

Editorial

The Tale of Two Trials

THIS ISSUE OF THE JOURNAL describes the results of two Phase I clinical trials in which gene transfer was evaluated in two very different diseases. The study by Flotte and co-workers, uses a classic gene replacement strategy with adeno-associated viral vectors to transfer a normal alpha-1-antitrypsin gene into subjects deficient in this enzyme. Melman *et al.* use direct injection of plasmid DNA expressing the alpha subunit of human smooth muscle Maxi K channel, hSlo, into penile tissue of subjects with erectile dysfunction (ED).

I found the juxtaposition of these studies illustrative of how the field has evolved from the notion of gene replacement for the treatment of autosomal recessive diseases to augmentation of function for acquired diseases of complex etiologies. The opportunities for therapeutic uses of gene transfer will only grow as we learn more about disease pathogenesis. The rationale for gene replacement of hSlo for treatment of ED was based on many years of basic research from these investigators studying the role of K channels in erectile function. They proposed that overexpression of one of these channels in cells of the corpus callosum would decrease the threshold for erection in individuals with ED.

It is important to note that these were phase I dose escalation studies in which the goal is to assess safety that will be relevant to the design of subsequent efficacy studies. Both clinical trials, however, did incorporate secondary endpoints to determine if gene transfer had occurred and whether it was capable of eliciting biological responses that may be therapeutic. The way in which this was addressed was another point of divergence in the two trials. One of the real advantages of a disease such as alpha-1-antitrypsin deficiency is that measurement of the recombinant protein in blood is a non-invasive and direct indicator of gene engraftment allowing unambiguous and quantitative evaluation of expression over time. In fact, the authors show some evidence of transgene derived protein in the blood that was not the result of antecedent protein replacement therapy. The levels and duration of expression were insufficient to be therapeutic. Assessment of hSlo gene transfer and expression in the ED trial was much more challenging. The investigators used the indirect but clinically relevant measure of erectile function as an indication that the gene was expressed. This assessment is based on a questionnaire administered to the subject prior to and after gene transfer; answers were validated by independent input by the subject's sexual partner. They in fact showed evidence of clinically meaningful improvements in ED in two of the subjects in the higher dose groups. As noted by the authors of this paper, these kinds of data could be heavily influenced by placebo effects. Until a controlled study that has been powered to address efficacy in a statistically significant way has been completed, one needs to be very cautious about speculation regarding the potential of this approach for treating ED.

The evolution of gene therapy from its early roots which focused on lethal and disabling genetic diseases to the current state in which it is being evaluated for a variety of less severe ailments may not be viewed as positive by some. Dr. Arthur Caplan, Chair of the Department of Medical Ethics at the University of Pennsylvania, has written a commentary in this issue of the Journal on the appropriateness of gene transfer in the treatment of diseases such as ED.

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