American Society of Gene + Cell Therapy

ASGCT Final Comments on NIDDK RFI

Advancing understanding of biological pathways and environmental contributors to health and disease.

The American Society of Gene & Cell Therapy (ASGCT) is appreciative of this opportunity to provide input on NIDDK's strategic priorities. ASGCT is a nonprofit professional membership organization comprised of more than 4,400 scientists, physicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology companies. Our comments focus on the importance of research on the genetic contributions to kidney diseases and the potential for gene therapies to treat diabetes and kidney, metabolic, and hematologic disorders with significant unmet need.

Kidney diseases, including genetic kidney diseases, affect as much as 13 percent of the global population. There are at least 80 identified genes associated with kidney diseases, and that number is continually growing, utilizing techniques such as whole-exome sequencing (Ashraf et al., *Nat. Commun.* 2018, DOI: 10.1038/s41467-018-04193-w; Hildebrandt, *Lancet* 2010, DOI: 10.1016/S0140-6736(10)60236-X; Rubin & Barry, *Mol Diagn Ther.* 2020, DOI: 10.1007/s40291-020-00467-6). While the resulting biology and natural history of many kidney diseases are well understood, the genetics and molecular mechanisms are still being elucidated. For example, in 2018 Rinschen, et al. (*Cell Rep.,* DOI 10.1016/j.celrep.2018.04.059) published findings that suggested new signaling pathways in podocyte cells which, when broken down through genetic defects or mechanical stress, are strongly associated with chronic kidney disease (CKD).

While effective therapies for type 1 and 2 diabetes are available under the current standard of care, they have limitations. The genetic contributors, natural history, and biological pathways of these disease are generally well understood, which has led to advanced gene therapy research. For example, mouse models of type 1 and type 2 diabetes treated with adeno-associated virus (AAV) gene therapies reported persistence of pancreatic alpha cells that were reprogrammed to produce insulin in type-1 mice (Xiao, et al., *Cell Stem Cell* 2017, DOI: 10.1016/j.stem.2017.11.020); Jimenez, et al. (*EMBO Mol Med.* 2018, DOI: 10.15252/emmm.201708791) induced murine liver, adipose cell, and skeletal muscle to produce fibroblast growth factor 21 with long-term effect; and Lee, et al. moderated the unfolded protein response in pancreatic beta cells to inhibit the diabetic autoimmune response (*Cell Metabol.* 2020, DOI: 10.1016/j.cmet.2020.03.002). Continuing to fund research that supports the development of new clinical therapies, particularly those like gene therapies that may provide long-lasting therapeutic effect, can provide patients with additional options that may have advantages over current treatments.

In addition to disease treatment through gene therapies, there may be opportunities for prevention of diseases that do not have a clear genetic cause. While CKD in many adults is thought to be caused by environmental or undefined genetic damage, gene therapy approaches may be viable to address and prevent further damage such as renal fibrosis (Ikeda, et al., *J Am Soc Nephrol. 2018*, DOI: 10.1681/ASN.2018040426; Miyazawa et al., *Nano Rev. Exp.* 2018, DOI: 10.1080/20022727.2017.1331099). While preventative gene therapy approaches are in very early stages of development, it is a promising field that could significantly reduce individual suffering.

The genetic causes of some metabolic disorders (see: Nagree et al., *Expert Opin Biol Ther.* 2019, DOI: 10.1080/14712598.2019.1607837) and hematologic diseases (see: Al-Saif, *Gene Therapy* 2019, doi.org/10.1038/s41434-019-0093-4) make up a number of the highly promising candidates for gene therapy. As these diseases fall within the purview of both NIDDK and a number of other NIH Institutes, we will not discuss them extensively in these comments. ASGCT supports continued funding for basic, translational, and early clinical research in these areas, to contribute to the development of treatments for diseases that under current standards of care may result in loss of productivity, lower quality of life, poor lifelong prognosis and early death for patients.

Gene therapy approaches for kidney diseases have not yet reached the clinical stage of development, though at least one clinical trial for a metabolic disorder that causes kidney damage is currently ongoing (see below). More research is needed to elucidate the biological pathways and genetic underpinnings of kidney diseases. One challenge for kidney gene therapies in particular is identifying an effective route of administration. The most common administration methods for gene therapies are intravenous infusion or direct to tissue/organ injection, which have proved effective for the most advanced clinical therapeutic gene therapy programs (including but not limited to ophthalmic disorders, hematologic disorders, and motor neuron disease). The unique structure and function of the kidney, however, wherein the glomerular filter blocks entry to all but the smallest particles from the bloodstream, makes intravenous administration difficult with current vectors which are nearly all too large to pass through the glomerulus. Thus, direct administration methods will most likely need to be developed for kidney gene therapies. Options explored in animal models have included infusion into the renal artery; retrograde infusion into the ureter or renal vein; and direct injection to the cortex or medulla (reviewed by Rubin & Barry, *Mol Diagn Ther.* 2020, DOI: 10.1007/s40291-020-00467-6). After an administered gene therapy successfully targets the kidney, the additional problem remains of selectively transducing the correct cell type for genetic correction out of the more than 20 that exist in the kidney. Thus, while gene therapies have the potential to provide novel treatment pathways for kidney diseases, including those caused by both genetic and environmental damage, these challenges must be overcome. Funding for additional research on effective delivery mechanisms could assist in actualizing the field's great potential.

As noted previously, gene therapy approaches for diabetes are more advanced than for kidney applications but are also in need of further research and development. Research in this area has resulted in at least one pre-clinical gene therapy targeting both type 1 and type 2 diabetes. An example of promising research from the metabolic disease space, which has shown promise for gene therapy approaches, is an ongoing clinical trial that addresses cystinosis, a lysosomal storage disorder leading to end stage kidney disease and other organ failure. The trial (ClinicalTrials.gov Identifier: NCT03897361) utilizes autologous transplantation of hematopoietic stem cells modified *ex vivo* using a self-inactivated lentiviral vector. The principal investigator of this trial received NIDDK funding in the course of developing the techniques now being tested.

Recombinant AAV vectors being used in many gene therapy development programs present challenges related to both innate and adaptive immune responses to the vector. Additional funding for investigations of the immunological profile of these vectors, including how to reduce the immunogenic features and improve the consistency and durability of therapeutic effects, would be a boon to the entire gene therapy field. Development of additional serotypes within existing vector types would be valuable to expand the universe of vectors with unique properties that can be used in the diverse fields of study within gene therapy.

NIDDK's role as a research funder can provide critical assistance to basic, translational, and early clinical studies. ASGCT encourages NIDDK to continue engaging grant reviewers who are knowledgeable about gene therapy, and to support innovative gene therapy approaches.

Promoting participant engagement -- including patients and other participants as true partners in research.

Patient advocacy groups can be important partners all the way from bench to bedside. Specifically, promoting patient engagement in gene therapies as they are developed will be critical to the continued growth of the field. Disease-specific advocacy groups are uniquely qualified to bridge the gap between patients and researchers. They can provide critical assistance in identifying patients, developing natural histories, obtaining human samples for research, coordinating and supporting funding opportunities, and disseminating research results within patient communities. Well organized and resourced organizations can provide support and information to patients throughout the clinical trial process, and sometimes stimulate treatment development. Patient organizations can also help researchers identify the benchmarks that patients themselves find meaningful, which is invaluable information in the clinical trial design process. By seeking out partnerships with patient groups from the beginning, researchers can engage patients as true partners and enrich their own research and clinical endeavors. ASGCT is pleased that NIDDK includes outreach to patient organizations among its core principles; we would advocate for the Institute to continue in that spirit of cooperation, and to promote opportunities for researchers and patient organizations to constructively engage with one another. The Society also appreciates the health information NIDDK provides online for patients and their families, and we encourage expansion of engagement in this way by developing, supporting, and/or promoting education about novel therapeutic approaches, such as gene therapy.

Advancing research training and career development to promote a talented, diverse biomedical research workforce.

ASGCT membership has doubled since 2016, reflecting the vast, rapid development of the field in recent years. ASGCT members who participate in academic research similarly report that trainees are highly interested in gene therapy as a research focus, particularly as the first therapies to treat monogenic diseases and oncologic indications have received FDA approval, and hundreds more are in clinical trials. ASGCT strongly supports policies to further grow the pool of gene therapy trainees, in particular trainees with diverse backgrounds and life experiences. Dedicated funding from NIDDK and other NIH Institutes for Research Training & Career Development is vital to that outcome, and ASGCT encourages the Institute to continue prioritizing trainee assistance.