MEETING SUMMARY

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Future Directions and Resource Needs for National Heart, Lung, and Blood Institute (NHLBI) Gene Therapy Research: A Report of an NHLBI Workshop

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Summaries of presentations of all meeting participants listed in the Acknowledgments section were included in this report.

INTRODUCTION

Over the past 30 years, the National Heart, Lung, and Blood Institute (NHLBI) has been a leader in gene therapy research and has proactively provided investigators with research resources through various programs. One such program, the NHLBI Gene Therapy Resource Program (GTRP), was first launched in June 2007 and is now in its third iteration, which runs through December 2023. To develop the next generation gene therapy resource and support program, NHLBI sought input from the research community. Therefore, the NHLBI convened a 2-day virtual workshop entitled, ''Future Directions and Resource Needs for NHLBI Gene Therapy Research'' on March 15 and 16, 2022.

The purpose of this workshop was to bring together experts in the basic science, preclinical, translational, and clinical aspects of gene therapy to evaluate the current, near, and future directions of the field of gene therapy, including the evolving role of gene editing. The panel was asked to address the hurdles faced in advancing research on emerging gene therapies for heart, lung, blood, and sleep disorders and to identify the resources, training, and other opportunities to advance the field.

EVOLUTION OF GENE THERAPY AND THE CURRENT STATE OF GENE THERAPY AND GENE EDITING

Autologous hematopoietic stem cell (HSC) gene therapy is a well-established paradigm and researchers have conducted trials with lentivirus/HSC agents for at least 15 disorders with positive results, though some adverse events have also occurred. Therefore, constant vigilance, transparency, and collaboration for risk mitigation to maximize patient safety remain the highest priority in gene therapy research.

Although researchers have made substantial progress in gene therapy, several goals remain, including replacing

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cytotoxic chemotherapy conditioning with safer alternatives; improving the consistency of engraftment of gene-corrected HSC, either lentivirus or edited; applying new methods of gene editing to more diseases; realizing *in vivo* gene delivery to HSC; reducing manufacturing costs for vectors and cell products; and developing noncommercial mechanisms to treat ultrarare diseases.

The field now has a line of sight for disease correction with genetic therapies, but rare disease programs have been deprioritized in industry, and the time and costs related to the development of gene therapies for *ultra*rare diseases are even more challenging. Because industry funding is not consistent or sustainable, other sources of support for gene therapy research and development remain critical.

The gene therapy field is now in the age of editing genes, which will transform medicine. Gene editing has a robust technical base with expanding clinical testing and solid delivery innovation. *In vivo* gene editing is being used in clinical research stage applications for various inherited diseases, but researchers continue to define its associated immune responses and efficient delivery to targeted tissue/cells. In the area of *ex vivo* gene editing, some experimental agents show clinical efficacy, and researchers are studying precision editing and next-generation clustered regularly interspaced short palindromic repeats (CRISPR) tools.

However, many promising preclinical findings are not moving to the translational/clinical phase due to challenges navigating the somewhat siloed preclinical and regulatory landscape, as well as due to bottlenecks in the chemistry, manufacturing, and control (CMC) space and supply chain issues. In addition, to realize the promise of CRISPR and other gene editing technologies as future therapies, the regulatory framework will need to be updated for better harmonization and efficiency in the setting of optimal safety. There is a unique role for federal and state governments in supporting and enabling clinical development in the academic/nonprofit sector.

EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

Remarkable progress has been made across various classes of genome editors—nucleases, base editors, transposases/recombinases, and prime editors. This has led to an explosion of future therapeutic possibilities.

Base editing and prime editing

There are methods to precisely correct genes, which can potentially treat the effects of pathogenic human genetic variants. This approach is possible because programmable nucleases are well suited to install or correct only a minority of pathogenic alleles in most cell types. Nucleases primarily disrupt target genes, and base editors correct single-base pair mutations without cutting.

Base editors install or correct the four most common types of point mutations at target DNA sites without requiring double-stranded break, donor DNA templates, or homology-directed repair (HDR). CRISPR-free base editors enable the first precision editing of mitochondrial DNA. Single-dose *ex vivo* and *in vivo* therapeutic base editing is ongoing in animal models as a potential treatment for hypercholesteremia. In addition, base editors can correct pathogenic mutations other than transitions.

Prime editing uses nicked target DNA to prime reverse the transcription of edited sequence encoded in a prime editing guide RNA (pegRNA) and to correct pathogenic alleles and sequence tags. Prime editing is a very versatile technique and allows researchers to make small insertions or deletions of dozens of base pairs. Prime editing efficiencies have been improved by identifying bottlenecks, resulting in improved pegRNAs. Directly copying edited information from a pegRNA into a target site is possible and has advanced with engineered pegRNAs and prime editing systems P4/PE5 and PEmax.

Gene editing for immune diseases

Throughout the past 20 years, the genetic basis for >400 inherited immune disorders has been identified. The study of these rare diseases has led to new insights into human immune function and this knowledge has the potential to generate novel therapies for more common immune disorders and cancer. The ultimate therapeutic goal is to efficiently correct genes or edit primary human cells for curative cell therapy and there is vast potential for curative cell-based genetic therapies.

A major technical advance toward this goal includes the efficient gene modification by HDR in primary hematopoietic cells. One example of a gene-edited therapeutic cell product is thymic regulatory T cells (tTregs) for autoimmune and autoinflammatory disorders. Clinical trials using tTregs are ongoing for type-1 diabetes mellitus, graft versus host disease, solid organ transplant, and viral acute respiratory distress syndrome. However, some major challenges to using Tregs in clinical trials include the low frequency of tTregs requires both extensive purification and *ex vivo* expansion, Tregs exhibit instability and plasticity *in vivo*, Tregs from patients may be defective, and there is no enrichment for antigen specificity.

However, researchers have developed strategies to harness antigen-specific Tregs and they can also generate engineered Tregs (engTregs) for the treatment of autoimmune disorders with engTregs exhibiting a natural Treg-like immunophenotype.

A second example is engineering protein-secreting plasma cells through HDR in primary human B cells. Codelivery of ribonucleoprotein and adeno-associated viral vector (AAV) donor templates results in efficient HDR and generation of long-lived plasma cells expressing therapeutic proteins. Therefore, engineered plasma cells could serve as

a therapeutic delivery platform for many different conditions. Another intriguing aspect is that it may be possible to engineer Tregs or B cells to allow for redosing.

Emerging genome editing therapeutics

In this inspiring era of promising genomic medicines, to realize the promise of gene and cell therapies, it is crucial to advance the intersection of three areas: control of DNA repair outcomes, deliver to the required cells and tissues, and specificity for the DNA target. Scientists have made remarkable progress across various classes of genome editors—nucleases, base editors, transposases/recombinases, and prime editors—which has led to an explosion of therapeutic possibilities. In addition, novel approaches including post-transcriptional editing to modify mRNA levels of target genes have seen success.

Prime editors are transformative for the field, and nuclease and base editor approaches have shown promise in treating sickle cell disease (SCD). Genome editing approaches to treating SCD include post-transcriptional reduction in BCL11A mRNA and disrupting BCL11A enhancer in SCD hematopoietic stem and progenitor cells (HSPCs), correcting HBB gene sickle mutation in SCD HSCs, and base editing of SCD HSCs. Of course, when delivering autologous cell therapies, the entire process is important, not just the gene editing *per se.* Safety issues must always be considered and can be improved by using advanced methods for defining genome-wide activity of genome editing nucleases or complementary cellular and biochemical methods.

Challenges for gene editing for curing SCD include the expense of *ex vivo* gene editing, current problems related to *in vivo* gene editing (*e.g.,* need to achieve a high editing rate and the potential of off-target organ/tissue editing), and difficulty achieving high efficiency in delivering the gene editing machinery to HSCs *in vivo.* In addition, viral vector-based *in vivo* delivery may suffer from uncontrollable expression of the editing machinery, causing immune responses and/or genotoxicity. Another problem is the pre-existing immunity to Cas9, which a large portion of humans exhibit, raising important efficacy and safety concerns for CRISPR/Cas9-based *in vivo* gene editing. However, animal research suggests that self-deleting AAV-CRISPR reduces this immune response.

When considering future directions for the field, it is important to build a shared pathway toward clinical trials of genomic medicines, with clear milestones along the way to investigational new drug (IND) clearance and clinical trials. In addition, funders should support trials that share and publish information. Safety can be improved by understanding the effects of pre-existing clonal hematopoiesis of indeterminate potential or unintended off-target mutations on cancer risk. Researchers might also perform important longitudinal characterization to establish baseline data and defining the impact of patient-specific genetic variation on editing to improve safety. Finally, researchers must attempt to anticipate and prevent safety issues rather than simply learning from emergencies.

Lipid nanoparticles for overcoming biological barriers to *in utero* mRNA delivery

Engineered lipid nanoparticles (LNPs) have the potential to overcome biological barriers to mRNA delivery into target tissues and cells beyond their use as vaccines. Such delivery technologies can target a wide variety of cells and tissues such as immune cells, stem cells, brain, heart, kidney, lung, liver, tumors, and bone. LNPs can serve as delivery technologies for nucleic acids *ex vivo, in vivo,* and *in utero*.

Ionizable LNPs may have the potential to be used for genome editing *in vivo* and also *in utero* to potentially knock out deadly mutations before birth. The benefits of *in utero* delivery include uptake into progenitor cells during rapid cell division, circumventing adverse immune responses due to the immature immune system, and allowing for treatment before the onset of irreversible pathology.

Nonviral gene editing technologies may overcome the limitations of viral vectors, but there are challenges with LNPs such as redosing and limited scalability. A major issue is efficiency of transduction of targeted tissues or primary cells. Redosing challenges may be addressed by rational design of anti-inflammatory LNPs for mRNA delivery. Scalability for formulating mRNA LNPs at an industrial scale might be addressed by the fabrication of a scalable polydimethylsiloxane-based parallelized microfluidic device for precise and large-scale LNP formation.

CHALLENGES IN CLINICAL TRANSLATION AND IMPLEMENTATION

Challenges and lessons learned in moving from bench to bedside

When addressing early life disease, adaptive immunity can be a barrier to effective gene therapy, preventing the use of gene therapy more than once in some cases. Immune responses in current studies include myocarditis, liver toxicity, and immune suppression for null mutations. Therefore, researchers need to understand how pre-existing immunity affects the response to gene therapy. Studies must manage environmentally acquired preimmunity (*e.g.,* ~50–60% of children may have prior AAV exposure, and preimmunity to AAV is an exclusion criterion for most studies and clinical eligibility).

Researchers can perform immune profiling with commercially available products and try to manage the immune response of patients. Patients can also show classical complement pathway activation. Although the immune response to the AAV capsid and transgene is universal or a drug-class effect, systemic AAV dosing along with immune modulating agents such as rituximab and sirolimus, and antibody blockade if needed, may allow for repeated dosing and mitigate the immune responses to the transgene in null mutations.

The path to clinical translation presents several other challenges aside from those related to immune issues. Academic laboratories that are supported by typical federal funding mechanisms are well suited to conduct proof-of-concept studies, but further studies to support IND applications are difficult to fund through these traditional federal grant funding mechanisms. In addition, early input from regulatory consultants could potentially streamline translational development as academic researchers often need regulatory consultants informed in biological therapies to develop study plans.

Other hurdles in advancing translational work include the costs of investigational agents and the animal studies needed for efficacy and toxicity studies. The production of large amounts of clinical-grade vector and gene-editing agents needed for clinical research is expensive, as are large animal studies conducted in a good laboratory practices environment for biodistribution and toxicity assessments. The total costs of these can be in the millions of dollars, which is prohibitively expensive for many, if not most, academic researchers. Although industry partnership is often available for the translation of agents with potential commercial viability, the translational development of agents for rare and ultrarare diseases may languish for lack of funding options.

Challenges and lessons learned in funding/conducting clinical trials

In the early phases of gene therapy clinical trial development for rare diseases, federal, charitable organizational, and institutional ''start-up'' funding can be key to success as it can be challenging to obtain outside funding such as from industry, government, or organizational sources. Even if funding from peer-review processes becomes available, major expenses have often already been incurred, discouraging science-driven translation and stymying innovation. Other challenges in clinical trials for rare genetic diseases are the long accrual timelines, high trial costs, and challenging regulatory requirements both domestically and internationally that specifically lack harmonization.

In addition, for gene therapy clinical trials, it is essential to have good natural history data as a comparator for the disease under study as it is difficult to include a placebo arm. These natural history data are also important for the development of appropriate, measurable, and biologically relevant clinical endpoints for the trials. To evaluate gene therapy platforms, the field needs studies that show improvement in functioning (*e.g.,* in neurodevelopmental or neurodegenerative diseases) rather than stabilization. Securing funding for the Food and Drug Administration (FDA) requirement for 15-year follow-up of participants in some gene therapy trials is also quite challenging for academic investigators.

Ideally, funding for long-term follow-up would be supported by the agencies that provide the short-term gene therapy initiation funding, and centralized facilities that can bank participant samples would be available.

The foundation for late-stage gene therapy clinical trials is similar to that of phase II trials and offers an opportunity for the field to learn, adapt, and improve for the future. Several key lessons have been learned, including the fact that developing the CMC work must occur in parallel with the basic science, translational research, and clinical development. The analytical characterization of gene therapy products, which the FDA expects, is in the very early stages and needs to be more robust and precise. The development of molecular tools to predict safety risks to trial participants before they occur is also an important goal. Organized leadership in this effort would benefit the entire gene therapy community.

In addition, clinical studies must be transparent when safety events occur, because of the heightened interest in these trials and intense scrutiny of this therapeutic modality. Safety in these trials is paramount, and researchers must work in partnership with the patients, and often disease groups, and recognize that individual factors contribute to safety. When there is a particularly noteworthy adverse event, there is extensive collaboration across industry, academia, and regulatory agencies both to address the current issue and to mitigate potential future risks.

Despite years of progress in gene therapy, one challenge that remains is that research still requires large number of vector or editing reagents. Making clinical-grade vectors, nanoparticles, and other means of delivery is generally out of the scope of individual investigator laboratories and is an area where support is needed. Funding to treat the initial participants to establish proof of concept in humans and provide the initial steps to derisk the therapy is critical for trials to transfer from academia to industry.

Possible solutions are being investigated, including methods to target fewer cells by enriching a particular cell subpopulation, approaches to enhance transduction efficiency, and reducing the number of cells used in gene therapy through CRISPR/Cas9-edited HSPCs. A second challenge is that gene therapy is limited to specialized facilities. Two possible solutions are manufacturing lentivirus gene-modified HSCs for gene therapy in portable devices and syringe-delivered *in vivo* gene therapy with nanoparticles (either polymer based or lipid).

FROM THERE TO HERE, AND WHERE THE FIELD IS GOING: IDENTIFYING RESEARCH GAPS, OPPORTUNITIES, AND RESEARCH OPPORTUNITIES

Directed evolution of AAV delivery systems for clinical gene therapy

For modification of nonproliferating target tissues, AAV vectors are a very good delivery method for gene

therapy as they are generally safe, somewhat efficient, have stable expression, are manufacturable, and have shown efficacy in multiple clinical trials. There is a deep clinical pipeline of AAV vectors for retinal, pulmonary, and cardiac applications with good results to date. Additional research is needed to improve this vehicle and optimize delivery efficiency to lower the doses required and further improve the safety profiles. Researchers also need to optimize AAV manufacturing capacity, which is a bottleneck for researching both rare and nonrare diseases.

Researchers can use platforms for CRISPR gene modulation to engineer cells for increased AAV production and, in fact, this approach has been used to engineer AAVs with enhanced efficiency, targeted delivery, and immune invasion. This technology has already been translated into multiple clinical trials. Genome-wide screens have resulted in fivefold increases in AAV production to date. Though better gene regulation mechanisms will be needed for some gene therapy indications, directed vector evolution can yield short, strong, and potentially cell-specific promoters.

Nucleic acid delivery systems for RNA therapy and genome editing

Intracellular delivery of nucleic acids will revolutionize medicine, but a crucial challenge is figuring out how to deliver them efficiently to cells *in vivo.* Small interfering RNA (siRNA) technology, which changes a sequence of small RNA, interferes to turn genes off. The major problem is delivering siRNA intracellularly as there are multifaceted barriers, such as nanocomplexation, transport to the cells of interest, avoidance of nontargeted cells, endocytosis, endosomal escape, release of RNA from nanoparticle, and nuclear transport. In addition, it will be important to determine the organs most amendable to targeting.

Turning nucleic acids into drugs is difficult as RNA and DNA are highly charged large molecules that do not cross cellular membranes, are prone to nuclease degradation, and can induce immune responses. However, researchers have developed tools (*e.g.,* sequence selection to target specificity and potency, chemical modification, and encapsulation) to turn nucleic acids into drugs. To deliver RNA, researchers are developing new ionizable lipids for nanoparticle delivery (*e.g.,* lipid-siRNA-nanoformulations). In fact, an open-label trial of delivery of siRNA (ALN-TTRO2/Patisiran) to the human liver, with findings of potency and specificity, led to the first siRNA LNP therapeutic approved by the FDA in 2018.

Through the development of this technology, scientists have achieved dramatic improvements in delivery potency over time through iterative ionizable lipids engineering. Through rational design and effort, the field now has formulations that are very low dose yet potent enough to knock down a gene in the liver. Importantly, nanoparticle-mediated RNA delivery is not limited to LNPs, vaccines, or hepatocytes. Polymer nanoparticles have great potential and have been shown to silence five genes in the lungs of mice and primates with just one dose. Other research has shown that 20 genes can be silenced simultaneously.

The same tools developed for siRNA have shown potential for mRNA, with polymer nanoparticles yielding better results than LNPs for delivery to the lungs. Changing the chemistry allows researchers to target specific organs, which can further expand the therapeutic potential for these molecules.

Summary of the past and the future of gene therapies

Both *in vivo* gene therapy and gene editing have great promise. To understand where the field is headed, it is best to review more recent research because clinical concerns are generally related to legacy programs. As scientists have gained a better understanding of human biology, gene therapy technology has improved. Gene editing is exciting, but as *in vivo* gene editing advances through the research pipeline, researchers must pay particular attention to weighing the risks versus benefits. Toxicity is always a concern, and despite preclinical work, the broader safety understanding is only gained with a broader application of the technology in humans.

Gene therapy platforms have the advantage that the application to one clinical indication could provide information about the use in other clinical conditions. A disadvantage is that if the FDA issues a clinical hold on a trial using a platform, it will affect other research trials using that foundation, and this loss of momentum can generate panic in rare disease genetic correction programs. Therefore, as technologies emerge and progress, it will be important to focus on programs that have a high chance of succeeding and on diseases with a significant unmet treatment need with a robust benefit-to-risk ratio.

To know whether an investigational agent is working in a clinical trial, biomarkers are critical and provide some indication that gene editing is affecting a biological pathway. If a phase I trial is successful, researchers need to consider the path to registration—particularly the endpoints that would convince others that the agent is effective and worthy of approval and distribution. However, the value of clinical trials is not necessarily the development of a successful commercial product, as researchers might learn additional important information about the condition under study.

The utility of animal models is never completely validated until results of human the clinical trials are available, but for gene therapy delivery, the differences in host response to the vector have generally been consistent. Large animal models are not appropriate for every application of gene therapy but will be important for selected cases to reduce the risk from an approach. An ongoing

limitation in rare diseases is the lack of animal models that phenocopy human disease and very often the lack of an evaluable adult disease population for first in human studies. CRISPR technology can be used to selectively develop these animal models.

Although the manufacturing of gene therapy vectors has greatly improved, current vector technology may not serve future needs. However, researchers should not abandon AAV vectors because (1) researchers have a deep knowledge of what they can and cannot do, (2) AAV can be modified to have properties that natural variant may not have, and (3) AAV produces good results. In addition, the scope of innovation should go beyond capsid biology, including addressing the need to perfect devices for injection, garnering a better understanding of the route of administration, and focusing on the expression of the trans-gene that can be specifically regulated in certain cells and tissues and ongoing analysis of rare insertional events.

Rapid heme panels using targeted next-generation sequencing (NGS) panels to identify genetic alterations are increasingly being explored as diagnostic tools for clinical medical practice. The validation and implementation of a recently designed comprehensive 95-gene NGS panel targeted for hematological malignancies are ongoing. One can anticipate that focused NGS tests will become the standard of care for many mutational integration-sensitive high-risk diseases over the next few years.

The analytical characterization of gene therapy products is in the very early stages and needs to be more robust and precise. A challenge is that safety assay information is often proprietary, but there may be inexpensive ways to improve analytical characterization, and the government or nonprofit sector could lead these efforts, which would benefit the entire community. Safety data must be shared in order for the field to progress. Often this does not happen, except with sponsors, and the field should build on their example.

Finally, a great deal of knowledge that could benefit the field of gene therapy could be gained from the support of experimental medicine. The California Institute of Regenerative Medicine (CIRM) and the NIH

Table 1. *Platforms for gene therapy and gene editing in clinical trials and the resources needed to pursue these*

Platform	*Research Grade Reagents*	*IND-enabling Resources*	*Clinical Trial Support*	*Quality Control*
Lentivirus (*ex vivo* and *in vivo)*	Human HSPCs for POC studies Plasmids for research-grade production SIN-LTR backbones and helpers for various envelope pseudotypes	Navigator services Regulatory assistance Manufacturing of vectors for Pharm-Tox studies GLP Pharm-Tox studies	cGMP vector manufacturing and *ex vivo* cell handling Navigator services Clinical care costs of gene therapy (stem cell collection, conditioning, transplant, transfusion/infection/ nutritional support) and trial assays Regulatory support Electronic data capture Study monitoring, including CRA and medical monitor Long-term follow-up and data repository Biorepository for patient samples	Titering assessments Reference standards Vector integration assays and its bioinformatics support
In vivo AAV	Vector and helper plasmids for various capsid pseudotypes (AAV1, 2, 3b, 5, 6, 8, 9 rh10) Packaged vectors in array of serotypes	Navigator services Regulatory assistance Manufacturing of vectors for Pharm-Tox studies GLP Pharm-Tox studies	cGMP vector manufacturing Navigator services Regulatory assistance Electronic data capture Study monitoring, including CRA and medical monitor	Titering assessments Reference standards
CAR-T cell and related systems	Human T cells Chimeric antigen receptor backbone (second and third generation)	Navigator services Regulatory assistance Manufacturing of vectors for Pharm-Tox studies GLP Pharm-Tox studies	cGMP vector manufacturing and *ex vivo* cell handling Navigator services Regulatory support Electronic data capture Study monitoring, including CRA and medical monitor Long-term follow-up	Titering assessments Reference standards
Gene editing	Bioinformatics consultation for design of sgRNA S*p*Cas-9 and S*a*Cas-9 plasmids, mRNA, and purified proteins LNP-Cas9-sgRNA for POC studies HDR-template plasmids with homology arms for GSHs	Navigator services Regulatory assistance Manufacturing of vectors for Pharm-Tox studies GLP Pharm-Tox studies	cGMP vector manufacturing and *ex vivo* cell handling Navigator services Regulatory support Electronic data capture Study monitoring, including CRA and medical monitor Long-term follow-up	Titering assessments Reference standards Off-target editing assessment Vector integration assays and its bioinformatics support

Some of these resources are readily available commercially.

cGMP, current good manufacturing practice; CRA, clinical research associate; GLP, good laboratory practice; GMP, good manufacturing practice; GSH, genetic safe harbor; HDR, homology-directed repair; HSPCs, hematopoietic stem and progenitor cells; IND, investigational new drug; LNP, lipid nanoparticle; POC, proof of concept.

Common Fund Somatic Cell Genome Editing Program might offer opportunities or models for partnership.

A summary of the resources that would benefit further research and development of the gene therapy platforms is given in Table 1.

SUMMARY OF RESEARCH OPPORTUNITIES

The following areas of opportunity in the gene therapy field were identified by the workshop participants:

- Advances in the production of good manufacturing practice-grade vectors, nanoparticles, proteins, and mRNA, with flexibility to include emerging technologies and assistance with meeting CMC challenges, could allow investigators to advance from innovation to the clinic faster, as well as facilitate better outcomes of the gene transductions with lower viral loads.
- A centralized biobank/repository for gene therapy with standardized procedures for banking and withdrawal for analysis of specimens from humans who received gene therapy agents could facilitate investigators' understanding of the natural history of conditions and responses to investigational agents.
- A mechanism to provide and share centrally sourced critical reagents could allow more cost-effective investigations among many different researchers and could be particularly important when samples need to be analyzed such as when adverse events occur.
- A facility for large animal studies, particularly those that will benefit the field broadly such as sophisticated monitoring of immune responses, and continued efforts to improve the supply of nonhuman primates for research, could help provide better predictions of the effects of the investigational gene therapy agents given greater genome homology with human than small animal models afford. This will also help FDA to better interpret/evaluate the outcomes of the animal tests when providing regulatory guidance.
- Expert assistance with safety analyses and a mechanism to share clinical safety data, particularly long-term safety data, regulatory affairs assistance and guidance specific to each stage of translational advancement, and assistance with intellectual property and commercialization issues could allow investigators to more rapidly advance their products along the translational pathway.
- Coordinated long-term follow-up of individuals who received gene therapy agents could alleviate duplicative efforts and siloed information, leading to improved understanding of the long-term safety data from gene therapy clinical trials.
- Expanded participation across the various NIH institutes and centers and a resource, perhaps through the NIH Rare Diseases Clinical Research Network (RDCRN), to capture and collate natural history data on orphan/rare diseases could result in an expansion of the diseases studied and a better understanding of the manifestations of disease. This could lead to better clinical trial readiness, biomarker identification, and determination of outcome measures that enhance our understanding of the efficacy of the gene therapy.
- A readily accessible matchmaking portal that provides transparent and accurate information to the rare disease community could more readily connect parents/patients, clinicians, and researchers, thereby facilitating the development of, and enrollment into, clinical trials for rare/neglected diseases.

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