ASGCT response to NCATS RFI: *Opportunities and Challenges for Platform Vector Human Gene Therapy Trials in Rare Diseases*

The American Society of Gene and Cell Therapy

The American Society of Gene and Cell therapy is the primary professional organization for gene and cell therapy, with a broad membership base including scientists, clinical researchers, physicians, patient advocates, and pharmaceutical, biotechnology, and other professionals. The mission of the Society is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease. This mission leads the Society to foster the development of cell and gene therapies for unmet patient populations by providing a forum for the exchange of information and the establishment of collaborations. ASGCT's credentials place it in a uniquely qualified position to advise the National Center for Advancing Translational Sciences (NCATS) on ways to improve the efficiency of gene therapy trials in rare disease, and thereby expand the potential use of viral vectors as platforms for therapeutic gene delivery.

Our response to the NCATS Request for Information highlights key areas that should be considered when addressing the issue of efficiencies that could be gained through platform vector gene therapy (PVGT) trials, which NCATS defines as clinical trials in which the same vector is used for multiple diseases resulting from defects in the same organ or cell type. This response was developed by a carefully selected task force of ASGCT member experts who represent diverse backgrounds and affiliations. Members involved in the task force include:

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Identifying Trial Process Efficiencies Is Essential to Success Against Rare Genetic Diseases

We wish to acknowledge the importance of this topic and thank NCATS for its leadership. ASGCT sees great value in achieving efficiencies of gene therapy clinical trials in rare diseases given the large unmet need for effective therapies in this area and the challenges in conducting clinical research on diseases with small patient populations. With limited funding available for rare disease trials, developing efficient means to improve economic viability is essential. Ultimately this will accelerate the development of safe and effective gene-based therapeutics that will benefit patients, an objective ASGCT strongly supports.

PVGT trials hold the potential for more efficient development of therapies for rare and serious genetic diseases. In particular, PVGT trials hold the potential to minimize some of the initial research and

development costs related to gene therapy product development. This potential is currently limited by a lack of harmonization between trials. Establishing standards within the space would facilitate the potential of PVGT trials and is an area that NCATS is well suited to support.

Although increasing efficiencies in PVGT trials would likely benefit the development of therapeutics for rare diseases, it is worth noting that for ultra-rare genetic diseases, some of which affect fewer than 50 Americans annually (often children), a greater level of efficiency would be required than is currently feasible. Nevertheless, because the Orphan Drug Act and other incentives are not designed or intended to effectively target these populations from a commercial perspective, we encourage NCATS to continue to work toward this ultimate goal. While current tools do not support this type of product development, we need to continue to believe there is a path forward, even if it remains undefined today. Our specific recommendations are intended to be the first step on that journey.

While harmonization in PVGT trials is a laudable goal, we also want to caution that gene therapy is a rapidly evolving field. The content of this document represents our best thinking based upon what is known today; however, the Society encourages periodic reassessment with a panel of gene therapy experts as scientific knowledge evolves. Following focused calls with the task force, listed above, we have identified two key areas we advocate as amenable to increasing efficiencies—***analytics*** *and* ***pharmacology/toxicology (pharm/tox) studies***. The feedback given below is not intended to be comprehensive, as we think that one of the most useful actions NCATS could take is to organize or fund a series of working groups including experts across industry and academia to continue the discussion on how best to implement strategies that will allow for the development of PVGT trials for rare disease clinical research.

Analytics

Understanding the safety, purity, potency, and stability of any therapy that may eventually be administered to patients is essential. Furthermore, once administered to patients, it is critical to define the pharmacokinetic effects of the gene therapy vector as well as immune responses to the vector and/or expressed transgene. Analytical methods that produce high-quality data are intrinsic to the drug development process.[1] Unlike vector production processes that are both vector specific and often proprietary, analytical assays are generalizable, and therefore can be used across different trials, making them a reasonable area on which to focus when looking to increase efficiencies across clinical trials.

Inconsistency in applying vector analytics and dosage units confounds inter-study comparisons and creates unnecessary complexities, i.e., costs for gene therapy commercial development.[2] The advantages of improving and harmonizing analytics within and between studies has been recognized by the U.S. National Institute of Standards and Technology (NIST), which has recently developed a generalized framework for designing and conducting cell counts.[3]

The standardization of analytics can broadly be considered at two levels: 1) **establishing a minimum set of specific *assays* used across groups**, and 2) **standardizing the *reporting* of methods**. Ultimately, harmonization of assays would be highly beneficial; however, achieving this is currently unlikely as it is unrealistic for different laboratories to use the same vector genome (vg) or particle titration reagents.[2] The vg titration method is likely an issue that is specific for adeno-associated virus (AAV), but the methodology issue applies to other vectors in different ways. Therefore, although much more limited in scope, the use of reference standard materials and the promotion of best practice are more likely to result in improved inter-study comparability.

A consensus on analytic standards in developing viral vectors for gene delivery would eventually increase efficiencies in investigational new drug (IND) application approvals and initiation of gene therapy trials. This would benefit stakeholders, without compromising proprietary processes, although the risk of enabling competitors cannot be discounted.

To recommend standardization of specific assays may be inhibitory and potentially limit the development of innovative assays, which are required to further develop the field.[1] Analytical assay standards are neither immutable nor permanent. For example, digital droplet PCR is state of the art and should be the standard instrument for vg determination. Since not all facilities can afford the investment, an NCATS-supported contract research organization (CRO) may be a feasible solution for investigators. As technology evolves, new assays may become the preferred standard, e.g., whole virus particle mass spectroscopy, but these advanced technologies are highly specialized and an NCATS-supported CRO would represent an alternative to individual end users attempting to become proficient in very specialized methodologies. Again, because this is a rapidly developing field, it is important to note that standardization needs to be applicable to future generations of vectors developed.

Viral vector based gene therapy is not alone in facing these issues. We recommend that NCATS look to other fields that have faced challenges in harmonizing analytics. For example, in stem cell therapy, the use of cytokine-mobilized peripheral blood stem cells in transplants faced the challenge of lack of uniformity of assays, leading to divergent data. In response, the International Society of Hematotherapy and Graft Engineering (ISHAGE) established a Stem Cell Enumeration Committee, which ultimately developed a set of guidelines to validate a method to quantify CD34+ cells that have since been widely adopted.[4,5] The creation of a similar committee to develop guidelines in analytics could benefit the field of viral vector gene therapy.

The use of *reference standard materials* represents an area that could contribute to increased efficiencies. Reporting against a standard can decrease intra-laboratory variation for a specific subset of assays. Certain reference standard materials exist; however, there is a need for further reference assays to be developed and widely used.[6] Other therapy areas can provide examples of how reference standard materials can be developed and validated. In monoclonal antibody therapeutics, there is a clear need for harmonization of approaches to facilitate cross-validation of methods between sites to ensure accuracy, precision, robustness, and suitability of techniques.[7] As such, a number of standards have been developed, including the recent reference material NIST RM 8671. NIST RM 8671 was developed in collaboration with industry and has been tested with collaborators from companies, regulatory agencies, and universities, and will hopefully allow for assessment of existing analytical methods as well as potentially faster adoption of new technologies. This collaboration between NIST, industry and academia to develop effective validated standards could be an example for developing reference standard materials for use in viral vector analytics.

The Standards Coordinating Body (SCB), (http://www.regenmedscb.org/) which includes ASGCT representation, could be a useful resource in developing consensus standards and reference materials. The SCB, launched in January 2017, is a consortium of non-government stakeholders that operates through public-private partnerships with government agencies, regulatory bodies, and other government organizations to efficiently and effectively support and improve the cost, time, and resources for sector product development.

Although reference standard materials pose a clear benefit to the field, they can be resource intensive for trials that are challenged by resource limitations. As reported in the AAV2 reference standard, most participating laboratories obtained less variability (± 14 percent) with particle quantification

using commercially obtained kits.[8] It could also be argued that inter-laboratory variation would remain an issue. It might be beneficial to establish a reference lab, such as that used by the CDC for standardization in other fields (https://www.cdc.gov/labstandards) and mandate the development of a contract research organization that would provide comparability data.

What may be more universally accepted as useful by members of ASGCT would be continued efforts by the FDA and the gene therapy community to achieve consensus on analytical methods appropriate for gauging specific forms of toxicity. One example would be the development of standard IVIM (*in vitro* insertional mutagenesis) in terms of insertional transformation risk assays to gauge the safety of specific retroviral and lentiviral vector platforms. While certain situations may be well suited to direct cross-referencing of safety data from highly similar vectors (see pharmacology and toxicology section below), many more programs could benefit from a standard of accepted analytic methods suitable for addressing these types of questions. In the past, such standardized methods have been the subject of FDA guidance documents, and we would encourage ongoing efforts in this area, including by way of NCATS-funded working groups.

The FDA guidance on testing for replication-competent retrovirus and lentivirus in the clinical setting is based on a small amount of data from many years ago. The absence of any reports on exposure to, or emergence of, replication-competent retro- or lentiviruses occurring in the clinical setting, along with the relative high burden placed on investigators for testing, suggest it is time for this guidance to be revisited.

Potential action from NCATS:

Recommendations need to be applicable to the various groups involved in developing viral vectors as platforms for therapeutic gene delivery (e.g., small biotech, large pharmaceuticals, and academia). As mentioned above, these complex issues warrant further discussion within focused work groups involving specialists representing the range of stakeholders in PVGT. Certain actions that NCATS could potentially take to improve efficiencies in the field include the following:

- Organize and support focused round-table meetings over six to twelve months to encourage the development of a set of guidelines that promote basic standards in analytics
- Organize and fund the development of reference standard materials and require reporting against a standard method in any trials that receive NIH funding
- Fund, or promote the idea of, a centralized lab for the assessment of viral vector preparations
- Establish guidelines for which assays would be required in trials using specific vector types, dose, and patient population, and advise on best practices on analytical methodology (including assay quantification, assay acceptance criteria, metrology, etc.)
- Lead discussions among investigators and the FDA to define new studies that could be performed to develop more evidence-based guidelines for testing of replication-competent retrovirus and lentivirus in the clinical setting, and support these research studies through grant or contract mechanisms.

Pharmacology and toxicology studies

Toxicology studies define the potential toxicities associated with a specific investigational product that will be administered to the patients in a proposed clinical trial. These studies can be a very costly, perhaps even an inhibiting factor in the translation of promising preclinical studies into the clinic. As such, there is a call from some groups to reuse toxicology data from existing PVGT trials to expedite new trials in rare diseases.[6] However, the toxicology profile of a gene therapy vector will be influenced not only by the properties of the particular viral vector, but also by the activity of the expressed transgene (on target and off-target tissues), the dose, potential impurities, route of delivery, disease state, etc. Thus, efficiencies in this area need to be considered very carefully in terms of safety implications. **The goal must be to ensure safety while identifying the most efficient way of bringing drugs to those who need them.**

Although the toxicology data package for an investigational drug should reflect the risks and benefits of that particular drug, wide variability exists in the design of toxicology studies used to support gene therapy clinical trials—even in cases where the same vector expressing the same transgene is being used by multiple groups to support clinical trials for the same disease. Thus, transparency about the animal models and study designs (duration, number of subjects) accepted by the FDA to support gene therapy clinical trials might result in efficiencies by enabling the streamlined study designs and identification of data that could potentially be cross-referenced, ensuring that no unnecessary studies are conducted. Later in development, it is possible that existing information about potential genotoxicity and/or reproductive toxicity associated with a particular vector type could be leveraged to avoid the need to repeat these studies prior to licensure of gene therapies for rare diseases. Efficiencies such as these could facilitate the initiation of clinical trials of gene therapies for rare diseases, for which little funding is available, by reducing the cost of toxicology studies.

Cross-referencing existing biodistribution data for gene therapies that use a previously trialed vector type which also rely on a similar mode of delivery could be beneficial. Again, transparency about the existing biodistribution study designs is needed to allow researchers to determine if the existing data would support clinical trials with their vectors. Furthermore, it is possible that production methods and formulation can affect transduction efficiencies, and conclusions about vector copy number within tissues can be influenced by tissue processing and nucleic acid detection methods, as well as the values reported (e.g., vector copies per quantity of DNA vs. per cell). Similarly, the possibility of reusing other pharmacology data that is not influenced by the transgene, such as vector shedding and germline transmissibility, should be considered.

One system aimed at facilitating cross-referencing available pharmacology and toxicology data across gene therapy studies is the National Gene Vector Biorepository (NGVB) (www.ngvbcc.org), which includes an NIH-funded database of pharm/tox information, hosted by Indiana University. The NGVB is a voluntary program that collates pharm/tox data from trials that have been submitted to the FDA in support of gene therapy clinical trials. The database is intended to be a resource to help investigators identify findings from previous studies and identify pharm/tox studies that could inform the design of future studies to support clinical trials with the same vector type.

The intended purpose of the database is for investigators to obtain a letter of cross-reference from the primary investigator of the relevant study that might result in the FDA agreeing to an abbreviated pharm/tox study requirement to support clinical trials with similar vectors. The database was established in May of 2008 and currently holds information on the outcomes of approximately 50 pharmacology and toxicology studies of various gene therapy vectors; however, it is unknown how effectively this resource has been used. It might be an appropriate time to analyze the data held in

the database to assess how best it could be used in guiding the design of preclinical studies of gene therapy vectors to support future clinical trials. Furthermore, reporting pharm/tox data to the database is not compulsory, even in NIH-funded trials. This could be an avenue NCATS may wish to consider, even if only to raise awareness of the database.

When considering cross-referencing existing pharm/tox data, it should be noted that the current totality of relevant toxicology data is not extensive across the different types of viral vectors that have been used. The FDA requires there to be no significant differences in products, target tissue, route of administration, and disease for cross-referencing to be permissible,[6] depending on what information is being cross-referenced and what other information is available in a particular IND submission. Given the large variability in factors such as vector constructs, manufacturing processes, formulation, and route of delivery, identifying suitable studies to cross-reference in support of a clinical trial with a new product is likely to be very limited. In relation to the analytics point made above, lack of common processing or analytics standards make reuse of even biodistribution data, or comparisons between trials, difficult and potentially inappropriate. Addressing some of the issues with harmonization may increase the feasibility that cross-referencing pharm/tox studies will become more possible.

Potential action from NCATS:

Pharm/tox standards need to remain high and the impact NCATS could have on directly influencing standards to increase efficiencies in trials is potentially limited. Some actions NCATS could take in this area are:

- Fund analysis of the existing NGVB database to assess the degree of heterogeneity in reporting in the studies reported to date and identify how the existing database could be used to increase the ability to leverage existing data to support PVGT trials
- Increase the profile of the NGVB database and require reporting to the database for any study that benefits from NIH funding
- Promote harmonization of PVGT study designs to increase the likelihood of future cross-referencing to support subsequent trials

Summary of recommendations

We have provided a brief overview of certain aspects related to the potential for PVGT trials to be improved to benefit those with rare diseases. Although we have made several recommendations, we encourage NCATS to consider funding (or developing) focused, expert working groups so that consensus can be reached on how to best effect change and increase efficiencies. Further to this, we also endorse the idea of the development of infrastructure that could be used to harmonize analytics and pharm/tox studies, e.g., by raising the profile of the NGVB, funding a centralized hub for testing individual groups' assays, or promoting the use of standard references in assays.

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