Good News on the Clinical Gene Transfer Front

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TWO ENCOURAGING REPORTS of the safety and potential efficacy of gene transfer in a congenital form of blindness called Leber’s congenital amaurosis (LCA) were presented on April 27 and 28, 2008 at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) and published in the May 22, 2008 issue of the *New England Journal of Medicine* (Maguire et al., 2008 [see http://content.nejm.org/cgi/reprint/NEJMoa0802315.pdf; accessed May 2008]; Bainbridge et al., 2008 [see http://content.nejm.org/cgi/reprint/NEJMoa0802268.pdf; accessed May 2008]). Crystal and colleagues report in this issue of *Human Gene Therapy* results of their phase 1 study of adeno-associated virus (AAV) gene transfer into the central nervous system of subjects with a lysosomal storage disease called late infantile neuronal ceroid lipofuscinosis (LINCL); assessment of efficacy in this model is more challenging than in the LCA studies, although the investigators report encouraging trends (Worgall et al., 2008).

Groundwork for the LCA clinical trials was provided by multiple investigators over many years of preclinical studies. The primary advantage in studying this disease is that successful gene correction should reconstitute function almost immediately, which is in contrast to most other forms of inherited retinopathies, such as retinitis pigmentosa, which require treatment of a large number of research subjects over an extended period of time to demonstrate slowing of the underlying degenerative pathology. The defect in this form of LCA is in the enzyme RPE65, which is expressed in the retinal pigmented epithelium (RPE) and is responsible for the production of rhodopsin, which is required for photoreceptor function and sight. Studies in preclinical models showed immediate restoration of visual function on correction of the genetic defect in the RPE that has been stable in dogs for at least 8 years. Both groups initiated their studies in adults for ethical and practical reasons, even though it was thought that the potential for functional restoration in this group may be limited because the absence of photoreceptor transduction from birth leads to eventual and irreversible retinal degeneration and possibly incomplete innervation of the visual cortex. Three subjects from each trial received vector, which was found to be safe, with some evidence of modest improvement in visual function in three of three subjects in the U.S. trial and in one-third of subjects in the U.K. trial. Both groups appropriately note that the studies are short term and that visual function is not completely restored, although the results are sufficiently encouraging to consider moving to younger subjects, in whom the potential for more substantial reconstitution of visual function may be possible.

The study of gene transfer to the CNS for treatment of LINCL is more challenging because it presents with global CNS pathology requiring wide distribution of gene correction. Furthermore, demonstration of efficacy would require slowing of the degenerative process, which can be variable although always fatal. Studies in a murine model of LINCL demonstrated biochemical and pathological evidence of efficacy. Ten children with relatively advanced disease were dosed with vector directly into multiple sites within the CNS; toxicity was observed, although the severity of underlying disease made it difficult to definitively attribute these findings to the vector. The treated group did indeed show a slower decline in magnetic resonance imaging findings and neurologic function as compared with untreated individuals. The investigators note that the study was not powered or designed to prove efficacy, although the encouraging trends do provide support for moving forward with better vectors and delivery systems. An important challenge in progressing to efficacy studies of rare diseases such as LINCL is the limited number of available subjects. Surrogate measures of efficacy and novel clinical trial designs may be helpful in these situations.

The preliminary clinical studies summarized above represent only the tip of the iceberg as to what we should see in the coming years. Substantial progress has been made in the development of improved vectors. Almost two decades of experience in the translation of gene therapy (i.e., bench to bedside and back) has yielded critical insights that better inform current and future treatment strategies. The editorial leadership of *Human Gene Therapy* expects the number of clinical trials submitted for publication to escalate, and that these studies will come from investigators around the world. In preparation for this, we have commissioned several commentaries on the conduct of clinical trials. Dr. Gregg Fromell, Executive Director of the Office of Human Research at the University of Pennsylvania (Philadel-
phia, PA), has summarized the concept of Good Clinical Practice (GCP) for work performed in the United States (Fromell, 2008). Dr. Klaus Cichutek, from the Paul-Ehrlich-Institut in Langen, Germany, and colleagues amplify on Dr. Fromell’s commentary by providing a perspective on GCP in the European Union (Barth et al., 2008). We refer the reader to a previous review by Hongzhang Yin of the Chinese State Food and Drug Administration (SFDA, Beijing, China) regarding regulatory oversight of gene therapy in China (Yin, 2006; see http://www.liebertonline.com/doi/pdfplus/10.1089/hum.2006.17.970; accessed May 2008).

We offer the commentaries by Drs. Fromell and Cichutek and colleagues as guidelines to follow for investigators undertaking clinical trials that they may consider publishing in *Human Gene Therapy*. As pointed out in both papers, the basic principles of GCP have been accepted by relevant constituents in the European Union, Japan, and the United States and these principles are harmonized by a document called the “International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use—ICH Topic E6” (see http://www.who.int/druginformation/vol14num3_2000/volume14-3.pdf; accessed May 2008).

To ensure that all clinical trials published in *Human Gene Therapy* meet acceptable international standards of conduct we require that the authors provide written assurance in the Materials and Methods section of the manuscript that the study was “…conducted in a manner consistent with the ICH—E6 Good Clinical Practice guideline document.” We look forward to continued good news as the field of gene therapy escalates its activities in clinical trials.

REFERENCES


