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Perspective

Perspectives on Best Practices for Gene Therapy Programs

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Abstract

With recent successes in gene therapy trials for hemophilia and retinal diseases, the promise and prospects for gene therapy are once again garnering significant attention. To build on this momentum, the National Institute of Neurological Disorders and Stroke and the Muscular Dystrophy Association jointly hosted a workshop in April 2014 on ''Best Practices for Gene Therapy Programs,'' with a focus on neuromuscular disorders. Workshop participants included researchers from academia and industry as well as representatives from the regulatory, legal, and patient advocacy sectors to cover the gamut from preclinical optimization to intellectual property concerns and regulatory approval. The workshop focused on three key issues in the field: (1) establishing adequate scientific premise for clinical trials in gene therapy, (2) addressing regulatory process issues, and (3) intellectual property and commercialization issues as they relate to gene therapy. The outcomes from the discussions at this workshop are intended to provide guidance for researchers and funders in the gene therapy field.

Introduction

Scientific American recently highlighted ''Gene Therapy's Second Act,''[1] a high-profile declaration that gene therapy is on the cusp of a renaissance, possibly even a ''tipping point.'' Whereas significant adverse events once discouraged the field and stake holders, recent successes in hemophilia and retinal diseases have led to a reinvestment in gene therapy research by venture capital and philanthropists (see ''Gene Therapy's Big Comeback'' in *Forbes* magazine).

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Regulatory approval and oversight of gene therapy projects is also adapting to new technologies and has led to renewed optimism for gene therapy. In May 2014, the National Institutes of Health (NIH) adopted the Institute of Medicine's recommendation that routine Recombinant DNA Advisory Committee review of human gene therapy protocols is no longer required, except under special circumstances. As progress in gene therapy has advanced, issues around commercialization and intellectual property (IP) are becoming more pertinent. It would be beneficial to share best practices to guide this clinically nascent field through current and future challenges in therapy development, regulation, and commercialization. All of these matters can have significant impact on the pathways, processes, and paradigms for future gene therapies to reach patients, and thus cannot be ignored.

With these issues in mind, the Muscular Dystrophy Association (MDA) and the National Institute of Neurological Disorders and Stroke (NINDS) jointly hosted a workshop in Rockville, Maryland, in April 2014 on ''Best Practices for Gene Therapy Programs.'' Researchers from academia and the private sector, along with representatives from the regulatory, legal, and patient advocacy sectors, convened to identify key challenges and discuss possible solutions to those challenges for gene therapy development in general and for neuromuscular disorders in particular. Methods for how to identify ''red flags,'' best practices, and broader applications of these guidelines were all part of the discussions. The focus of the workshop was on broad issues and process, rather than on the latest technical advances in the field. The following summary represents the views of the individual authors and not that of the NIH or FDA.

The workshop was organized into three panel sessions: (1) establishing adequate scientific premise for clinical trials in gene therapy, (2) addressing regulatory process issues, and (3) IP and commercialization issues as they relate to gene therapy. In addition, Katherine High, MD (The Children's Hospital of Philadelphia, Howard Hughes Medical Institute, and Perelman School of Medicine of the University of Pennsylvania), shared her experience on these issues across several translational programs. James Wilson, MD, PhD (Gene Therapy Program, University of Pennsylvania), presented a case study of Glybera, the first regulatory agency-approved gene therapy (European Medicines Agency [EMA]). Wilson Bryan, MD, Director of the Division of Clinical Evaluation and Pharmacology/Toxicology, Office of Cellular, Tissue and Gene Therapies (OCTGT), Center for Biologics Evaluation and Research (CBER) of the U.S. Food and Drug Administration (FDA), provided a perspective from the U.S. regulatory agency responsible for reviewing gene therapy products.

Establishing Adequate Scientific Premise for Clinical Trials in Gene Therapy

As with many other translational research fields, one of the major challenges in gene therapy is determining when there is sufficient preclinical rationale for a candidate therapeutic to enter human clinical trials. The discussion on this topic centered around five major themes: (1) starting with the end product in mind by creating a target product profile (TPP), (2) adequacy of decision making as to when optimization is sufficient to move forward, (3) use of the appropriate animal model/species for the intended purpose, (4) determining the feasibility of delivery to the necessary target tissues, and (5) the need to keep gene therapy data, especially as it relates to translational experience, in the public domain.

Critical importance of defining a target product profile

Several workshop participants noted that one of the most common mistakes in therapy development is not having a well-defined TPP in place. A TPP includes a clear goal for the desired effect of a therapy in humans. Phrased differently, the TPP is the anticipated product label that demonstrates the product to be safe and effective. Developing a well-defined TPP at the beginning of therapy development is standard practice in industry, but utilized less in academia and smaller biotech firms. Workshop participants recommended developing a TPP as early as possible and prior to commencing pivotal animal studies. Not only does the TPP guide the design, conduct, and analysis of preclinical studies and subsequent clinical trials, but it also facilitates early communication with the FDA or funding agencies and minimizes the risk of late-stage failures. A well-developed TPP can thus decrease the duration of therapy development overall, generating cost and time savings that more than justify its inclusion in any therapy development program, and funders should consider requiring a TPP in grant applications.

Decision points in moving a candidate forward to clinical testing

Many fundamental questions remain in this rapidly developing field: What is the best vector serotype and delivery route for a given indication? What is the optimal therapeutic transgene construct that fits within a suitable vector yet retains function and minimizes immunogenicity? What are the best model systems to address these questions? Discussion among participants revealed that the answers to most of these questions are still unknown and/or depend on the specific circumstances. For example, structure–function studies on purified therapeutic proteins are revealing the complexities of how removal of certain domains to accommodate vector-carrying capacity can affect the stability of a therapeutic protein. Early studies to ensure that an engineered transgene still encodes a functional, stable protein once delivered to a patient can thus be critical. Other studies have shown that viral vector serotype tropism can differ significantly between animal models and humans, leaving the informative power of these preclinical studies to be interpreted with discretion. During optimization, production process development is a critical consideration; any changes in vector production processes during the scale-up toward good manufacturing practices (GMP) may impact the comparability of product across studies.

It is therefore challenging to find the right balance between optimization of vectors and/or constructs and proceeding with an elected clinical candidate for investigational new drug (IND)–enabling studies and other development activities. On the one hand, a large investment is required to move a candidate to the clinic, and therefore it is desirable to select the most optimized and state-of-the-art agent to go forward. On the other hand, gene therapy will likely improve in an iterative process from the bench to animal models to early phase human studies and likely back again. In her opening remarks, Katherine High stressed that ''perfect is

the enemy of the good,'' a warning not to let time slip by pursuing perfection when an adequate therapeutic candidate may already be in hand.

The use of animal models in preclinical gene therapy research

A significant point of discussion was the utility and value of animal models in preclinical gene therapy development. The fact that animal models do not recapitulate the entire pathophysiology of human disease or side effect profiles following treatment is widely accepted, yet we have learned a tremendous amount from the study of *in vivo* model systems. The critical issue in this discussion was choice of an appropriate animal model in the context of a particular combination of vector, disease, and therapeutic intervention. Large animal models may allow for a more relevant comparison to the human setting in terms of scale, delivery route, surgical access, and host response to vector and/or transgene product. Many of these aspects can be explored in unaffected animals. Regardless of what animal system is used however, Mercedes Serabian, MS, DABT (CBER/FDA), summed up the discussion eloquently by noting that ''animals don't predict, they inform.''

Several workshop participants stressed the importance of setting a high bar for the magnitude of effect in animal studies to justify human trials. A reduction in efficacy from animal models to humans is to be expected due to several factors, including complications with vector scale-up or delivery, immune response (discussed below), and the more heterogeneous nature of human populations. A robust therapeutic effect in animal models, and not just attaining statistical significance, is thus important for increasing the chances of sufficient expression levels and therapeutic effect in humans. The thought that modest effects in an animal model may be exceeded in human studies was not regarded as a likely scenario and therefore not considered as adequate rationale for proceeding to clinical trials. This bar for efficacy in preclinical animal studies should be included in the TPP.

Lastly, the potential for intrinsic differences in immune response to gene therapy in animals versus humans was discussed. Viral vectors can elicit dramatically different immune responses (or even a lack thereof) in humans versus animals, complicating interpretation of efficacy studies in many cases. To better understand how the immune response may be affecting results, neutralizing titer studies on both the vector and transgene product should be conducted and reported both acutely and by long-term monitoring. Host immunity is also an important factor in deciding what species transgene to use in an animal model, an issue that is often approached inconsistently in the field. For example, many researchers have delivered the human transgene to an animal model that carries the potential for a significant immune response confounding their results, or have used immune-suppressed animals to avoid that complication. To avoid this, some workshop participants suggested that the transgene sequence to be evaluated for efficacy and preliminary safety should be from the same species as the animal model it is being tested in. However, one caveat to this is that delivery of the host species transgene to a ''null'' animal model in which the gene is deleted can also lead to a significant immunological response. Thus, for the evaluation of preclinical efficacy and safety, the transgene species used should be carefully considered based on the biology, the approach, and regulatory input. Good laboratory practice (GLP) safety studies typically need to use the final human product.

It was clear from the discussions that animal models remain a critical tool for researchers in the gene therapy field. However, workshop participants also acknowledged that we cannot rely on them solely, and that small clinical trials can be highly informative in reorienting a field based on human data. The overarching recommendations from the workshop on the matter of animal model use for efficacy and safety evaluation included the following: (1) *in vivo* models should be used to test specific hypotheses or answer-specific questions that the model can provide information on (fit-for-purpose), (2) large animal models should be utilized when available and appropriate, (3) a robust magnitude of therapeutic effect is an important consideration for translation to humans, and (4) exploratory clinical trials with few subjects can be valuable in ensuring a therapy's safety and potential for efficacy in patients.

Determine the feasibility of delivery to the necessary target tissues

Gene therapy for neuromuscular diseases offers some specific challenges with respect to delivery of gene therapy products. For example, when delivery to skeletal muscle is required, a considerable mass of body tissue must be adequately transduced. In some diseases, it is thought that delivery to muscle without correction of the heart could be harmful and vice versa, and so development of strategies for codelivery to skeletal and cardiac muscle is required. Considerable research into adeno-associated virus (AAV) vector tropism is addressing the issue, but it is currently unclear how the vector tropisms will translate from animals to humans. A further consideration with muscle disease is that currently available AAV serotypes do not target muscle stem cells, raising at least one reason why readministration may be required in pediatric populations. For neuromuscular diseases with central nervous system (CNS) consequences, the challenges include crossing the blood–brain barrier. In pediatric diseases where the primary therapeutic target lies in the CNS (e.g., spinal muscular atrophy [SMA]), early diagnosis and systemic treatment may have potential. Otherwise, intrathecal delivery strategies may be needed (e.g., amyotrophic lateral sclerosis, myotonic dystrophy, also SMA).

Learning from what has come before: keep gene therapy data in the public domain when possible

The therapy development literature is replete with cases of promising therapies in mice or other preclinical models moving on to clinical trials only to fail to show efficacy. Similarly, negative publication bias can result in the unintentional duplication of efforts likely to fail. Many therapeutic development studies also lack critical factors needed to avoid potential bias, including randomization, blinding, and sufficient statistical rigor. Workshop participants unanimously agreed that complete and detailed descriptions of experimental design, methods, and analysis are critical for ensuring that therapies moving forward are based on rigorous preclinical data.[2] Additionally, keeping data and/or reagents in the public domain via resources

such as the National Gene Vector Biorepository and the Genetic Modification Clinical Research Information System (GeMCRIS) would be profoundly beneficial for allowing researchers to learn from what others have done and for integrating this material and knowledge into the design of future experiments and trials. Many noted that sharing data can be more complicated when the data are collected or supported by the private sector, but added that some companies are becoming more open to making at least some of these data publicly available. Indeed, various forums exist for publishing preclinical data related to pharmacology, toxicology, and biodistribution, as well as data relevant to regulatory review and commercial development.

Addressing Regulatory Process Issues

We are at a significant juncture in the progression of gene therapy development. Starting in 2014, the first gene therapy approved for sale, Glybera, is expected to become available to patients in Europe. As highlighted here and discussed more extensively elsewhere,[3] trailblazing is never easy or without issues, and this was certainly the case for Glybera. However, we now have a case study from which we have already learned important lessons on what can be expected of gene therapy developers and regulators in the future.

The Office of Cellular, Tissue and Genetic Therapies (OCTGT) within CBER at the FDA is tasked with reviewing gene therapy products. Wilson Bryan discussed the general stages of FDA review and reiterated the importance of having a TPP. He also stressed the importance of early interactions with the FDA, describing both pre-pre-IND interactions and pre-IND meetings where establishing proof of concept, the target patient population, and planned dose and route of administration are all discussed. The FDA has the difficult task of evaluating the risk and benefit evidence provided, and determining what is acceptable in the context of a given disorder on a case-by-case basis. Given the wide variety and heterogeneity of disorders and therapies, the FDA has a number of approval mechanisms to help meet these challenging demands, including accelerated approval (approval based on surrogate endpoints for serious conditions), breakthrough therapy designation (based on preliminary clinical data indicating that a therapy is a substantial improvement over what is currently available), and orphan drug designation (to encourage the development of therapies for rare disorders), among others. Wilson Bryan recommended gene therapy developers start with a TPP, have an idea of how phase 1–3 clinical trials might look early in the process, and stressed the importance of starting natural history studies early if such data are not available yet, given the long timeframe and critical details these studies provide. One factor Bryan reiterated throughout his presentation was that a trial should be scientifically valid—meaning that it has a high likelihood of generating informative data, and is based on a compelling scientific rationale. Trials lacking a strong scientific rationale risk not only patient safety but also the significant expenditure of resources with little to no generation of new knowledge.

Considerations for gene therapy trials in pediatric patients

One of the most significant areas of discussion that occurred during this session was on the issue of gene therapy trials in pediatric patients. Because children are unable to provide informed consent, the acceptable risk for a trial is significantly less and investigators must provide evidence of possible direct benefit. It was pointed out, however, that assessing risk is inherently subjective. Indeed, a 2005 report in the *Journal of the American Medical Association* concluded that institutional review boards implement the federal minimal risk standard for pediatric research inconsistently as a clear interpretation of the standard is lacking.[4] All of this makes for a complicated calculus in determining how studies should be conducted in this underserved but vulnerable population, leading Katherine Klinger, PhD (Genzyme Corporation, a Sanofi Company), to suggest that we need to determine the equipoise between ''a right to safety and a right to treatment for pediatric patients.''

Weighing risks versus benefits is particularly challenging for pediatric patients with neuromuscular disorders, as many are progressive and have an early onset. A large number of workshop participants felt that the best chance for treating many childhood-onset neuromuscular disorders was early intervention in very young patients. However, Wilson Bryan urged the community not to give up hope that interventions later in disease progression could be effective, stressing again the difficulty in weighing the risks and benefits of novel therapies in young children or even infants. Valuable insight on this issue has recently emerged with the IND approval of a gene therapy for SMA type 1 in patients 9 months of age or younger (ClinicalTrials.gov number NCT02122952). The trial is being conducted at Nationwide Children's Hospital and provides an example of an interventional trial in a neuromuscular disease being approved in very young patients.

Case study: lessons learned from Glybera, the first gene therapy approved in the West

There is also now for the first time precedent for regulatory marketing approval of a gene therapy. In 2012, the EMA approved Glybera (alipogene tiparvovec), an AAV-based gene therapy for lipoprotein lipase deficiency (LPLD), a condition leading to lipid accumulation in the blood and pancreatitis. As most first efforts go, the approval process was not without a few setbacks, most notably rejection by the EMA on the first three attempts. James Wilson presented a case study describing the lengthy approval process of Glybera and the lessons that could be learned from it.[3] Perhaps one of the most significant challenges for the investigators developing this gene therapy was the exceedingly small number of patients available. LPLD is an ultra-rare condition, affecting approximately one in one million people. This made patient recruitment challenging and complicated statistical analyses. Additionally, the natural history of the disease was not thoroughly characterized, which complicated nearly all aspects of the clinical development plan. In fact, the primary efficacy endpoint was determined to be too variable to provide meaningful information in the course of the trials, and subsequently changed to a more suitable marker.

Demonstration of efficacy was hampered by the fact that it was difficult to detect the therapeutic transgene and there were only minimal changes in clinical endpoints. Early studies suggested that an immune response may have been

suppressing expression of the therapeutic transgene, and so the trial sponsor added immunosuppressants in subsequent clinical trials. This had proven beneficial in gene therapy trials for hemophilia, and so there was precedent for such a move. However, in the case of Glybera, there was no correlation of immunosuppression with efficacy, and in fact, quality-of-life outcome measures were decreased in immunosuppressed patients. Thus, the use of immunosuppression in clinical trials should be considered judiciously. Another challenge encountered during the development of Glybera related to the use of the human transgene in the preclinical efficacy studies in a feline model of LPDL. While the feline model served as a good approximation of the human disease, the animals developed a robust immune response to the human transgene product, confounding the interpretability of the preclinical efficacy data.

Finally, like all biologic therapies, manufacturing and production can have a significant impact on the safety and efficacy of a biological therapy. During the initial trials for Glybera, the trial sponsors changed their vector production system to be more amenable to large-scale production. Since ''process is the product'' in biologic therapies, this introduced a number of new variables that may have confounded efficacy and safety data. In fact, during the approval process, the developers of Glybera were forced to repeat several critical safety and efficacy studies using vector produced from the scaled-up process in order to ensure that this vector was comparable to that produced with the initial system. Because of the significant amount of time and capital required to scale up gene therapy vector production, it is unlikely that these systems will be in place for most initial human clinical trials. Thus, the issue of vector production and scale-up will remain a critical factor that researchers need to consider as they move therapies forward. While many issues were raised and discussed regarding what can be learned from the lengthy approval process for Glybera, it is worth noting that pharmacology and toxicology data were quite promising throughout the trials and that, in the end, Glybera is a significant milestone in the field.

IP and Commercialization of Gene Therapy Development

As an increasing number of gene therapies are reaching pivotal clinical trials, the issues of IP and commercialization will need to be addressed in order to ensure that effective gene therapies can be brought to patients as efficiently as possible. Discussions in this session centered on the highly complex nature of IP in gene therapy and potential ways to catalyze its development and commercialization.

Luk Vandenberghe, PhD (Massachusetts Eye and Ear Infirmary and Department of Ophthalmology, Harvard Medical School), highlighted the two-sided nature of IP protection in gene therapy, with IP as both a friend and a foe. At present, there are patents relating to most aspects of gene therapy ranging from the capsid and transgene cassette design to the manufacturing method, route of administration, and quality control assays utilized. Patents in these areas are scattered in terms of ownership and licensing rights across dozens of parties in the academic and private sector. Vandenberghe pointed out that IP is incredibly important for driving a field forward by creating an incentive to create and disclose information and data while helping to promote economic growth and development. However, IP can also be a hindrance by blocking access to critical tools and reagents, often with high licensing fees leading to a disincentive for innovation, possibly complicating the maturation of a budding clinical and commercial era in gene therapy. One possible way to address IP concerns is to expand the precompetitive space, where development costs could be reduced, manufacturing standardized and centralized, and the open sharing of data enabled. The importance of the precompetitive space was also emphasized as being especially critical for rare disorder therapy development, where commercial support may be more difficult to recruit. Models for this kind of precompetitive resource can be found in the World Intellectual Property Organization Re:Search program, which pools IP for development of new therapies for neglected tropical diseases.

Other panelists noted that a further complication is that much of the IP in gene therapy remains untested in court, creating a significant amount of uncertainty. The *Myriad Genetics* Supreme Court case regarding the patenting of the *BRCA* genes was discussed as a recent high-profile example, which made it clear that isolated, native gene sequences are no longer patentable. While many patents covering isolated gene sequences are beginning to expire, thereby dampening the effects of *Myriad*, the effect of *Myriad* on patents directed to other types of subject matter is still unclear. In response to the Supreme Court ruling, the U.S. Patent and Trademark Office (U.S. PTO) released guidance stating that anything found in nature or synthetically manufactured but still identical to what is found in nature is not patentable, expanding the decision to other naturally occurring products beyond genes. Furthermore, making only routine or conventional changes to a natural product may not be sufficient to create patentable subject matter. How one defines ''routine'' or ''conventional'' remains unclear and may change over time, however. Would adding a promoter or other regulatory element to a therapeutic transgene be considered routine or conventional and thus render the subject matter not patentable? The full effect of *Myriad* on the strength and obtainability of patents in the gene therapy space will likely remain uncertain for many years as the U.S. PTO and courts gauge the breadth of the *Myriad* holding.

Given the rapid advances we have seen in the gene therapy field and subsequent changes to IP policy and laws, one question discussed was how involved should a preclinical researcher, therapy developer, or patient advocacy group be in the IP realm? While researchers cannot ignore IP concerns, several workshop participants felt that given the still relatively young stage of the field, it would be better to focus on developing the best possible therapy independent of IP concerns, and that it would not always be reasonable for funding bodies to ask researchers to ensure that they can operate without IP restrictions. Other participants noted that more patient advocacy groups should take a keen interest in IP, and that IP in some cases can give these groups powerful leverage and be essential for partnerships and commercialization. In any event, with a significant body of the IP surrounding gene therapy approaching expiration, there is the possibility that some of these concerns may become less significant while others may become even more complicated.

Table 1. Summary of Recommendations from Workshop

Establish a target product profile early.
Determine an administration route that is feasible, based on vector dose, frequency, and targeted tissues.
Optimize a gene therapy product early in development and commit to a candidate prior to initiating investigational new drug–enabling activities; plan for manufacture and scale-up.
Aim for a robust therapeutic margin in preclinical efficacy studies and make use of large animal models when available.
Consider potential impact of immune response to vector capsid or transgene and explore use of immunosuppression based on the best animal data available, and reconsider after initial clinical data are obtained.
Plan for what clinical trials will look like and keep this in mind during development.
Conduct natural history studies early if needed for obtaining robust clinical data and readouts (time points for intervention, clinical endpoints, and biomarkers).
Talk early and often with FDA Center for Biologics Evaluation and Research and European Medicines Agency (EMA).
Share data openly as much as possible.
Work toward standardization of methods, assays, and protocols, to the extent appropriate and possible.
Consider expanding, and utilizing more extensively, the precompetitive space to facilitate efficient and unfettered technology development.
Move toward harmonizing regulations at EMA and FDA.

Conclusions and Recommendations

Gene therapy for neuromuscular disorders faces a number of challenges, including reaching the vast amount of muscle distributed throughout the body, accessing motor neurons behind the blood–brain barrier, the early onset and relative low prevalence of many progressive neuromuscular disorders, and the complex regulatory processes, IP, and economics underlying therapy approval and commercialization. One of the most significant themes that underlay several of the sessions was that of ''identifying a path forward'' during therapy development. This includes establishing a well-defined TPP, having a plan for what phase 1–3 clinical trials might look like, and making decisions on endpoints and model systems with these goals in mind (see Table 1). Howard Federoff, MD, PhD (Department of Neurology, Georgetown University Medical Center), recommended that researchers ask themselves, ''Is there a path forward, and what does it look like?'' at each stage of development.

In a similar vein, discussion throughout the day revealed that the field lacks or does not sufficiently utilize standardization criteria that could facilitate comparisons ranging from models to laboratory practices to regulatory policies. Can a standard set of viral vectors be agreed upon? Can standards for the use of animal models, and most notably what model to use and when, be determined? Can standard screens be agreed upon for toxicology and pharmacology studies? Similarly, could standard methods for vector production at preclinical and clinical stages be established? Could guidelines to aid investigators in pursuing an IND for use in pediatric populations be established? At present, many of these questions are addressed uniquely by individual investigators at different institutions. While workshop participants cautioned against stifling the ingenuity of these solutions by creative minds in the field, having standard models or protocols could allow for more direct comparisons of studies across laboratories and also serve to inform the regulatory process. If and when any of these standards are established, getting buy-in from researchers, funders, and regulatory agencies will be critical.

Finally, no research enterprise can thrive without the funding to support it. Before the recent re-investment by venture capital and industry, the gene therapy field was primarily sustained by scientific societies, patient groups, academic medical centers, and federal sources. While funding was limited, the nature of these sources allowed researchers to proceed free from commercial pressures and to pursue the most critical scientific questions. The newly burgeoning interest of the private sector creates new opportunities but should serve as a reminder to be mindful of how limited resources can best be allocated depending upon the interests and missions of each type of funder. Industry by its nature is driven by economic motives and thus is likely to focus on therapies with a more rapid return on investment and market size that meets its economic needs. This leaves federal and philanthropic funders to support more long-term projects in complex and rare conditions. Many participants felt that leveraging the available funds from nongovernmental organizations and federal sources would be critical to maximize the reach of these resources, potentially through data sharing, cost sharing, or other new innovative funding models. Regardless of the source, the clear interest from venture capital, industry, patient advocacy groups, and federal funders supports the palpable optimism underlying this renaissance for gene therapy.

Disclaimer

The views expressed in this summary are those of the individual authors and do not represent the views of the NIH or FDA.

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Author Disclosure Statement

Robert H. Brown is a consultant of Voyager Therapeutics. Barry J. Byrne is an inventor of IP owned by the Johns

Hopkins University and the University of Florida related to this research. B.J.B. is also a founder of Applied Genetic Technologies Corporation (AGTC) and owner of founder equity. B.J.B is an unpaid member of the Scientific Advisory Board of Audentes Therapeutics and Solid GT, LLC. Dongsheng Duan is a member of the Scientific Advisory Board for Solid GT, LLC. Howard J. Federoff is the founder and an advisor to MedGenesis Therapeutix, an advisor to Ovid Inc., and the chair of the Gene Therapy Resource Program, NHLBI. Katherine A. High is currently the president and chief scientific officer of Spark Therapeutics. K.A.H. holds equity in Spark Therapeutics. Brian K. Kaspar had intellectual property filed through Nationwide Children's Hospital and an equity interest related to work that is licensed to AveXis Inc. and Milo Biotechnology. B.K.K. also serves as a paid consultant for AveXis and Milo. The relationships are managed through a conflict management plan at Nationwide Children's Hospital. Katherine W. Klinger is employed by Genzyme Corporation, a Sanofi Company, which has gene therapy programs. Jane Larkindale has had and may have consulting work with companies and nonprofit groups that operate in the gene therapy space. James McLaughlin is employed by Voyager Therapeutics, which is currently developing rAAV therapeutics. Luk H. Vandenberghe holds equity in GenSight Biologics, consults for Novartis Pharmaceuticals and Jefferies, and is inventor on patents related to gene therapy that are licensed to several nonprofit, pharmaceutical, and biotechnology entities, some with programs or interest in muscular dystrophies. James M. Wilson is an advisor to REGENXBIO, Dimension Therapeutics, Solid Gene Therapy, and Alexion, and is a founder of, holds equity in, and has a sponsored research agreement with REGENXBIO and Dimension Therapeutics. In addition, J.M.W. is a consultant to several biopharmaceutical companies and is an inventor on patents licensed to various biopharmaceutical companies. No competing financial interests exist for all other authors.

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