluate the feasibility of developing this approach for clinical application. These findings and related work demonstrate that the combination of gene delivery technology with established and developing analytic and therapeutic methods holds truly exciting prospects for a new era in muscle research and medicine.

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