Gene Therapy

An End and a Beginning

Since its inception only 15 years ago, gene therapy has embodied all of the promise that advanced technology could bring to bear upon disease. Indeed, much of the excitement surrounding this form of intervention derives from its conceptual simplicity: correcting genetic disorders by replacement of the defective genes. Rapid translation of gene therapy paradigms into human clinical trials, however, served only to highlight the complexity of the technical barriers to realization of those ends.

A valid criticism of the gene therapy field a few years ago was that none of the first 200 human trials had demonstrated any effect approaching a therapeutic end point. This recognition provoked a re-evaluation of the gene therapy enterprise, which took the form of an NIH-sponsored report written by Stuart Orkin of Harvard University and Arno Motulsky of the University of Washington. They suggested fundamental endeavors to improve the design and efficacy of gene delivery vehicles prior to further human experimentation.

It may be difficult, in light of these considerations, to appreciate why human experimentation was undertaken so rapidly. Recall that gene therapy was first conceived as an approach to inherited genetic disorders for which effective therapies did not exist. An early criterion was that human trials had to take place in contexts where no treatment was available and the target disease was life-threatening.

The same criterion applied to gene therapy for many cancers, even though the gene therapy approaches that were tried had not always demonstrated efficacy in stringent model systems. Criteria by which other cancer therapies were judged did not always apply to gene therapy, and many of these trials were repetitive iterations of a basic theme in different cancer contexts.

Certainly the early public embrace of the new gene therapy technology motivated investigators to test its usefulness in cohorts of patients who found the idea acceptable. As well, enthusiastic backing of fledgling gene therapy companies by venture capital created corporate pressure to realize results in human subjects.

Finally, the nature of the regulatory process sent confusing messages to investigators. Approval of a gene therapy trial by the Recombinant DNA Advisory Committee of the NIH validated only its safety, but such approvals were often taken as endorsing therapeutic rationales, with the implicit expectation of clinical advancement.

Against this backdrop, the death of a patient in a gene therapy trial last September dramatically increased the controversy surrounding the field and even called into question the integrity of the overall enterprise. The specific adverse event occurred in a clinical trial for an inherited liver disorder called ornithine transcarbamylase deficiency. The 18 year old male patient was treated with a recombinant adenoviral vector delivered via the hepatic artery. At the highest tested adenoviral vector dose, the patient developed hemodynamic instability with the rapid advent of shock, and he subsequently died.

Of note, before that trial, adenoviral vectors were considered one of the more promising gene delivery vehicles. The death of a patient therefore had direct implications for the increasing number of trials employing this vector system, as well as others.

The initial reaction in the scientific community focused on the openness of the investigators and their cooperation with federal regulatory agencies. Many in the gene therapy field viewed it as fortunate that such an inevitable event during the development of a new form of therapy had taken place at the University of Pennsylvania's Institute of Human Gene Therapy, the largest and one of the most clinically active gene therapy centers in the world.

Investigations initiated by regulators along with intense press coverage served to sustain public interest in the events leading to the tragedy. There have been two revelations of importance.

First, a basic question was raised about the trial's use of a gene delivery vector that was potentially inappropriate considering the natural history and pathogenesis of the target disease. The metabolic liver disorder develops because of an inborn genetic error. Logic dictates that such a chronic disorder would require a permanent genetic correction to allow long-term rectification of the pathobiology. Whereas some classes of vectors can achieve long-term expression in target cells, their use for liver cell correction has been relatively inefficient.

Adenoviral vectors, alternatively, can achieve relatively more efficient gene transfer to the liver, but the genetic correction is only transient. It was thus fundamentally problematic that the test subject incurred therapy-related risks when it was not clear that a potential therapeutic gain truly existed.

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Of greater concern, irregularities in the process of informed patient consent were alleged to have occurred. The two issues together were of sufficient gravity to warrant formal investigations by the FDA and the Recombinant DNA Advisory Committee of the NIH. These investigations as well as direct congressional scrutiny turned up additional problems.

Specifically, it became clear that other therapy-related deaths had occurred during gene therapy trials for coronary artery disease, carried out by separate groups at Cornell University in New York and St. Elizabeth's Hospital in Boston. Apparently favorable clinical results had already focused great attention on these trials, but initial enthusiasm was tempered substantially by the surprising disclosure that the deaths of patients may not have been reported to the FDA or NIH as is required.

In addition, in both of these cases as well as in the University of Pennsylvania case, investigators have links to corporate entities with interests in the outcomes, suggesting that fundamental issues of conflict of interest might have been operative. Clearly, the unfortunate death of the patient in Philadelphia has served as a nidus for an examination of issues far beyond the initial concerns of safety and oversight.

Beneath the headlines related to these events are many ironies and some verities that bear consideration. The first truth is that therapy-related deaths are an inevitable outcome of any experimental therapy. Consideration of just about any modern therapeutic agent from a historical perspective will demonstrate such events, even in the case of therapeutic agents currently offering the most exciting clinical results, such as anti-tumor monoclonal antibodies. That particular events have led to deaths during gene therapy does not belie the inevitability of such deaths.

Gene therapy has been unique among new medical fields in the scrutiny that has attended its development since inception. It is fair to say that no other field in medical history has proceeded under such rigorous oversight, and on that basis, it must be concluded that errors did not happen because of a lack of scrutiny. More accurately, confusion and lack of coordination among the overseers was more relevant. None of the serious issues raised during the recent investigations is unique to gene therapy or to its practitioners.

Perhaps most unfortunately, wide publicity of these events has obscured developments of greater significance. In recent months, the first clear evidence of clinical benefit afforded by gene therapy has been published by three different groups conducting clinical trials for adenosine deaminase deficiency, hemophilia, and atherosclerotic heart disease. Each of these trials was a phase I study, designed only to determine treatment-related toxicity. Such studies usually use lower doses of vector than would be required to elicit a therapeutic effect, so achieving therapeutic benefits is especially noteworthy.

In each of these positive trials, the fundamental logic of gene therapy intervention was the same as in earlier attempts to treat the same diseases. That is to say, no advances have occurred in understanding the disease pathophysiology or the genes involved.

What has happened is that advances in gene therapy technology achieved first in animals have been incorporated into the design of these trials, as Orkin and Motulsky recommended. Successful outcomes predicated on new vector designs highlight the concept that the difference between clinical benefit and its lack may be ascribed to the most basic aspects of gene delivery technology.

Gene therapy at the moment is rife with ironies. The most scrutinized of all medical fields is faulted for inadequate scrutiny; a delivery vector is the basis for gene therapy's nadir and almost simultaneously for its first glimmer of hope; a gene therapy protocol provokes a death while other protocols offer the promise of extending life.

Whereas the passage of time will provide perspective and context for gene therapists, recent events may make their scientific lives more difficult in the meantime. At the moment when the gene therapy field should rejoice in its first successes, it is instead the subject of withering censure.

Ironies notwithstanding, the path forward for the field is clear. Increased scrutiny of human clinical trials has resulted in the design of protocols with more clearly measurable end points. In addition to obligatory phase I safety and toxicity indices, interval end points have evolved that validate basic vector efficiency and clinical effects.

On this basis, trial-derived data can be exploited more directly in the design of advanced-generation vectors: delivery agents that have been engineered to address the biology relevant to achieving effective gene delivery. More stringent trials in conjunction with the evolving science of "vectorology" will provide a mutually reinforcing dynamic that will advance the field toward achieving the full promise that its technology has long been recognized to possess.

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