

## *Non-Technical*

Patients in this trial will have proven sarcoglycan deficient limb girdle muscular dystrophy (LGMD). The primary objective of this trial is to determine a safe dose using gene transfer to deliver a normal gene product to a small muscle in the foot, the extensor digitorum brevis. Four types of LGMD will be targeted for this study ( $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\Delta$  sarcoglycan deficient LGMD).

In pre-study tests patients will be asked to provide blood for DNA testing and a muscle biopsy for analyses with specific antibodies, to determine if they have a sarcoglycan deficiency, and to determine which corresponding gene is required for the study ( $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\Delta$ ). Once a specific sarcoglycan deficiency ( $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\Delta$ ) has been clearly identified, the patient will be enrolled in the protocol for treatment with a viral vector that contains the specific sarcoglycan gene. The virus to be used for delivery of the gene is an adeno-associated virus (AAV), which apparently does not result in any known disease in humans.

The study will involve delivery of a recombinant AAV vector carrying one of the human sarcoglycan genes ( $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\Delta$ ) by doing needle injection of the extensor digitorum brevis muscle. One foot muscle of the patient will receive the AAV-sarcoglycan vector and the other will receive only a salt solution (saline) as a negative control. A designated staff member at our institute will know the code for the vector or saline, but this would be unknown to the clinical team injecting these samples in the different foot muscles. If successful gene transfer can be achieved in the absence of toxicity, this preliminary study would be critical to further studies for gene therapy in LGMD.

Measures of safety and toxicity will be assessed throughout the study. Specifically, 43 days post gene therapy a biopsy of the extensor digitorum brevis muscles will be taken and analyzed. This is a non-essential muscle in the foot, and only a portion of the muscle would be removed for analysis of gene transfer. This will be a dose escalation study consisting of two groups of patients. A minimum of three patients will be enrolled into each group. Safety and toxicity will be assessed for each patient within each group.