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Gene therapy: cautious optimism

The recent gathering in Denver of gene therapists from around the world for the third annual meeting of the American Society for Gene Therapy (ASGT) 31 May–4 June provided a forum to reflect on the tumultuous events of the past year and the considerable challenges that lie ahead. Symbolizing the mood of reflection was a poignant moment of silence to pay respect to Jesse Gelsinger, whose recent death during a clinical trial of adenovirus-mediated therapy cast intense public scrutiny on the behavior of workers engaged in clinical trials of gene medicine. In a mere 10 years, the field of gene therapy has moved from a small coterie of academics with a then-futuristic vision of directly correcting genetic defects into an industry that may very soon treat and even cure major human diseases such as cancer, hemophilia and cystic fibrosis. This transition has been accompanied by much hype and inflated expectations—and what some have perceived as a premature rush to the clinic. In Denver, gene therapists made it clear that they have gotten the message; they realize that they must act more cautiously and that their success hinges on winning a skeptical public's acceptance of this still-nascent technology.

Acceptance will only come with education. In his address, outgoing ASGT president Savio Woo stressed that "...a better-informed public will certainly be [more] able to appreciate the benefits and risks in gene therapy." Accordingly, this year's meeting included an outreach program to educate college and high school teachers on the basic principles and potential applications of gene therapy. Moreover, Woo believes that the society must take a more proactive role in working with the membership to develop methods to provide better information for both patients and the public. We applaud these measures and urge incoming president Inder Verma to redouble these efforts to cultivate a role for the ASGT as educator and collective 'conscience' of the community.

Of course, the news this past year certainly has not been all bad, as evidenced by the positive preclinical and clinical results presented at the meeting. These include the first successful application of gene transfer to treat a life-threatening disease in humans. French scientists, let by Alain Fischer, replaced a defective gene in the lymphocytes of two children with severe combined immunodeficiency, a rare and lethal immune disorder. Mark Kay and Katherine High presented exciting results of a phase I clinical trial using adeno-associated virus (AAV) to transfer factor IX into humans suffering from hemophilia B. Clinical effects were seen even when low doses of the vector were delivered. Also encouraging were the stage II clinical trials of an adenovirus vector (Onyx-015) that had been engineered to kill tumor cells while leaving normal cells unscathed. Combining intratumoral injection of the virus with traditional chemotherapy had a substantial effect on the growth of otherwise untreatable head and neck cancer (*Nature Medicine*, in the press). Although the mechanism of cell killing by this selectively-replicating adenovirus is not fully clear, Frank McCormick, one of its developers, points out that the precise mechanism of action of many traditional cancer therapies remains unknown, and he and many gene therapists argue that these concerns should not prevent public access to these new treatments.

The key to successful gene therapy is the development of vectors that can deliver therapeutic genes both safely and efficiently to the correct tissues. Although no dramatic advances in vector development were forthcoming, part of the excitement of the Denver meeting derived from the important incremental progress across the board in the various cutting-edge viral vector systems for genetic disease, such as AAV and lentiviruses. The latter include HIV-based vectors prized for their ability to replicate in non-dividing cells. Advances in non-viral delivery were also demonstrated, such as those leading to blood vessel development for cardiovascular disease.

Have these new systems rendered adenovirus obsolete as a gene therapy tool? Although inappropriate for long-term therapy of genetic disorders, adenovirus has found a niche in the treatment of certain forms of cancer, as the Onyx results illustrate. Despite the continuing debate regarding the safety of this vector, the ASGT has no intention of playing 'Big Brother' to the society's membership and will not set the rules regarding which vector should be used for a specific application. Nevertheless, the ASGT should take the lead in urging caution in any further proposals for human clinical trials using adenovirus. The tragedy of the 'Gelsinger affair' laid bare the need for more basic research into the body's immune response to all viral vectors, and the ASGT should work with federal funding agencies to encourage additional studies in this area.

In the end, although most arrived bemoaning the increased monitoring requirements for clinical trials, everyone was talking enthusiastically about the exciting new results in clinical and preclinical studies. French Anderson summed it up best: "What a difference four days makes!"