During the last several years, we have witnessed “the best of times and the worst of times” in the embryonic field of gene therapy. Rapid advances in human genomic sciences, the development of novel mouse models of human diseases, and the construction and characterization of new vector systems for in vivo gene transduction have significantly expanded the potential feasibility of human gene therapy. On the other hand, the tragic events surrounding the gene therapy–related death of Jessie Gelsinger and subsequent revelations about additional unreported gene therapy–related complications have seriously damaged both the scientific credibility and public confidence in gene therapy. Given these recent events, this would seem to be an opportune time to pause and carefully reassess where we are and, more importantly, where we should be going in this promising but controversial field.

Toward this end, I would like to consider 3 distinct but related questions. First, does the currently available scientific evidence support the feasibility of human gene therapy? If so, what types of preclinical data are necessary to justify human clinical experimentation? Second, what can be learned from our recent experiences about the design of future human gene therapy trials? And, third, what safeguards are necessary to ensure the objectivity of investigators in the field and to thereby inspire the required level of confidence on the part of patients and their families, the scientific community at large, and the general public?

The Science: Genes, Vectors, and Devices
Most successful gene therapy approaches require the combination of an efficacious therapeutic gene, an appropriate vector for delivering and expressing that gene in the desired cell type in vitro or in vivo, and, in some cases, a device (eg, a catheter, stent, or implantable polymer) to facilitate in vivo gene delivery. The identification of potentially useful therapeutic genes has progressed rapidly during the last decade. Such genes include those involved in inherited single gene disorders such as hemophilia (factors VIII and IX), cystic fibrosis (CFTR), or Duchenne muscular dystrophy (dystrophin) as well as genes that could be used to treat more complex diseases, such as restenosis after balloon angioplasty (eg, the retinoblastoma gene product [Rb] or herpes simplex virus thymidine kinase gene [HSVtk]) or ischemic cardiomyopathies (eg, vascular endothelial growth factor [VEGF] or fibroblast growth factor). This already large list of potential therapeutic genes promises to expand considerably over the next several years with the completion of the human genome project and the identification of additional human disease-related genes.

An essential first step on the road to human gene therapy, and one that has often been forgotten in the rush to human trials, is a careful assessment of the efficacy and safety of expressing potential transgenes in different tissues in animal models of human disease. In some cases, it is clear from
preclinical experiments that expression of the appropriate transgene in a specific cell type or tissue will likely ameliorate or cure the disease. Examples include the expression of factor IX in muscle or liver for the treatment of hemophilia B or the expression of HSVtk in vascular smooth muscle cells (in conjunction with systemic ganciclovir therapy) for the treatment of restenosis. However, in other cases, we know very little about either the therapeutic or toxic effects of overexpressing these genes in different cell types in vivo. The angiogenic proteins, such as fibroblast growth factor and VEGF, represent an excellent example of this issue in the cardiovascular arena. Despite the fact that these genes are already being tested in humans, important questions about both their safety and efficacy remain unanswered. It is not clear whether the ectopic expression of proteins such as VEGF leads to the formation of organized, functional, and stable vessels or, instead, results in the formation of leaky hemangiomas with limited ability to augment blood flow to regions of ischemic muscle or myocardium. Nor is it entirely clear whether VEGF overexpression might promote pathological angiogenesis at distant sites, eg, retinal neovascularization in patients with diabetes mellitus. Such questions are readily answerable with the use of both transgenic and gene transfer approaches in rodents and primates, and it is incumbent on investigators in the field to do so before beginning human trials.

Progress in the areas of vector and device development has lagged considerably behind the discovery of therapeutic genes. Indeed, long-standing unresolved difficulties with vectors and devices continue to hamstring the field of gene therapy. The ideal vector should efficiently transduce quiescent cells in vivo, be capable of accommodating large transgenes, produce prolonged and, in some cases, regulated transgene expression in immunocompetent hosts, and result in minimal or no local tissue inflammation or damage and no long-term neutralizing immunity. Simply stated, such a vector has not yet been developed. Currently available retroviral, adenoviral, lentiviral, and adeno-associated virus (AAV) vectors each fall short of these idealized specifications. Retroviral vectors are difficult to produce in high titer, require cell replication for efficient infection, and integrate into the host genome. Although capable of efficiently transducing many cell types in vivo, adenovirus vectors produce intense inflammation, transient transgene expression, and long-term cell- and antibody-mediated immunity. AAVs are much less inflammatory than their adenovirus counterparts and indeed appear to be capable of programming long-term gene expression in immunocompetent animals in vivo. However, these vectors can only accommodate transgene cassettes of \(<4.5\) kb and stimulate neutralizing antibodies that prevent their readministration. In addition, it has been difficult to produce high-titer stocks of AAV, and the vector does not efficiently transduce all cell types in vivo. Like AAV, lentivirus vectors efficiently transduce many quiescent cell types in vivo and appear to be relatively noninflammatory. Moreover, these vectors can program stable transgene expression in immunocompetent animals. However, concerns have been raised about the use of HIV-based vector systems in humans, and it has been difficult to produce large high-titer stocks of these vectors that would be suitable for human therapy. Finally, many of the more promiscuous vectors, such as adenoviruses and lentiviruses, can infect many different cell types in vivo, raising the risk of inadvertent infection of the wrong tissue after in vivo administration. Tissue-targeted, tissue-specific, and physiologically and pharmacologically regulated vector systems have been described only recently. The use of such vectors will be particularly important for gene therapy of many diseases.

Devices for cardiovascular gene therapy have not yet received the attention that has been devoted to therapeutic gene discovery and vector construction. The result is a dearth of devices that can effectively and safely deliver gene therapy vectors to localized regions of the organism. Thus, for example, local vascular delivery catheters tend to produce uneven patterns of vector delivery and to leak vector distally and into coronary side branches. Similarly, recent studies have demonstrated that many currently used gene delivery catheters rapidly and efficiently inactivate adenovirus vectors and will therefore not be useful for adenovirus-mediated gene therapy. Rigorous and systematic improvement of currently available devices is necessary before proceeding to human trials of catheter-based gene therapy.

In summary, the current scientific data support the long-term feasibility of human gene therapy. However, despite the discovery of numerous potentially useful therapeutic genes and the recent development of more efficient and less inflammatory vector systems, much work remains to be done to optimize both the safety and efficacy of gene therapy approaches. Most, if not all, of this work can be carried out in cells and animals, thereby minimizing the risk to patients participating in future gene therapy experiments. It should also be emphasized that non–gene therapy approaches are currently being developed for many of the same diseases that have been approached by gene therapists. Examples include the use of radiation therapy for restenosis and the development of smart implantable pumps for the treatment of serum protein deficiencies, such as diabetes mellitus or hemophilia. Thus, it will be important to carefully compare the safety and efficacy of gene therapies with those of such non–gene-based treatments.

Clinical Trials: When and How to Proceed to Human Experimentation

The basic principles underlying human gene therapy trials are fundamentally no different from those that form the foundation of all modern clinical research. All clinical experiments must offer potential short- or long-term benefit to patients. Of equal importance, the nature and likelihood of clinical benefit must be carefully weighed against the risks to individual patients resulting from the novel therapy. These simple and well-established principles have several important implications for gene therapy research. First, as in all clinical experimentation, the efficacy and toxicity of gene therapies must be rigorously and exhaustively tested in animals before proceeding to human trials. Such animal experiments are typically the only way to accurately assess (and adjust) the risk/benefit ratio of the therapy in patients. Because it is difficult to scale up gene therapy approaches from rodents to
humans, it will be important to frequently and carefully assess toxicity in large animals (including primates) before initiating human experiments.

In addition to assessing the risks of acute toxicities, gene therapy investigators must consider the potential of precluding future gene or drug therapies in treated patients because of the long-lasting immune responses generated against vectors or, more importantly, therapeutic transgenes. Finally, new and potentially toxic therapies and vectors should be tested first in desperately ill patients, because such patients unfortunately display the best risk/benefit ratios for evaluating such untested therapies. The poor prognosis of these patients often makes it difficult to obtain unbiased informed consent.

The use of lay advocates has been proposed as one potential method of protecting patients’ rights in these situations. Taken together, these guidelines suggest that early human gene therapy trials should typically involve carefully consented critically ill patients and use gene therapy approaches in which therapeutic benefits might be derived from transient and localized transgene expression.

Because the time between the initial conception and completion of human gene therapy trials is often long (several years) and because the field is changing so rapidly, it is also essential that the design of clinical trials is continuously reevaluated in light of advances in our understanding of vectors, transgenes, and devices. Such reevaluation may often result in the need to alter or even halt ongoing clinical trials.

Ethical Considerations: How Do We Recapture Lost Trust?

A number of factors have contributed to the loss of confidence in gene therapy by both the scientific and lay communities. First, we, as investigators, have simply promised too much and delivered too little. We need to be honest and proactive in communicating the concept that gene therapy is an embryonic and difficult field that is unlikely to produce miraculous cures over the next 5 to 10 years. In this respect, it is not unlike organ transplantation or stem cell therapies, in which therapeutic benefits might be derived from transient and localized transgene expression.

Like many other fields in modern medicine, gene therapy has also been plagued by real and perceived conflicts of interest among many of its leading investigators. Financial interests of clinical investigators in pharmaceutical or biotechnology companies are correctly perceived by the public as incompatible with responsible and ethical patient experimentation. It is critically important that all clinical investigators involved in patient selection and data analysis in gene therapy trials do not have personal financial relationships (of any magnitude) with companies that can benefit from the results of their clinical trials.

Open and timely communication is one of the critical elements needed to build trust between scientists and the general public. Lack of honest, open, and timely reporting of both efficacy and toxicity data has seriously damaged the credibility of the gene therapy field. Given our poor record of past performance in this area, it is likely that extraordinary efforts will be required to rebuild the public trust. Such efforts might include an organized system for rapidly disclosing the results of gene therapy trials both in published form and on the Web, formal mechanisms for the confidential exchange of toxicity data among all investigators using a given vector, device, or transgene in humans, and the creation of local safety-monitoring boards at all centers carrying out gene therapy trials. In addition, informed consent forms must be scrutinized carefully by both investigators and institutional review boards and must honestly present both the risks and benefits of experimental gene therapy approaches to patients and their families.

All of the issues described above are straightforward and obvious. Most are not unique to the field of gene therapy. In fact, one can make a strong argument that gene therapy should be held to the same scientific and ethical standards as more well-established fields of clinical investigation, such as cancer chemotherapy, organ transplantation, and new-device testing. As has happened in each of these fields in the past, an appropriate combination of scientific rigor, clinical judgment, and professional ethics will allow gene therapy to move forward safely and to establish its value in the therapeutic armamentarium. As in all areas of medicine, translating scientific promise into clinical efficacy is a difficult challenge that requires much hard work, time, and patience on the part of both physicians and patients. Only by working together in relationships of trust with our patients can we hope to succeed in this effort.

Acknowledgments

This work was supported in part by grants from the National Institutes of Health (DK-48987 and AR-42885). Dr Leiden is a scientific consultant for Boston Scientific, Inc, a manufacturer of gene delivery catheters. I would like to thank Drs David Ginsburg, Elizabeth Nabel, Gordon Huggins, John Lepore, and Eugene Kaji for helpful comments and advice about the manuscript.

KEY WORDS: gene therapy catheters adenovirus biocompatibility
Human Gene Therapy: The Good, the Bad, and the Ugly
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Circ Res. 2000;86:923-925
doi: 10.1161/01.RES.86.9.923

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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