

## **Cell and Gene Therapies: Challenges in the Development of Novel Therapeutics.**

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The prospect of curing genetic diseases by supplying a normal copy of a defective gene remains one of the most exciting frontiers in molecular medicine. However, viewed from a pharmaceutical perspective, gene therapy is perhaps one of the most complicated biologics yet targeted for drug development, consisting of both a vector, or gene delivery vehicle, often derived from a virus, and a transgene that encodes a therapeutic product. A wealth of data in animal models, and a more modest dataset in humans, demonstrate that gene transfer approaches can cure both genetic and acquired disorders. At this point, over 4000 human subjects have been enrolled in gene transfer studies, and it can be argued that these trials have been critical in identifying the problems that must be solved to make the approaches safe and effective in humans. Some of the obstacles that have slowed development of gene transfer are scientific and/or technical issues unique to gene transfer, e.g. risk of inadvertent germline transmission of the donated DNA, or issues related to scaleable and consistent manufacture of a viral vector. Others such as fragmentation of intellectual property required for a single therapeutic entity -are issues common to all complex biologics. Perhaps the greatest challenge has been the absence of defined paradigms for the testing and licensing of gene transfer vectors and cell therapies, and a consequent need to develop a plethora of assays that must be established and validated to manufacture the biologic, and then track its effects in human subjects. This has occurred largely through the efforts of academic and industry investigators, since the FDA Office of Cell, Tissue and Gene Therapy has not had the resources to spearhead the development of key assays that could be used for general classes of vectors or cell therapies. The model of the scientist-regulator at the FDA has been challenged by some, but the participation of FDA staff members who are experienced in the investigation of cell and gene therapies will be key to the successful development of these new therapies. Finally it should be noted that a few high profile adverse events in this field resulted in added layers of complexity in the regulatory process. This had the predictable consequence of slowing timelines for development, which resulted in the dropout of smaller biotechnology firms with limited resources, further slowing progress since these had been engines of development for these therapies.

In some respects the pace of development of cell and gene transfer therapies recapitulates that seen with other biologics, including recombinant proteins and monoclonal antibodies. Currently, because many cell and gene therapy protocols

are sponsored by academic investigators, it will be critical for the NIH and academic centers to maintain funding mechanisms such as Program Project grants or U01 mechanisms that can support the teams of investigators required to conduct these studies. Elimination of redundancy in the regulatory process, and maintenance of the scientist-regulator model at the FDA, are other key elements for success.