



## **Challenges in Advancing the Field of Gene Therapy: A Critical Review of the Science, Medicine, and Regulation**

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The 225 participants attending the 2005 American Society of Gene Therapy (ASGT) Stakeholders' Meeting held in Washington, D.C., on April 7 and 8 were greeted by warm weather, a city in full cherry-blossom bloom, and an enthusiastic organizing committee. The focus of this year's meeting centered on scientific, medical, and regulatory challenges in advancing the field of gene therapy, which drew members from academia, industry, government agencies, disease foundations, and the press. The ASGT jointly sponsored the meeting with the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia, with additional support from Genzyme, the Biologics Consulting Group, and Avigen. This article summarizes clinical gene transfer barriers faced by those in the field and possible strategies for circumvention as discussed in a series of presentations focusing on vectorology, immunology, vaccine design, and real stories.

### **Introduction**

Katherine High (Children's Hospital of Philadelphia), co-chair of the conference along with Daniel Salomon (The Scripps Research Institute), began by emphasizing that the goal of the conference was to identify and discuss the challenges to advancing clinical gene transfer research. In sum, the field is currently progressing only slowly despite a significant medical need and is beset by a general but false perception that gene therapy has not been successful. She delineated several obstacles to progress that would be revisited many times throughout the 2-day forum.

Although the principles behind gene transfer are sound, High noted that secondary scientific problems have emerged, such as tissue-specific immune responses elicited against the vector and transgene and the need for targeted delivery to specific organs or tissues. The changing climate for clinical investigation in U.S. multi-center trials also presents a major obstacle. For example, the multi-layer review process slows approvals, and institutional review boards (IRBs) from participating institutions, with individualized rules and regulations, further complicate and delay the review process. Notably, a small number of unexpected serious adverse events have caused increased federal and IRB scrutiny of trials, which further slows timelines, sucks up funding, contributes to an increased sense of risk, and forces many smaller biotech companies to drop out of the process entirely. Financial hurdles also present obstacles, since big pharmaceutical companies typically do not enter the clinical trials process and provide funding until phase 3 trials are underway. This leaves principal investigators (PIs), small biotech companies, and disease foundations to foot the bill for pre-clinical, phase 1, and phase 2 studies.

As early-phase clinical trials become more frequently based at academic medical centers, adjustments in staffing will be needed since clinical trial research is not easily divided into projects for post-doctoral researchers and fellows. In addition, the responsibility for pushing the clinical trial timeline forward falls solely on the shoulders of the PI backing the trial—an unsatisfactory arrangement since these individuals typically bear many other responsibilities and are often not prepared for or experienced with the rigorous formal conduct required for enabling a phase 2 clinical trial. At a minimum, this situation constitutes a serious disincentive for the participation of new investigators who will represent the next generation of gene therapy researchers.

Trial momentum can degenerate into a jerky ride of starts and stops in the face of recurrent clinical holds. High noted, however, that as experiments with a given class of vectors proceed and knowledge is accrued, clinical studies are expected to progress more smoothly. Commercial obstacles include complications arising from intellectual property issues that limit information sharing prior to commercial development and industry pressure to develop therapies for large-market indications, even though these may not be the most straightforward choices from a scientific standpoint. Other hurdles High mentioned include the scalability, manufacture, and access to clinical-grade vector and public perceptions of the relative risks involved in participating in gene transfer studies.

In conclusion, High compared the current problems confronted in advancing clinical gene transfer trials to those tackled not long ago by researchers studying monoclonal antibodies as a class of therapeutics. The therapeutic potential of this technology was appreciated, but years of clinical trial failure prevented its clinical application. Indeed, the considered wisdom at one point was that there was little or no potential in this area, and many large pharmaceutical companies walked away from millions of dollars in investments and intellectual property. Slowly but surely, however, problems were identified and solved, thereby eventually permitting the huge and growing clinical and commercial success today. It appears that the field of therapeutic gene transfer is at a similar crossroads today.

## **Vectorology**

Arthur Nienhuis (St. Jude Children's Research Hospital) and Barrie Carter (Targeted Genetics Corporation) co-chaired the first session on vectorology barriers to gene transfer clinical trials, which included six presentations covering the range of gene transfer vectors currently used in experimental studies. David Williams (Cincinnati Children's Hospital Medical Center) began with a discussion of retroviral and lentiviral vectors employed in gene transfer studies of Fanconi's anemia (FA), a disease typically affecting children characterized by progressive bone marrow failure due to mutations in any of 11 different genes. Roughly 30% of patients with a human leukocyte antigen (HLA) matched sibling donor receive the standard FA therapy of bone marrow transplantation. For the remaining 70%, the next-best therapy—stem cell transplantation using unrelated donors—has a high associated morbidity and mortality. Consequently, corrective gene transfer using a retrovirus vector presents an attractive, alternative therapeutic option, especially given the efficacy demonstrated in the FA mouse model. Carrying this success over to humans, however, has been troublesome, as *ex vivo* manipulation of FA hematopoietic stem cells (HSC) is complicated by their genetic instability and low abundance at the time of critical disease progression. To ameliorate these difficulties, Williams says that he and his colleagues have been able to obtain a better source of HSC by collecting the cells before the onset of aplastic anemia, isolating more cells during collection, and optimizing cryopreservation and thawing procedures. *In vitro* cell culture has also been improved by

implementing shorter culture times and better cytokines, while gene transfer efficiency has been greatly enhanced by using a high-titer murine leukemia virus vector pseudotype with a Gibbon ape leukemia virus (GALV) envelope protein, which is administered in one to two exposures over 36 hours. Several FA genotype A children with no HLA-identical sibling donors are currently enrolled in a pilot trial employing a murine stem cell virus backbone. This study encountered no significant regulatory obstacles prior to trial initiation, although the investigators had to extensively evaluate patients for clonal hematopoiesis following the serious adverse events seen in the French X-linked severe combined immunodeficiency (X-SCID) trial.

In light of the adverse events of the X-SCID trial, Cynthia Dunbar (National Heart, Lung, and Blood Institute, NIH) presented data from long-term non-human primate studies regarding whether integration toxicity in humans is cause for concern. She began by throwing out a question many wonder about: Is gene therapy with integrating vectors safe? Forty-six rhesus macaques receiving stem cells transduced with retroviral vectors have been studied for a median follow-up of 4.5 years—representative of 6,000 “insertion years”—and during this time no clinical or molecular evidence for progression to a pre-leukemic or a leukemic state has yet been observed. However, one 3-year-old macaque that received a retrovirally transduced stem cell transplant following total body irradiation in 1999 demonstrated an adverse event 5 years later. In 2000, this animal exhibited an unusual gene-marking pattern, with two dominant clones identified—one in chromosome 15 and the other in chromosome 19. In 2001, the animal received 1 dose of cytotoxic drug treatment. The animal demonstrated normal blood counts every 6 months until September 2004 when the animal’s health rapidly deteriorated and it died. Necropsy analysis revealed myeloid sarcoma infiltration, and molecular evidence for elevated vector levels in the tumor was found. The retroviral vector inserted at the locus encoding BFL-1, an anti-apoptotic member of the BCL2 family that prolongs cell survival while allowing for proliferation and some differentiation. Hence, retrovirus integration at this locus possibly induced over-expression of BFL-1 in the kidney tissue, thereby precipitating tumor formation. Subsequent mapping of 702 insertions in the other treated monkeys revealed a significant over-representation (1.8%) of independent insertions at the MDS1-EVI1 locus in 9 different animals. The MDS1 (MyeloDysplasia Syndrome 1) and EVI1 (Ectopic Virus Integration 1) genes encode transcription factors implicated in human leukemias. Despite the propensity to integrate at this locus, no evidence of clonal expansion in 5 individual clones has yet been observed for periods up to 7 years. Dunbar concluded that these integration events do not represent integration at a “hot-spot.” She also believes that lifelong follow-up is required for those treated with integrating, persisting vectors, and this analysis should be complemented by prolonged non-human primate and murine studies.

Philip Gregory (Sangamo BioSciences) next turned the discussion toward gene correction as an alternative therapeutic modality. Instead of gene addition, gene correction provides site-specific, permanent modification of the genome using transient delivery of the corrective vector system and requires no need for ectopic gene insertion or a heterologous promoter. Zinc finger DNA binding protein nucleases (ZFNs) are genome editors that can be harnessed to promote gene correction, gene disruption, and site-specific integration. For example, designer nucleases combining zinc finger proteins and FokI (a non-specific restriction endonuclease) have been created in which the ZFNs bind to a targeted DNA sequence and cleave the DNA to cause a double-strand break. Homologous recombination in human cells occurs in approximately  $1 \times 10^6$  cells; however, homology-directed repair of a double-strand break using a sister chromatid as a template is more than 1000-fold more efficient. The ZFN system can not only create a double-strand break at a site-specific location to induce the process of homology-directed repair, but donor plasmid DNA can also be transferred into the cells to further control the gene correction

process in the event that the intact sister chromatid is defective. Initial ZFN studies in cell culture and human T cells have provided encouraging results when correcting IL2R (Interleukin-2 Receptor) gene mutations related to X-SCID. But what obstacles might hinder clinical applications of this technology? First, Gregory explained that designing potent ZFNs is non-trivial when factoring in the specificity and architecture of the system. Second, the range of mutations or deletions that can be targeted is restricted since the efficiency of conversion becomes greatly diminished when the mutation and ZFN cleavage site are greater than 100 base pairs apart. Third, the current delivery approach is *ex vivo*, making either plasmid DNA or viral systems the best methods for ZFN delivery—both of which require additional research. Moreover, researchers have yet to demonstrate system safety and efficacy in appropriate model organisms.

In turning to adeno-associated virus (AAV) vectors, Terence Flotte (University of Florida) stated that continuous identification and management of long-term gene transfer risks associated with recombinant AAV vectors is needed, specifically focusing on insertional mutagenesis, inadvertent germ-line transmission, and immune responses to capsids and transgene products. AAV vectors are typically used for long-duration gene transfer, and more than 110 serotypes have been identified in humans and non-human primates since the virus lives symbiotically within primates. Flotte's research is specifically focused on constructing a safe and effective AAV vector system to treat patients deficient for Alpha-1 Antitrypsin (AAT), a cause of genetic emphysema. Initial studies of murine skeletal muscle transduced with AAT using an AAV2 vector demonstrated long-term, functional AAT protein secretion from muscle cells. These analyses progressed to a phase 1 study beginning in March 2004 focused on (a) assessing the safety of intramuscular administration of human AAT in adult AAT-deficient patients and (b) determining the dose of the vector-transgene system required to achieve a detectable level of AAT in these patients. Based on preliminary findings, 8 patients have been safely treated, and no serious vector-related adverse events have been observed. Serum muscular AAT levels are initially elevated but then diminish over time, anti-AAV2 antibodies develop steadily over time, and no anti-AAT antibodies have been detected thus far. These subjects are scheduled to participate in long-term follow-up for 15 years, so future data will provide more insight. The only obstacle Flotte mentioned in moving the research to the clinic was compliance with an extensive good manufacturing practice (GMP) scheme for the AAV2 vector, although this is now being refined.

Arthur Beaudet (Baylor College of Medicine) presented a discussion of helper-dependent adenoviral (HDAd) vectors for liver- and lung-directed gene therapy. Similar to Flotte, Beaudet has devoted much time and effort to improving the quantity and quality of HDAd vector production. The major obstacle with translating adenoviral-based vectors to the clinic, however, has been substantial vector toxicity. Initial adenoviral toxicity studies revealed acute toxicity within the first 24 hours after vector injection, followed by viral gene expression from Days 2-4. An immune response then arose during Weeks 2-6 when chronic viral expression was in effect. In humans and non-human primate studies, the efficiency of adenovirus-mediated hepatic transduction following systemic injection increased with increasing vector doses, but so too did toxicity. Subsequent toxicity-limiting studies in mice revealed that hydrodynamic injection of HDAd resulted in increased hepatic transduction, reduced systemic vector dissemination, and less severe elevation of pro-inflammatory cytokines than conventional injection. Hydrodynamic injection into baboons using a balloon system to block hepatic venous outflow to thereby increase intrahepatic pressure also demonstrated stable, long-term, high-level transgene expression with no chronic toxicity. Studies of HDAd-mediated, lung-directed gene therapy are also being carried out in baboons using a pressure-actuated Intratracheal AeroProbe aerosol

delivery catheter. Thus far, the vector doses administered have been well tolerated with minimal toxicity, and widespread transgene expression is seen. Based on these data, Beaudet hopes to initiate a clinical trial for hemophilia A or B and a clinical trial for cystic fibrosis by February 2007. Before these trials can proceed, however, the Baylor group must achieve clinical grade vector production in addition to gaining regulatory approval.

Joseph Glorioso (University of Pittsburgh School of Medicine) ended the vectorology section with a presentation on replication-defective herpes simplex virus (RD-HSV) vectors and their use in treating pain and neuropathy associated with sensory nerve disease. Use of RD-HSV vectors in neuronal tissues is advantageous given the large load capacity of the vector, targeted delivery to sensory ganglia by retrograde transport, stable persistence in neurons in a non-integrated state, a lack of neural toxicity, short- or long-term gene expression, and scalable vector manufacture with no wild-type recombinants produced. Glorioso and colleagues are employing the HSV vector to treat chronic pain, an unmet medical need that affects 60 million Americans. Nociceptors transmit noxious stimuli, which are ultimately transmitted to the spinal cord and brain. To block nociceptor signaling, mice were transduced with HSV-mediated proenkephalin (vector SHPE), which indeed reduced mechanical allodynia (pain caused by a normally non-painful stimulus) in a spinal nerve ligation model of neuropathic pain. Moreover, gene transfer did not induce tolerance and was additive with morphine treatment. These preclinical results support a phase 1/2 randomized dose-escalation study in humans to evaluate the safety and clinical efficacy of the vector SHPE system. Other uses of RD-HSV technology include reversing diabetic neuropathy via axon regeneration using HSV-mediated delivery of nerve growth factor or neurotrophin-3. One of the major rate-limiting steps for clinical trial assessment of this technology is HSV vector manufacture.

## **Immunology of Gene Therapy**

The next session topic, co-chaired by Savio Woo (Mount Sinai School of Medicine) and Michel Sadelain (Memorial Sloan-Kettering Cancer Center), focused on the problems associated with gene therapy immunology. Daniel Salomon, a conference co-chair, began with a frank discussion of innate immunity and the paradoxes of viral pathogens and tissue injury in gene therapy. He reminded the audience that (a) many gene delivery vectors are built on pathogen skeletons, some of which still retain pathogenic genes; (b) the delivery of therapeutic genes, whether by injection/inhalation or ex vivo cell separation and manipulation, often causes direct tissue injury; and (c) therapeutic gene delivery by nature will often alter the state of the target cell and/or host. These combined factors often induce cells to produce “danger signals.” Innate immunity is the body’s first line of defense to acute injury and occurs within the first 12 hours of invasion; it is primitive, operates by pattern-recognition receptors, and has no memory. In contrast, adaptive immunity, activated next, represents a complex system that responds to specific antigens; it evolves, operates by determining self from non-self, and has memory. Innate immunity and adaptive immunity are linked such that activation of innate immunity will induce activation of adaptive immunity. Salomon stressed that innate immunity is good in the context of therapeutic vaccines, as it leads to enhanced adaptive immunity, both locally and systemically. In the context of a tumor vaccine or therapy, innate immunity could also trigger a very acute, tumor-destructive local response. In addition, bestowing a competitive advantage on gene-modified cells could enhance the selection of healthy over diseased cells. In contrast, he argued that innate immunity could be bad if tissue injury created at a transplant site triggers these potent natural defense mechanisms and targets the host cells expressing viral proteins for destruction by the immune system. To help move the gene therapy field forward, Salomon

advocated more basic research regarding innate immunity activation and regulation. Clinical applications should also employ strategies to limit tissue injury during gene delivery, and immune monitoring during clinical trials should be expanded to include assessment of innate immune markers (e.g., cytokines; chemokines; altered activation of dendritic cells, macrophages, NK cells, and downstream T or B cells).

Hildegund Ertl (University of Pennsylvania and Wistar Institute) continued the discussion by delving more deeply into the topic of adaptive immunity to viral vectors and transgene products. Her research has shown that innate immune responses are triggered in response to both human and simian replication-defective adenoviral vectors, subsequently causing a potent transgene-product-specific CD8<sup>+</sup> T cell response that is obviously unwanted. In analyzing several AAV vector serotypes, Ertl and her colleagues found that AAV2 vectors elicit a very low adaptive immune response in animals. Preliminary analysis of liver-directed, AAV2-mediated factor IX delivery in dogs with hemophilia B proved effective, thereby prompting a phase 1/2 trial in humans with hemophilia B. Initially, one subject demonstrated transient transaminitis caused by immune-mediated liver destruction, namely, in response to the transduced hepatocytes. The trial protocol was subsequently modified to deliver less vector to participants, yet another patient still developed transient transaminitis with no detectable levels of factor IX observed. To account for these results, Ertl explained that most humans are naturally infected with AAVs that trigger the innate immune system, thereby later activating an adaptive immune response to AAV antigens and any associated helper viruses. As a consequence, humans have immunological memory to AAV that can be re-activated when the patient is exposed at a later time to AAV products, for example, the viral capsid. To overcome this problem, Ertl proposed using transient immunosuppression to prevent the loss of transduced cells, or she suggested that AAV vectors could be derived from species other than primates.

Whereas Ertl discussed the use of AAV vectors as vehicles for delivering genes recognized as “self” by the immune system, Philip Johnson (Children’s Hospital of Philadelphia) discussed using AAV vectors as vaccines for delivering genetic material recognized as “foreign” and intended to produce an immune response—a situation where the objective is to elicit innate and adaptive immunity. Johnson described the use of AAV vectors in an HIV vaccine delivering the HIV-1 *gag*, protease, and a portion of the reverse transcriptase genes to cells following intramuscular injection. Preclinical trials in rhesus macaques using a human-equivalent dose range proved encouraging, with 100% of the animals producing antibody against HIV-1 Gag at 12 weeks and 100% continuing to do so at 52 weeks. Studies of the vaccine have now progressed to human (HIV-negative) clinical trials, with safety, immunogenicity, and efficacy recognized as the key outcome variables. To overcome one of the biggest hurdles—funding—in getting the trial launched, the study was initiated in Europe as opposed to the United States because a sponsor was readily available (International AIDS Vaccine Initiative) and because the study could be quickly implemented since sites were already operational. Preclinical safety assessments—specifically, of the cell substrate and the biology of the vector—also presented significant hurdles prior to trial initiation. Although the results are preliminary, short-term safety of the vaccine has been demonstrated in trial participants, and dosage-boosting studies are now being initiated.

## **Vaccines—Cancer and Other Diseases**

Hildegund Ertl and Dale Ando (Sangamo BioSciences) co-chaired the session on hurdles faced by researchers investigating vector-based vaccines for treatment of a variety of diseases. Malcolm Brenner (Baylor College of Medicine) led off by discussing the problems associated

with using gene transfer to augment immune function—a purpose for which more than 15 investigational new drug (IND) applications have been filed. Brenner first detailed several phase 1 trials of vector-based vaccines used to elicit immune function, for example, using interleukin-2 (IL2) as a neuroblastoma tumor vaccine with either autologous or allogeneic tumor cell injections and generating a latent membrane protein 2 (LMP2)-specific cytotoxic T cell response to provide immunity against Epstein Barr virus and hence prevent lymphoma. Brenner mentioned several difficulties in bringing many phase 1 studies to trial. First, small-scale, iterative studies are often impeded by too many regulatory bodies, including governmental organizations, IRBs, lawyers, and insurance companies, among many others. Another difficulty is that pharmaceutical indifference to cell therapy, given its complexity, low profit margins, complex regulation, and poor public perception, impedes larger efficacy studies. Other problems include a lack of explicit expectations among PIs regarding their role at each stage of the clinical process and a lack of representative democracy that subsequently delays innovation—after all, the primary stakeholder is the patient, and committees should not decide on behalf of patients unless public health risks are present. To solve these problems, Brenner suggested conflating regulatory bodies by having only one local and one federal regulatory body, obtaining GMP-like manufacturing assistance for the creation of vectors to relieve some of the burden placed on PIs, and increasing patient input when making approval decisions.

Speaking next, Karin Jooss (Cell Genesys) addressed the preclinical evaluation of the granulocyte-macrophage colony stimulating factor (GM-CSF) vaccine (GVAX for short). GVAX is a genetically modified tumor cell vaccine derived from tumor cells engineered to secrete GM-CSF. At the site of vaccine injection, resident dendritic cells take up tumor antigens, process them, and present them to naïve T cells in draining lymph nodes to ultimately induce a systemic anti-tumor response. To make the GVAX vaccine as efficacious as possible, Jooss and colleagues considered the possibility that the cytotoxic T-lymphocyte-associated protein 4 (CTLA4), which can play an inhibitory role in immunity by downregulating T cell responses, could be effectively inhibited by producing anti-CTLA4 antibodies to thereby increase the anti-tumor activity of the GVAX system. Indeed, this method proved effective in preclinical mouse and hamster studies. Despite this success, Jooss noted that 7 years lapsed between her team's initial discussion of the GVAX + anti-CTLA4 system and phase 1 enrollment of patients with hormone-refractory prostate cancer. To sidestep some of the difficulties that she encountered in getting the GVAX/anti-CTLA4 system to the clinical trial stage, Jooss acknowledged that use of murine homologs is essential for identifying safety and efficacy problems early on and that preclinical studies should use a treatment schedule similar to the one that will be used in the clinic to maintain as much consistency in the trial design and potential outcomes as possible.

John Nemunaitis (Mary Crowley Medical Research Center) discussed some of the hurdles he encountered in the product approval process during tumor vaccine trials employing adenovirus. The first obstacle was simply understanding the situation: the FDA approval process for cytotoxic chemotherapy has been established for 50 years, whereas “new” targeted therapies lack this history and are subject to much greater scrutiny. In using these new therapies optimally, the activity of the therapies should ideally be focused on the malignancy portraying the target of the therapy and should not be used in populations of patients for which only a proportion carry the target. Although several vaccines have proven efficacious in clinical trials (e.g., adenoviral ONYX-015, GVAX, other GM-CSF gene-transduced vaccines, several other oncolytic-virus-based vaccines), standard hurdles to product approval include patient accrual for trials, the focus of the grant award (basic science vs. clinical), biotech financing and protection, governance (investor focused vs. product-approval focused), profitability, and loss of insurance coverage for research participants. Nemunaitis further defined hurdles that will present

themselves as targeted therapies unfold, such as developing technologies to better define patients physiologically amenable or sensitive to the vaccine. Moreover, Nemunaitis hopes that regulatory bodies will become more accepting of “proof-of-principle” trials with regard to vector toxicity to allow researchers to move forward more quickly when delivering a different or additional gene with the same delivery vehicle.

Stephen Russell (Mayo Clinic) rounded out the session by discussing problematical issues associated with oncolytic RNA viruses. Early clinical evidence indicated that virotherapy does not usually work as a systemic therapy. Although it is still not known why the impact of intravenous administration is so limited, researchers speculate that the virus may fail to infect tumors efficiently, tumor cells could induce rapid extinction of viral gene expression, and/or viral spread may rapidly be controlled by immune responses. To address these and other issues, Russell suggested that researchers incorporate noninvasive pharmacological monitoring studies into their clinical trial designs. That is, pharmacokinetic analyses should be pursued to determine the fate of the virus in the body, and pharmacodynamic assessment should be carried out to identify how the virus works in the body. Preliminary studies with the measles virus demonstrate that it effectively infects and kills human tumor cells, and two treatment strategies using the measles virus as an oncolytic agent are currently being pursued: one using the soluble extracellular domain of carcinoembryonic antigen as a soluble, secreted reporter for viral gene expression in patients with ovarian cancer and another using a virus expressing the thyroidal sodium iodide symporter to facilitate noninvasive imaging of viral gene expression (using radioactive iodine) in patients with multiple myeloma. Despite the promise that this technology holds, the challenges in translating measles gene transfer to the clinic include difficulties managing timeline expectations, maintaining momentum (lack of contingency funds available), getting expert help and financial support, finding a PI fully committed to the clinical process from start to finish, staffing the vector manufacturing and toxicology/pharmacology operations, learning the GMPs and GLPs, agreeing on a safe and feasible trial design, and choosing an appropriate animal model for preclinical toxicity evaluation. Moreover, the question as to who should develop intravenous virotherapy—industry or academia—remains unanswered. Although many may feel that the research is safer in the hands of academics, the capability of translating initial studies to phase 2 and 3 trials is generally lacking. However, Russell strongly advised that academic centers should develop translational capabilities to ensure that they can at least perform iterative phase I clinical testing before seeking industry partnership.

## **Real Stories 1**

“Real stories” were presented at the Stakeholders’ Meeting to provide insight into the experiences and difficulties faced by a representative set of researchers progressing through the clinical trials process. Glenn Pierce (Avigen), a co-chair of the first session of real stories along with Samuel Wadsworth (Genzyme Corp.), advised investigators involved in gene transfer studies to learn from the experiences of the presenters, and also from those in other fields such as the antibody field, so as not to reinvent history. Jean Bennett (University of Pennsylvania Scheie Eye Institute) began by discussing her experience with preclinical studies for Leber Congenital Amaurosis (LCA), an inherited retinal degenerative disease, and the successes her group has attained in correcting this defect in dogs. Bennett acknowledged the inherent difficulties in working on gene therapies for orphan diseases. Industry will rarely fund such endeavors because they stand to gain no profit since so few people have the disease. Related to this, the regulatory environment for such heavily scrutinized studies makes it increasingly difficult and expensive to get research from the bench to the bedside. Moreover, resources become fragmented when

information sharing is ignored to protect intellectual property rights. Patient selection for orphan disease trials is especially problematic since very few individuals actually have the disease of interest. To that end, Bennett recognized the need for a national database with comprehensive clinical and genetic data to identify potential participants. Preclinical ocular disease studies are further challenging because all animal models, with the exception of primates, lack a macula—the tissue of interest. Other challenges Bennett encountered are issues common to other diseases, such as the age of the subjects and stage of the disease. Because retinal photoreceptors die as LCA progresses, children represent the ideal target population for this therapy. However, informed consent issues, ethical concerns, and PI inexperience with children complicate the matter. These problems may be overcome by using only adults with advanced LCA disease in phase 1/2 studies to assess safety and efficacy and then allowing children in proof-of-principle phase 3 studies. Moreover, Bennett acknowledged a problem with heightened expectations in that the significant rescue of vision shown in dogs may not be as dramatic in humans. Consequently, patients and the general public should be educated regarding realistic expectations for the treatment.

Mark Kay (Stanford University Medical Center) presented his experience with two phase 1/2 clinical trials of AAV-mediated gene therapy for hemophilia B. Following the demonstration of safety in a phase 1/2 trial of AAV-delivered factor IX in muscle of patients with severe hemophilia B and the demonstration of safety and efficacy in preclinical dog studies employing liver-directed factor IX delivery, approval was granted for progression to human phase 1/2 studies targeting the liver. A total of 3.3 years lapsed from the IND submission until the enrollment of 7 patients due to Recombinant DNA Advisory Committee (RAC) delays stemming from an unrelated gene transfer death and disagreement between the RAC and the FDA regarding the preclinical studies. Soon after the phase 1/2 dose-escalation trial of liver-directed factor IX was finally initiated, it was halted by the FDA when AAV vector was found transiently in the semen of the first two subjects. This ultimately took 11 months to resolve. When the trial again proceeded, transient transaminitis observed in one patient led to a 9-month delay for a treatment protocol amendment followed by necessary FDA approval. Other delays were caused by patient attrition, contract negotiations between the corporate sponsor and the clinical treatment sites, and coordination of the approval process among the many regulatory bodies. These delays culminated in withdrawal of corporate sponsor support, a loss of infrastructure and momentum, and disappointment from families. Given this experience, Kay stated that he and his colleagues know what they need to do next to advance hemophilia clinical trial studies, but they are limited by prohibitive clinical trial costs and the manufacture of clinical grade vector. Kay suggested that many of the problems he encountered could be obviated with more NIH and pharma financial support during early clinical trials and by consolidating and streamlining the regulatory process.

Mark Tuszynski (University of California—San Diego) ended the first real stories session with the developmental challenges he sees with gene-based therapies for the nervous system. The nervous system represents an ideal target for gene-based therapy because a small area can be targeted with a small quantity of vector thereby resulting in less vector exposure. In addition, the central nervous system (CNS) provides partial immuno-privilege with less potential for a systemic immune response, and this area has a great unmet medical need. In contrast, vector administration to the CNS is invasive and expensive, a lack of regulation exists, outcome measures for efficacy need improved clinical scales or surrogate markers of disease activity, informed consent in dementing illness presents a unique conundrum, and control groups involving sham surgery are cumbersome and costly. Despite these factors, a number of trials of nervous system gene therapy have been initiated. To promote the advance of this field,

Tuszynski recommended that researchers initiate clinical trials based on sound efficacy and safety data from the best animal models available (e.g., primates for CNS). Moreover, the treatment design should be kept simple, such as targeting small, isolated regions with low-dose vector. Tuszynski commented that unjustified pessimism should be addressed while avoiding exaggeration, and RAC bureaucracy should be reduced since it is redundant with other regulatory agencies such as the FDA.

As a co-chair of the next real stories session, Alan Kinniburgh (National Hemophilia Foundation) began by putting forward the question, “Why is there a dearth of funding for gene therapy?” He answered that this is due to the relatively few gene therapy successes that have been achieved, the few highly publicized cases of morbidity and mortality that paint gene therapy in a bad light, and the fact that gene therapy is no longer sexy. He suggested that voluntary health advocacy groups can aid in accelerating gene therapy research by directly funding more research and by advocating for additional funding from other organizations. Moreover, put forward the possibility of creating a funding consortium to support all gene therapy research and clinical trials.

The president of the World Federation of Hemophilia, Mark Skinner, presented his agency’s experience with moving gene transfer forward for hemophilia treatment. Hemophilia is typically treated by administering recombinant or plasmid-derived clotting factor. Although this therapy is effective, it is not curative and quite expensive, meaning that access is typically limited to individuals in developed countries. Consequently, the World Federation of Hemophilia adopted a goal in 1992 of promoting all research, including gene therapy, focused on finding an affordable and globally accessible cure for the disease. Many smaller hemophilia organizations have provided researchers huge monetary grants toward the same goal. Hemophilia represents an ideal disease to cure since it is well characterized genetically and clinically, there is a large market for the therapeutic product, there is a large unmet need for such treatment, and it is a simple monogenic disease with a wide therapeutic window. In reaching a cure, Kinniburgh acknowledged several areas that must be addressed. First, patient expectations must be managed so as to not elicit unfounded hope, and to that end, carefully defining what a cure will entail is important—that is, a cure may not be immediate, and physical, psychological, social, and financial burdens may not all be resolved at the same time. Second, challenges beyond basic scientific hurdles must be addressed, such as ethical concerns, informed consent issues, and the geographic variables of global clinical trials. Last, and perhaps most important, Kinniburgh stressed that achieving a cure cannot be met by the efforts of one individual, organization, company, or country; a collaborative approach is imperative.

Representing the Stop ALD Foundation, Rachel Salzman presented her organization’s experience with funding gene transfer trials for adrenoleukodystrophy (ALD), a rare, X-linked, monogenic disorder that leads to elevated very long-chain fatty acids. Approximately 45% of ALD onset occurs cerebrally in young boys and causes demyelinating disease, and the remaining incidence occurs in young adults and causes peripheral neuropathy. The current ALD therapy is allogeneic stem cell transplantation, but not everyone has a match and the procedure has a 40% mortality rate. ALD gene therapy involves ex vivo correction of autologous CD34+ cells using a lentiviral vector with an ABCD1 payload (the gene responsible for X-linked ALD). Impediments to clinical gene transfer, a process in which Salzman’s organization is closely involved, included challenges with the vector design and transduction protocol; fear of adverse events among investors and the public; weighing the risks versus benefits associated with safety versus efficacy; a lack of PI experience with gene therapy trials, regulatory affairs, and intimate knowledge of the ALD disease; and limited funds in addition to a limited number of scientists. Salzman’s suggested solutions to these problems included forming an advisory committee of

experienced PIs, partnering clinicians with PhDs and basic researchers, investing in public relations to draw favorable attention to the research being conducted, and focusing on diseases amenable to gene therapy to garner foundation involvement for enhanced support. She concluded by stressing that orphan diseases provide a unique opportunity for treatment, because a small scientific community can speak with a united voice.

## Real Stories 2

The second day of the meeting began with another round of real stories in a session co-chaired by Richard Mulligan (Children's Hospital Boston) and Cynthia Dunbar. Kenneth Fischbeck (National Institute of Neurological Disorders and Stroke/NIH) began by discussing the use of gene therapy for muscular dystrophy (MD), a disease in which muscle fibers degenerate and regenerate thereby causing progressive muscle weakness. At least 22 genes involved in MD have now been identified, and opportunities for MD therapeutic intervention entail correcting or replacing defective genes, blocking the deleterious effects of gene defects that lead to muscle degeneration, and enhancing muscle regeneration. For example, several animal and human studies have focused on replacing dystrophin, an important structural protein at the muscle plasma membrane. Although the method worked well in animal models, human studies demonstrated low gene delivery efficiency with few muscle fibers corrected. Another therapeutic approach uses antisense oligonucleotides to promote skipping of mutant or downstream exons to restore the reading frame in faulty MD genes. This method rescued dystrophin production in MD mice and cultured muscle cells from Duchenne MD patients. The only drawback is the need for individualized treatment depending on the specific gene defects requiring antisense oligonucleotide targeting. Mulligan indicated that the success of the MD therapies currently being investigated stem from the common treatment approaches taken by investigators, which facilitate an efficient use of clinical research funds and an increased chance for commercial development, especially given the connection between MD and other common diseases (e.g., age-related muscle loss).

Carl June (University of Pennsylvania) next presented the lessons he has learned from lentiviral gene transfer therapy for HIV/AIDS. HIV therapy uses a long antisense oligonucleotide targeting the HIV *env* gene encoding the viral envelope protein required for virus production and infectivity. High-efficiency transduction of primary human T cells with lentiviral vectors carrying antisense *env* has been demonstrated and suppresses HIV replication in vitro by > 2 logs. In a phase 1 trial assessing the safety and tolerability of T cells transduced with antisense *env* in 5 HIV-positive patients, no adverse events related to the protocol drug occurred and HIV viral load decreased in all patients over time, although the reduction was sometimes delayed. Moreover, the lentiviral gene transfer was sustained out to 1 year, as evidenced by the persistence of gene-modified CD4+ T cells, which suggests that multiple dosing may be possible. June explained that the major hurdles in launching the first human trials of lentiviral vectors involved regulatory obstacles (which he felt were appropriate given the potential for insertional mutagenesis with this system), patient enrollment, trying to advance to clinical trials without substantial animal model data, and ensuring institutional commitment for therapy translation. June also learned that gene therapy research funding independent of biotech is needed, because venture capital funding does not typically cover the costs of mechanism-driven studies, immunologic testing, and lifelong safety analyses that are nonetheless required in such cutting-edge trials. He also stressed the need for both empiric phase 1 trials so as not to over-rely on animal model studies, since the late-onset antiviral effects that he saw in patients would have been missed in animal studies. Another lentiviral HIV trial is currently planned—this one a

multi-dose, structured treatment interruption study—and will begin once FDA approval is attained.

Douglas Jolly (Advantagene, Inc.) related his experience in moving retroviral-based factor VIII gene transfer from preclinical to phase 1 clinical trials. Studies in animals receiving the human factor VIII retroviral vector administered by peripheral vein injection demonstrated no toxicity, boosted protein expression with higher or multiple vector-transgene doses, and prolonged factor VIII expression. For example, about 30% of dogs with hemophilia A exhibited long-term factor VIII protein expression, and almost all dogs demonstrated significantly reduced clotting times for up to 2 years, although interpretation was complicated by antibodies to the human protein in dogs. These findings enabled a phase 1 study of the treatment beginning in 1999 enrolling 13 patients with severe hemophilia A (factor VIII < 1%). Over 53 weeks, no serious adverse events occurred, no factor VIII antibodies were observed, and factor VIII expression levels ranged from 1% to 19% in 23% of all observations taken. In addressing why the vector worked well in animals but poorly in humans, Jolly surmised that the animal models were not predictive of certain prohibitive vector-human interactions (e.g., human restriction on the murine leukemia virus). Technical complications involved different vector preparations from the same packaging cell line exhibiting different properties, primarily in terms of titer. How this variability may affect preclinical or clinical outcomes is unknown. During the phase 1 study, 1 time point (out of 10 total) for 1 patient turned out positive for vector presence in semen. Although no additional positive tests appeared for this or other patients in the study, lifting the clinical hold placed on the study created a significant delay. Like many others, Jolly acknowledged that clinical research costs are substantial. He ended by arguing that extensive characterization of the vector system will promote rational responses to setbacks, which will inevitably happen. He also noted that preclinical studies are typically less expensive than clinical studies, but in the end, the clinical money must be spent; deciding when to progress to the clinical phase is the hard part.

Concluding the real stories was Ronald Crystal (Weill Medical College of Cornell University) who discussed gene therapy for Batten disease, also known as Late Infantile Neuronal Ceroid Lipofuscinoses (LINCL). This fatal, inherited disorder of the nervous system is caused by mutations in the CLN2 gene, which encodes the soluble lysosomal enzyme TriPeptidyl Peptidase 1 (TPP1) that cleaves membrane proteins to prevent their accumulation. The gene transfer strategy to treat LINCL involves delivering the normal human CLN2 gene via an AAV2 vector. Initial studies done in wild-type rats demonstrated long-term (18 months) expression of TPP1 in neurons far removed from the injection site—results then essentially repeated in non-human primates. Following a safety assessment of the clinical vector in rats and monkeys and the demonstration of restored protein cleavage following TPP1 production in the CLN2<sup>-/-</sup> mouse model, the decision was made to move these studies to the clinic. To date, 4 children have received the clinical vector by direct injection into the brain. Three children are stable at 7.5 or more months out, whereas 1 child died 49 days after the operation from complications due to status epilepticus. Because children are the primary targets for this therapy and given the risk of death, several ethical issues arise. To preclude some of these difficulties, the protocol is given to the families of potential participants for review, and a sincere attempt is made to dispel all therapeutic misconceptions. At the time of enrollment, the consent process is carried out by the co-investigators, the research coordinator, and a Cornell research subject advocate; the PI is not involved. Like other orphan diseases, Batten disease falls into a funding gap between NIH support and venture capital/pharma monies. The total costs of the clinical study are estimated at \$4 million over 3 years. As a result, funding provided by various foundations (i.e., NIH PI funding, Department of Genetic Medicine, and Nathan's Battle

Foundation) is critical for enabling the research to get done. However, Crystal noted that donating foundations are divorced from control over the clinical research to safeguard against personal motives and to promote the greater good of all.

### **FDA/NIH Perspectives**

The last of the sessions, co-chaired by Stephanie Simek (Office of Cellular, Tissue, and Gene Therapies [OCTGT]/Center for Biologics Evaluation and Research [CBER]) and Kenneth Cornetta (Indiana University/National Gene Vector Laboratory [NGVL]), centered on the FDA/NIH's perspective regarding the challenges in advancing the field of gene therapy. Simek prefaced the session by indicating that although the number of active gene therapy INDs in later phase trials are few in number—more than 160 in phase 1 versus slightly more than 60 in phase 2 and only about 5 in phase 3—the FDA is strongly committed to moving the field forward. She laid out a number of questions focused on safety and efficacy that all parties should keep in mind when devising how to advance their gene transfer research (Table 1). Furthermore, she stressed that academic researchers should remain involved in the transition to phase 3 trials given their wealth of knowledge about the basic gene delivery system that must be carried forward—knowledge that becomes critical if the project encounters a problem and needs to be stepped back to the phase 1/2 level for further refinement.

### **Table 1. Questions Researchers Should Consider to Advance Gene Transfer Research**

- In an ongoing phase 1 clinical trial of a specific gene therapy product, what product changes would require a new IND versus performing a preclinical bridging study to demonstrate safety?
  - If the product changes prompt a sponsor to perform a comparability study,
    - what type of testing should be included in the study?
    - how should the study be conducted?
      - Must a direct, side-by-side comparison of the old and new products be done?
      - Can data from previous lots of old product be used?
  - What type of assay would the FDA accept for use as a measure of product potency?
    - What is the importance/benefit of having a quantitative potency assay?
    - Will the agency accept a qualitative assay if a potency assay cannot be quantified?
  - Do animal studies need to be conducted with the product?
    - Do vector biodistribution studies need to be conducted if there is published data with this type of vector?
    - Do vector toxicology studies need to be conducted if there is published data with this type of vector?
  - What is an appropriate animal model for the vector of study?
    - Must non-human primates be used?
    - Can analogous vectors or transgenes be used in species other than non-human primates?
    - Does the agency accept data in animal models of disease for demonstration of activity? Safety?
    - Do all animal studies need to be GLP-compliant?
  - At what point in time should CBER be contacted to discuss preclinical studies?
  - What types of control groups might be needed for conduct of “adequate and well controlled” clinical studies to support registration for a gene transfer product?
  - How does the FDA determine a study’s designation (i.e., phase 1, 1/2, 2, or 3)? Does the FDA have specific criteria for making this designation?
  - Does the FDA accept clinical study data from trials conducted in countries outside of the US?
  - What advantages does the “fast track” development program designation confer to sponsors?
- 

Daniel Rosenblum (OCTGT/FDA) led off the trio of speakers with his perspective on the preclinical and clinical challenges of gene transfer studies. He stressed that safety represents the primary factor for improving the prospects for gene transfer success. In conjunction with this, he suggested that researchers seek FDA advice and keep the organization informed regarding changes in research plans, be able to adapt strategies to account for new developments, characterize the product mechanism of action to facilitate bringing the product to licensure, begin with a label in mind, and maintain focus throughout it all. He stated, “The first step in

developing products for clinical use is to establish that they are reasonably safe to test in humans.” To that end, the FDA relies heavily on relevant preclinical data to make the assessment regarding a safe starting clinical dose, a safe scheme for dose escalation, and whether a clinical benefit can be obtained without excessive toxicity. The FDA also carefully examines the scientific basis for the clinical study design to verify that the rationale is sound, elements of the protocol have established data to back them, and adequate preclinical data are available to support the proposed clinical trial design. The FDA exists to safeguard against excessive patient toxicity that may occur during phase 1/2 exploratory studies. Hence, all phase 1/2 designs should define the optimal population that is predicted to have the largest clinical benefit at the smallest risk. Phase 2/3 confirmatory studies should be designed with the objective of demonstrating efficacy.

Andrew Byrnes (CBER/FDA) continued this theme by specifically focusing on common challenges in the development of gene therapy products. He stated that researchers are not ready to proceed to pivotal clinical trials until the product has been adequately characterized. Product characterization entails undertaking specific tests to demonstrate product consistency between lots and assuring comparability after manufacturing changes. Above all, product characterization should demonstrate (a) correct identification of the product to verify that the vial contents match the label, (b) potency of the product based on a unique assay to measure biological function (ideally a quantitative measure of bioactivity; e.g., a measure of oncolytic adenovirus viral replication), and (c) product stability throughout all phases of the production process, which can be used to determine expiration dating and shipping and storing conditions. To quell any collective groan from audience members, Byrnes argued that good product development does not just help to get products passed by the FDA; it also can aid in product development and the clinical trial process by generating solid data. In contrast, not properly characterizing one’s product may lead to difficulty in attracting partners and investors, and pivotal trials may be placed on hold until such analyses are carried out. Byrnes further advocated for product characterization by arguing that it is better to uncover problems sooner rather than later, the transition to pivotal trials and commercialization will be easier, a poorly characterized product may lead to unpredictable clinical results, and the expense of product characterization is small compared to the expense of repeating a clinical trial. To succeed at product characterization, the product and manufacturing process should be designed with consistency in mind at the very start, and product characterization should be initiated early.

The last of the presenters, Kenneth Cornetta, discussed clinical trial challenges from the perspective of the NGVL. Formed roughly 10 years ago, Cornetta explained that the NGVL is an interactive, NIH-sponsored group with the goal of supplying investigators with clinical-grade vectors and toxicology support for gene therapy applications. Major lessons that Cornetta has learned in the past several years are that (a) cell lines generated in investigators’ laboratories often do not meet quality standards and (b) investigators are struggling with grant timelines and regulatory issues related to adverse events that stifle the progress of many trials. Cornetta observed that scientists also face many challenges stemming from the rapidly evolving field of vectorology. He mused that “today’s hot vector is tomorrow’s dinosaur,” which limits the availability of guidance documents and tacks on time to the vector production process due to new production and certification assays. In addition, investigators are strapped by financial difficulties owing to limited NIH support that does not last through the many review board hurdles PIs must overcome before clinical trials gain approval; some investigators may need three or more sources of funding for a single trial. PIs also face toxicology challenges since the wide variety of viral vectors makes standardized testing difficult and because traditional toxicology studies are not ideally suited to study biologicals. On the positive side, Cornetta

noted that the science and vectors keep getting better. Moreover, the NIH has had outstanding advocates for research and patient safety, the FDA and scientists from academia have been extremely dedicated to getting the research done, and academic institutions have made major investments in fostering clinical gene therapy.

Following the conclusion of the talks, additional panelists—Maritza McIntyre (CBER/FDA) and Mercedes Serabian (OCTGT)—joined the session participants for a general discussion with meeting participants. One issue that emerged was that, although not traditional, academic institutions can perform phase 3 trials and take a product all the way to licensure if they so choose; biotech/pharma control is not required. Some participants took issue with the fact that phase 1 trials often administer sub-therapeutic doses to patients. The panelists argued that there are ways to design safety trials where sub-therapeutic doses are not administered to all patients. The FDA also indicated that intra-patient dose escalation is a possibility if investigators can prove that the escalation will be safe. One participant asked whether there is any interaction between U.S. and European regulatory bodies to harmonize their regulations, as this becomes an issue for multi-center trials with European partners. The FDA noted that European participants in U.S.-sponsored trials have to comply with FDA requirements just like all U.S. participants. Returning to a common grievance, someone from the audience asked, “No one doubts the importance of regulations, but is there a way to make the process more streamlined for faster production?” For example, the role of the RAC is a source of contention for many researchers, because although it is not an official regulatory body, many IRBs regard it as such, and PIs are forced to follow suit. It was noted that FDA reporting has become more streamlined since the NIH Genetic Modification Clinical Research Information System (GeMCRIS) now allows online filing of reports, and the FDA is also willing to work with investigators when protocol changes are made so that researchers need not necessarily return to square 1 if they can empirically demonstrate that the protocol changes will not affect patient safety.

## **Conclusion**

The concluding portion of the meeting was co-chaired by the co-moderators of the conference, Salomon and High. Salomon recapped issues discussed throughout the meeting by presenters and in conversations following the sessions, emphasizing above all the approaches that will enable the gene therapy field to move forward in clinical trials. To move vectorology forward, Salomon recapitulated that new strategies should be developed to direct integration safely, more attempts should be made to deliver or repair genes without insertional events, gene expression requires better regulation and tissue specificity, and the process of sorting out the best applications for specific vectors must continue. Moreover, he noted that it is critical for academics to approach the gene transfer “product” in the context of the entire process from phase 1 to phase 3 to facilitate biotech and pharma support. Whereas some audience members agreed that scientists need to have the end product in mind to garner funding, others felt this is an inefficient and unnecessary approach since pharma will likely alter the basic characterization of the product to tailor it to their methodology.

In turning to immunology, Salomon commented that immunity should not be viewed as an insurmountable barrier but just as a challenge. To move immunology forward, he noted the potential for developing therapies that do not activate the innate immune response and the use of immunosuppressive therapy, ideally only short term, to repress the innate and adaptive immune responses. More headway can be gained in this area if scientists team with immunologists to overcome immunological problems due to gene transfer.

Major progress has been made in the area of gene transfer vaccines, although persisting uncertainty regarding the selection of appropriate animal models requires resolution and more rigorous pharmacokinetic and pharmacodynamic analyses of gene transfer systems are needed.

In turning to the important topic of the regulatory climate, Salomon observed that multiple players in the evaluation and approval process for clinical trials, each with perfectly appropriate but intensely held views of what is best for the many different stakeholders involved, are actually creating disincentives, delays, and significant obstacles to successfully initiating clinical trials. Everyone agreed that this is not the intention of any group involved and that the whole environment in the United States for the review, approval, and conduct of clinical trials is difficult. In other words, all invested parties have to be careful not to assume that every obstacle is unique to gene therapy. In trying to address these issues, Salomon argued that the best current target for refining the regulatory process involves establishing a constructive dialog with the local IRBs on a national level; however, this can only be done with great sensitivity and must fully respect IRB autonomy and each's special mandate for protecting research subjects and insuring ethical conduct of clinical research. An IRB director in the audience made the salient point that the mission of IRBs does not require justifying their process or their decisions to the physician investigators. Nonetheless, there was a consensus that everyone involved, especially the patients, have a major stake in supporting the success of clinical research. Thus, the ASGT should begin to reach out to IRBs and offer to provide necessary scientific expertise and support when requested in ways that improve the process. However, it is equally important that investigators begin to determine and understand the concerns of the IRBs with applications for clinical trials in gene therapy and work to address these issues proactively with their colleagues.

Other strategies for advancing the field involve improving public perception of gene therapy through education and public outreach efforts. Indeed, since the workshop in April 2005, ASGT has launched a new committee to take on this task. Another need is to increase the level of experience at academic centers regarding clinical trial conduct to support and train the next generation of investigators.

A major sticking point—and one of the most commonly heard grievances at the meeting—involves the issue of funding. First, the focus of pharma on “big markets” creates a funding gap for many current gene therapy targets aimed at relatively small “markets” such as single-gene-defect diseases. This lack of enthusiasm from pharma, albeit understandable in some terms, hinders translation of clinical gene therapy. One line of discussion was that some gene therapy should take on approaches in the major markets like cardiovascular disease, obesity, and diabetes. It was also pointed out that a significant amount of work in gene therapy is now directed at cancer, which is certainly a big market area. Proof of the success of gene therapy in a small-market disease would effectively bring about the necessary attention of pharma. In fact, a venture capital investor in the audience emphasized this point and noted how these issues of success perception were negatively impacting investment in small biotech companies for gene therapy. The discussion also considered the value of academic investigators taking more responsibility for starting projects with a more pragmatic development plan that considers issues to be encountered at later stages of production and implementation for clinical trials. The argument was made that a better plan from the very initiation would position academic advances for much easier acceptance by both small biotech and big pharma when success is demonstrated at the early phase 1/2 stage. However, others argued that this may be difficult to consistently execute when working with cutting-edge technologies where a clear view of later manufacturing and implementation issues is impossible. Finally, the NIH was recognized and applauded for its pivotal role in funding the development of gene therapy and supporting clinical trials through resources such as the NGVL and the NCI's Rapid Access to Intervention Development (RAID)

program. However, it was noted that the technical structure of classic NIH funding does not always mesh well with the timelines faced by researchers trudging through the regulatory process. This may limit early-phase research, reduce institutional interest in supporting this critical but risky stage, and narrow the field, particularly by serving as a major disincentive for young investigators with few of their own resources. A constructive suggestion was to create a more flexible funding structure for clinical trials as well as strategies to support investigators in dealing with the process of planning and approvals. In fact, this strategy is currently in development as part of the NIH Director's Roadmap.

In the final analysis, all workshop participants agreed that there has clearly been significant progress in gene therapy in the last few years, and there remains strong support for the field in many areas. The recent advances in anti-tumor vaccines and in delivery of genes with new vector designs suggest that the gene therapy field is gaining momentum. Identification and mechanistic understandings of the problems the field now faces in vectorology, insertional mutagenesis, and immunity are necessary first steps to designing strategies to successfully address these challenges. In the meantime, the consensus was that the ASGT should work on two areas: (a) educating the public about the successes of and significant progress in gene therapy while ensuring that the failures are not unreasonably exaggerated, and (b) working with all involved stakeholders in the approval and review of clinical trial protocols to improve the process and reduce the disincentives currently recognized.

Many of the summary slides for this workshop can be found on the ASGT web site: [www.asgt.org](http://www.asgt.org).

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