American Society of Gene + Cell Therapy

June 14, 2024

Joni L. Rutter, PhD
National Center for Advancing Translational Sciences
6701 Democracy Boulevard
Bethesda MD, 20892

RE: Comments on Predecisional Draft NCATS Strategic Plan 2024-2029

Dear Dr. Rutter:

The American Society of Gene & Cell Therapy (ASGCT) appreciates the opportunity to comment on the National Center for Advancing Translational Science (NCATS) draft strategic plan. The Society is a nonprofit professional membership organization comprising more than 6,200 scientists, physicians, patient advocates, and other professionals working in gene and cell therapy (CGT) in settings such as universities, hospitals, and biotechnology companies.

The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease. Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies.

General Comments

Since the first CAR T-cell therapy approval in 2017, the field has developed an exponential pipeline with over 4,000 therapies in development and over 2,000 active clinical trials.[1] The field has grown rapidly in recent years and offers the potential to deliver safe, effective, and transformative therapies to patients who often have no other options. There are over 10,000 rare diseases,[2] up to 80% of which can be traced to mutations or changes in a single gene.

Gene therapy aims to address the underlying cause of disease, such as gene mutations. As genetic mutations for rare diseases continue to be identified, there is also a greater need for funding to support translational research – bridging studies which help advance potential new gene therapy approaches toward clinical research. Continued investments in basic, translational, and early clinical research for rare diseases is needed

[1] American Society of Gene and Cell Therapy, Citeline. (2024). *Gene, Cell, & RNA Therapy Landscape: Q1 2024 Quarterly Data Report.* https://www.asgct.org/global/documents/asgct-citeline-q1-2024-report.aspx
[2] National Center for Advancing Translational Science. (2024). *Delivering Hope for Rare Diseases.* https://ncats.nih.gov/research/our-impact/our-impact-rare-diseases

to build the scientific underpinnings of gene therapy. ASGCT supports robust funding for the National Institutes of Health (NIH) to ensure the US remains a global leader in medical innovation

ASGCT believes the draft strategic plan addresses crucial challenges that resonate with the field's efforts to improve and ensure equitable patient access to these innovative treatments:

1. The limited number of diseases with treatments: CGTs hold immense potential to address numerous rare and complex diseases that currently lack effective treatments. ASGCT recognizes the need to accelerate research and development efforts to expand the therapeutic reach of these cutting-edge modalities. Collaborative efforts between academia, industry, and regulatory bodies are crucial to overcoming scientific and regulatory hurdles, ultimately increasing the number of diseases that can benefit from these therapies.
2. The need to bring more individuals and communities into the translational science space: Ensuring equitable access to CGTs is a paramount concern for ASGCT. These therapies are often developed for rare diseases, and their high cost and complex manufacturing processes can create barriers to access for underserved and underrepresented communities. The Society supports initiatives that promote diversity and inclusion in clinical trials, foster community engagement, and address socioeconomic and geographic disparities in healthcare access.
3. The inefficiencies in translational science that slow efforts: ASGCT acknowledges the challenges associated with translating promising CGT research into clinical applications. Inefficiencies in areas such as manufacturing, logistics, and regulatory pathways can significantly slow the development and delivery of these therapies. The Society advocates for streamlining processes, supporting innovative manufacturing strategies, and collaborating with regulatory agencies to address these inefficiencies and ensure timely patient access to safe and effective cell and gene therapies.

The challenges the draft strategic plan aims to address are also tackled across the Department of Health and Humans services. For instance, the FDA is in the process of launching designation programs for drug platforms and advanced manufacturing technologies, HRSA works to implement and oversee the newborn screening program, and CMS is grappling with the access and post-market data collection for patients covered by the federal government. To that end, there are several areas of the strategic plan that would benefit from documenting collaborative efforts to ensure that there is coordination and acceleration of the overarching goals and NCATS is breaking down silos that can slow translation from bench to bedside.

Specific Comments

Goal 1: Apply Approaches to Foster the Identification of, Development of, and Access to More Treatments

Gene therapy aims to address the underlying cause of disease. In the US, 10 percent of the population is affected by rare disease;[3] and 95 percent of patients have no FDA-approved treatment. Rare disease drug development is complicated by a myriad of factors that touch translational science, including issues with small patient populations. ASGCT supports expanding abilities and capacities to enable these smaller populations to obtain diagnoses, participate in clinical trials, and eventually access these transformative therapies.

Among the rare disease population, around half impact children; the United States alone has approximately 15 million pediatric rare disease patients. The CGT pipeline offers a unique opportunity to address pediatric diseases, many of which do not have available treatment options. Expeditious development through well-supported translational science is therefore imperative to meet this high unmet need for diseases that often have great morbidities and childhood mortality, and those that may otherwise be limited in commercialization.

Objective 1-1: Develop strategies to advance diagnosis and targeted interventions that address multiple diseases at a time, particularly for rare diseases and others with unmet needs.

ASGCT appreciates the acknowledgment of platform technologies as a key factor in accelerating the development of treatments for rare diseases. ASGCT supports this work and encourages NCATS to work collaboratively with FDA to help both inform the development of the Platform Technology Designation Program and ensure that NCATS platforms can meet the regulatory requirements for deployment. Platform technologies can streamline CGT development by allowing a single technology, such as a nucleic acid sequence or a vector, to be used across multiple products. Without an increased ability to assess product platforms and rely on data previously generated for earlier drugs on the same platform, the likelihood of translation from bench to bedside is drastically reduced. The Society was pleased to see language creating the program in the 2022 Food and Drug Omnibus Reform Act[4] and plans to submit comments to the Food and Drug Administration's recently released draft guidance on the Platform Technology Designation Program and encourages NCATS to weigh in as well.[5]

Objective 1-2: Support and leverage existing national clinical and translational networks to conduct high-impact clinical research, clinical trials, and translational science and disseminate and implement successful interventions and treatments into the clinic and the community.

Currently, oncology and rare diseases are the top areas of gene therapy development in both the overall pipeline (preclinical to pre-registration) and in the clinic (Phase I to pre-

[3] Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development. (2010). *Rare Diseases and Orphan Products: Accelerating Research and Development.* https://pubmed.ncbi.nlm.nih.gov/21796826/

[4] U.S. Congress. (2023). *Consolidated Appropriations Act.* https://www.congress.gov/117/bills/hr2617/BILLS-117hr2617enr.pdf

[5] Food and Drug Administration. (2024). *Platform Technology Designation Program for Drug Development.* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/platform-technology-designation-program-drug-development

registration).[6] As evidenced by the development pipeline, gene therapy offers great promise for people with rare inherited disorders. While there are more therapies for rare diseases in the clinic, there remains a great scientific need to investigate the preclinical application of gene therapies to treat new diseases and improve the design of vector technologies.

Gene therapies are often developed for the treatment of rare diseases with high unmet need. As a function of being a rare disease, this can limit clinical trial size and duration. As a result, gene therapy trials may have Phase I and II trials of between 5 and 20 patients for initial dose-finding and efficacy. This is significantly smaller than trials for common diseases. Fortunately, gene therapies often demonstrate efficacy early in development; promising results can be seen as early as Phase I. ASGCT supports consideration on how registry and natural history data can be effectively utilized as controls to better understand CGT. External controls, including those based on RWE, are particularly relevant for CGTs which can cure or prevent disease progression for patients with rare genetic diseases. Greater utilization of RWE also has the potential to facilitate the inclusion of more representative patient populations to reflect the risks and benefits of products more accurately.[7]

We are encouraged by the progress NCATS has made to conduct natural history and readiness studies for so many rare diseases. However, there are real regulatory barriers that make utilization of these data difficult, especially in conditions where the natural history of the disease exhibits significant heterogeneity, which is often the case for rare diseases.[8] Additional flexibility is needed when utilizing this data to advance drug development. Therefore, we encourage NCATS to work with FDA to enable greater use of natural history data and innovative trial designs to overcome challenges posed by small patient populations.

Objective 1-3: Support the discovery, development, and use of tools, technologies, models, methods, and assays for preclinical testing, drug development, and preclinical screening to enable identification of disease and to treat disease progression.

For CGT products, a major hurdle in early development is the creation of potency assays which link product characteristics and clinical performance, and ideally reflect the product's mechanism of action (MOA). This is critical to ensure effectiveness for patients. However, there are technical and scientific challenges associated with potency test design, execution, and analysis. The MOA may not be fully understood-this is particularly true of early-stage development for CGT products. We encourage NCATS to consider the development of tools and techniques to improve potency assay development.

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[6] American Society of Gene and Cell Therapy, Citeline. (2024). *Gene, Cell, & RNA Therapy Landscape: Q1 2024 Quarterly Data Report.* https://www.asgct.org/global/documents/asgct-citeline-q1-2024-report.aspx

[7] American Society of Gene and Cell Therapy [Regulatory Comments]. (2023). *Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on CGT Products; Listening Session.* https://www.asgct.org/advocacy/policy-statement-landing/2023/post-approval-cgt-products-listening-session

[8] American Society of Gene and Cell Therapy [Regulatory Comments]. (2023). *Scientific Challenges and Opportunities to Advance the Development of Individualized Cellular and Gene Therapies; RFI.* https://www.asgct.org/advocacy/policy-statement-landing/2023/rfi-scientific-challenges-and-opportunities-to-adv

Goal 2: Enable All People to Contribute to and Benefit From Translational Science

ASGCT believes that more representative clinical trial populations are essential to properly understanding and evaluating the benefit-risk profile of innovative medical products, specifically cell and gene therapy products. Cell and gene therapy products are often developed to treat rare diseases, many of which have small patient populations and disproportionately affect minority populations.[9],[10]

Objective 2-1: Work toward broader inclusion of patients, their families and caregivers, and care providers as participants in translational science.

ASGCT appreciates NCATS' focus on what is most important to patients. Emphasis should be placed on patient-focused benefits and their assessment by patient-reported outcomes (PROs). Traditionally, these PROs must be validated based on large amounts of clinical data. However, it should be recognized that such large amounts of data would not be available for small, rare disease patient populations. In small patient and clinical trial populations, obtaining statistical significance of effects can be challenging – even if the clinical benefit seems clear to a physician, patient, or their family. As NCATS works to fulfill this objective, ASGCT suggests engagement and collaboration with FDA to ensure that PROs can be used in the evaluation of drug products for rare patient populations.[11]

Objective 2-2: Broaden engagement efforts and create more inclusive approaches that build trust and engage people at different levels to benefit translational science.

Historic injustices and abuses of racial and ethnic minority populations by the clinical research enterprise have contributed to a general lack of trust in the healthcare system amongst these populations, which has undermined efforts to broaden engagement in translational science. Towards this end, ASGCT emphasizes the importance of acknowledging these past injustices and working with principal investigators and clinical trial managers on communication and educational initiatives to build trust and increase enrollment. ASGCT believes that continual collaboration with principal investigators and clinical trial managers from diverse backgrounds is essential to developing trust.[12]

Traditional clinical trials may face challenges in recruiting a diverse range of participants due to geographical limitations or lack of awareness, and these issues are heightened in rare disease trials. Some disparities in clinical trial participation, and lack of

[9] American Society of Gene and Cell Therapy [Regulatory Comments]. (2022). *Diversity Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Trials Guidance.* https://www.asgct.org/advocacy/policy-statement-landing/2022/diversity-plans-to-improve-enrollment-of-participa
[10] American Society of Gene and Cell Therapy [Regulatory Comments]. (2021). *21st Century Cures 2.0 [Introduced].* https://www.asgct.org/advocacy/policy-statement-landing/2021/21st-century-cures-2-0-introduced
[11] American Society of Gene and Cell Therapy [Regulatory Comments]. (2023). *Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on CGT Products; Listening Session.* https://www.asgct.org/advocacy/policy-statement-landing/2023/post-approval-cgt-products-listening-session
[12] American Society of Gene and Cell Therapy [Regulatory Comments]. (2022). *Diversity Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Trials Guidance.* https://www.asgct.org/advocacy/policy-statement-landing/2022/diversity-plans-to-improve-enrollment-of-participa

representation in clinical data, stem from logistical barriers (such as lack of transportation, interference with work and family responsibilities, as well as out-of-pocket expenses). These same considerations also are relevant in the post-approval setting, especially for patients living in remote areas who may be less likely to travel to tertiary institutions.

Clinical trials for CGT products often require specialized infrastructure, manufacturing, and clinical administration facilities, which can further limit patient participation. However, we believe that this may be mitigated by embracing new trial design approaches. Incorporating decentralized study designs can aid researchers in gathering data from patients in their natural environments, which may provide a more accurate assessment of treatment outcomes and long-term safety. RWE can complement the findings from controlled clinical trial settings, enhancing the overall understanding of the therapy's impact. Innovative study designs can also offer a more patient-centered, and efficient way to collect pre- and post-approval safety and efficacy data, ultimately leading to better treatment outcomes. We encourage NCATS to examine these types of alterative designs and, in partnership with FDA, determine how best to utilize these to speed the translation of therapies from bench to bedside.

Objective 2-3: Apply translational science to address health disparities and health inequities.

ASGCT believes methods should be implemented to increase diversity in clinical trials. Studies show minority groups are as willing to take part in clinical trials but are less likely to be invited to participate.[13] As the NCATS strategic plan notes, the disparity in trial participation is also due to lack of access to medical treatment due to logistical barriers (such as lack of transportation/financial burden, interference with work/family responsibilities, and out-of-pocket expenses), and being less likely to be offered trial information. One solution is to increase the awareness of clinical trials among patients and their families.

Since minorities are less likely to be offered information about clinical trials, [14] providing educational materials on clinical trials in general, and gene therapies in particular, needs to be tailored to the specific audiences and disseminated through channels that can effectively reach these communities. For example, recruitment by familiar and credible individuals, such as community service centers and community health centers.[15] ASGCT is interested in partnering with NCATS and other stakeholders in adapting and distributing our patient education materials to minority patients and families on clinical trials.

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[13] Comis, R., Miller, J., Aldige, C., Krebs, L., Stoval, E. (2003). *Public attitudes towards participation in cancer clinical trials.* https://pubmed.ncbi.nlm.nih.gov/12610181/

[14] Allison, K., Patel, D., Kaur, R. (2022). *Assessing Multiple Factors Affecting Minority Participation in Clinical Trials: Development of the Clinical Trials Participation Barriers Survey* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9127181/

[15] Linden, H., Reisch, L., Hart, A., Harrington, M., Nakano, C., Jackson, C., Elmore, J. (2007) *Attitudes toward participation in breast cancer randomized clinical trials in the African American community: A focus group study.* https://pubmed.ncbi.nlm.nih.gov/17666974/

Goal 3: Accelerate Translation by Addressing Both Scientific and Operational Challenges

The pipeline for CGT is robust and we agree that manufacturing technology needs to keep pace. As more products receive FDA licensure and approval, improvements will be critical to meet real-world patient demand, bring manufacturing closer to the bedside, and reduce production costs.

Objective 3-1: Remove, reduce, or bypass scientific and operational barriers that slow translation.

New innovations in manufacturing have lagged behind other areas in the field. The National Academies of Medicine published a report in 2021[16] which suggested that FDA implement a pathway to review novel advanced manufacturing technologies separately from individual products to de-risk their use in product applications. The Society was pleased to see the Advanced Manufacturing Technologies (AMT) Designation Program included in the Food and Drug Omnibus Reform Act (FDORA) in 2022.[17] The creation of a product agnostic pathway is an important step toward the field's adoption of new translational technologies. If implemented properly, the program could help address the challenges currently facing the manufacturers and sponsors of CGTs. Realizing these goals will require collaboration with NCATS, contract manufacturers, and other third parties who can develop and implement new advanced manufacturing techniques in a way that benefits numerous developers. ASGCT encourages NCATS to work with FDA to establish the parameters of the new program, including how biologics can reference previously submitted data.

Objective 3-3: Use innovative approaches to develop technologies and models that can accelerate diagnosis, support prevention, or minimize the impact of disease.

Genetic testing and genome sequencing hold tremendous potential for diagnosing patients—many of them children—with rare genetic disorders. Early diagnosis is critical for patient access to care and to treatments such as gene therapy, which may halt progression of serious and potentially fatal diseases. In addition, diagnosis facilitates access to ongoing and future clinical trials.[18] ASGCT is supportive of the Newborn Screening Program which provides funding and recommendations for states to screen babies for "actionable" genetic diseases. The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), within the Health Resources and Services Administration (HRSA), establishes the Recommended Uniform Screening Panel (RUSP), which lists the conditions that states must aim to screen for in order to qualify for certain federal funding. NCATS can play a key role by helping to facilitate the

[16] National Academies of Sciences, Engineering, and Medicine. (2021). *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations*. https://doi.org/10.17226/26009
[17] U.S. Congress. (2023). *Consolidated Appropriations Act.* https://www.congress.gov/117/bills/hr2617/BILLS-117hr2617enr.pdf
[18] American Society of Gene and Cell Therapy [Regulatory Comments]. (2021). *21st Century Cures 2.0 [Introduced].* https://www.asgct.org/advocacy/policy-statement-landing/2021/21st-century-cures-2-0-introduced

development of screening tests and partner with HRSA to assess the effectiveness for the RUSP process.

Another important factor is engaging in both disease-specific and broad education campaigns among health care providers given their critical role in facilitating early diagnosis. Plain language summaries of medical materials can be critical for equipping patient communities (e.g., patients and caregivers) and educating them regarding accurate diagnosis and management of their condition. We encourage NCATS to consider community engagement like this to contribute to the education.

Goal 4: Broadly Utilize Research and Operations Strategies That Cut Across Translational Science Efforts

The Accelerating Medicines Partnership in Gene Therapy, including the Bespoke Gene Therapy Consortium, which NCATS is co-leading, is a public/private partnership that will support gene therapy development for ultrarare conditions. The Society supports this effort and encourages the establishment of additional partnerships to advance development in the sector. Additional solely public efforts that support gene-targeted therapies could inform potential future public/private partnerships, including the Regenerative Medicines Innovation Project (RMIP), Somatic Cell Genome Editing Consortium (SCGE), and the Ultra-rare Gene- based Therapy (URGenT) program.[19]

Objective 4-2: Develop novel and effective partnerships and collaborations in a variety of settings to foster translational science advances.

To accelerate delivery of safe and effective treatments, ASGCT supports policies incentivizing the development of platform technologies and innovative manufacturing approaches. Public-private partnerships fostering these priorities, like the Bespoke Gene Therapy Consortium, are critical for field-wide solutions. The Society also encourages NCATS to facilitate the adoption of innovative statistical methods and novel trial designs suitable for small populations. Coordinated efforts between NCATS, FDA, industry, and other stakeholders in this space are critical for bringing gene and cell therapies to patients more quickly.

Objective 4-4: Communicate and raise awareness of the value and applications of translational science and its principles.

ASGCT has a Patient Education Program, initiated in 2018, that has been successful in communicating with patients and families regarding gene therapies and translational science. As treatments for more rare diseases enter the clinical pipeline, additional resources may be beneficial to accelerate the expansion of this content and to facilitate greater distribution of this information to those in need of it. ASGCT's processes exemplify methods that should continue to be used for multi- stakeholder collaboration on accurate, reliable, accessible educational content. A needs assessment identified a

[19] American Society of Gene and Cell Therapy [Regulatory Comment]. (2021). *Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies [RFI].* https://www.asgct.org/advocacy/policy-statement-landing/2021/facilitating-the-early-diagnosis-and-equitable-del

clear gap in dynamic gene therapy educational content for the lay audience which ASGCT is well positioned to address through its members' expertise. In addition to leveraging ASGCT's membership expertise, a key aspect of the Patient Education Program is engaging with patient advocacy organizations impacted by the diseases covered throughout the resource production process To date, ASGCT has collaborated with approximately 50 different groups on patient-focused programming.

Through collaborative relationships with patient advocacy organizations, ASGCT identifies patient and caregiver educational needs on each topic, obtains feedback during content creation; and shares completed units with organizations that are willing to disseminate the materials to their patient networks. This distribution may include embedding the videos on their own websites and sharing via social media. ASGCT would welcome opportunities to expand dissemination channels to patient and family populations for this information. Our resources are free to share, and we encourage open access for their utilization. ASGCT collaboration with additional stakeholders is an area of opportunity for furthering communication with patients and families.[20]

The Society has been previously supportive of the translational science field and promoted their efforts at events like the Annual Meeting and Policy Summit. As a convener in this space, the Society is uniquely situated to promote team science and interdisciplinary solutions. ASGCT looks forward to continuing this open dialogue with NCATS and partnering to develop educational programs.

Conclusion

ASGCT supports the goals and priorities outlined in NCATS' draft strategic plan. Translational science plays a vital role in advancing cell and gene therapies from promising concepts to realized treatments for patients with unmet medical needs. ASGCT believes NCATS' leadership in areas such as platform technologies, innovative clinical trial design and enrollment, enhanced genetic screening, and translational tools tailored for rare disease populations will be instrumental for streamlining the path to clinical testing and regulatory approval. ASGCT appreciates this forward-looking strategic vision and looks forward to continued synergies between ASGCT, NCATS, and HHS to advance curative genetic medicines.

Thank you for your consideration of these comments. If you have any questions, please do not hesitate to contact Margarita Valdez Martínez, Chief Advocacy Officer, at mvaldez@asgct.org.

Sincerely,

David Barrett, JD
Chief Executive Officer

[20] American Society of Gene and Cell Therapy [Regulatory Comment]. (2021). *Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies [RFI].* https://www.asgct.org/advocacy/policy-statement-landing/2021/facilitating-the-early-diagnosis-and-equitable-del