



Comments for National Eye Institute Strategic Plan RFI

The American Society of Gene and Cell Therapy (ASGCT) appreciates this opportunity to provide input on NEI's strategic priorities. ASGCT is a nonprofit professional membership organization comprised of over 3,500 scientists, physicians, and other professionals working in gene and cell therapy. A core portion of the Society's mission is to advance the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

The most significant scientific discoveries in vision research since 2012:

-The identification of the genetic cause of disease, now known for approximately two thirds of patients with inherited retinal disorders (Consugar MB, *Genet Med.* 2015;17).

-The first FDA approval of a gene therapy for a genetic disease in 2017 for Luxturna—an adeno-associated virus (AAV) gene transfer to treat an *RPE65* gene mutation. NEI supported the original clinical trial for this treatment.

-Multiple clinical trials currently ongoing using AAV-based gene transfer for other mutations (www.asgct.org/clinicaltrials), including trials sponsored by the NEI.

-The 2019 initiation of patient enrollment for the world's first *in vivo* study of a CRISPR-based gene editing clinical trial, for the treatment of an IRD caused by mutations in the *CEP290* gene (<https://ir.editasmedicine.com/node/9436/pdf>).

-The discovery of optogenetics as a platform to render cells other than photoreceptor cells light-sensitive to restore retinal light response in patients with photoreceptor degeneration (Chaffiol A, *Mol Ther.* 2017;25[11]).

New opportunities that have been enabled by scientific discoveries:

-Discovery of additional disease genes in the approximately one third of patients who do not have identifiable mutations in currently known IRD genes (Duncan JL, *Transl Vis Sci Technol.* 2018;7[4]).

-Additional research on gene therapy for both IRDs and non-hereditary eye conditions (Rodrigues GA, *Pharm Res.* 2019;36[29]).

Needs and gaps in research that should be addressed by the NEI:

Because the development of treatments to slow or stop disease progression of IRDs has been limited, and gene therapy clinical trials have provided some successes (Edwards TL, *N Engl J Med.* 2016; 374; MacLaren RE, *Lancet* 2014;383; Weleber RG, *Ophthalmology* 2016;123), the need exists for additional gene therapy studies on other monogenic IRDs. ASGCT supports NEI's continued funding of gene therapy-related basic, translational, and early clinical research.

Within gene therapy research, many of the needs and gaps relate to vector development, particularly:

-Development of next-generation AAV capsids that target a high percentage of all cell populations in the retina by an intravitreal injection with doses and volumes that are clinically feasible. Current clinical methods require highly specialized surgical interventions that treat only a small fraction of the retina. Ideally such next-generation capsids could transduce a larger area of the retina without detaching it (Cukras C, *Mol*

Ther. 2018;26); third-generation capsids may also address cell tropism (Davidsson M, *Proc Natl Acad Sci USA* 2019;116[52]).

-Further study of natural or synthetic cell-specific promoters (Simpson EM, *Hum Gene Ther.* 2019;30[3]) and other regulatory elements, such as enhancers and silencers, in both humans and animal models.

-Development of non-AAV vectors to improve efficiency and specificity, and to address innate AAV immunity and packaging capacity (Hui DJ, *Mol Ther Methods Clin Dev* 2015;2; Zallocchi M, *PLoS ONE* 2014;9), such as lipid- and polymer-based carriers and lentiviral vectors (Ramamoorth M, *J Clin Diagn Res.* 2015;9[1]; Zallocchi M, *PLoS ONE* 2014;9).

Other key gene therapy-related research needs include:

-The study of large animal models to replicate human disease phenotypes for preclinical testing of therapies. As the rodent retina lacks a fovea and the models tend to display a more rapid rate of degeneration than what is seen in human disease, the utility of mouse models is limited. The establishment of more primate, pig, and dog models is needed.

-Research of the potential for gene therapy approaches for multigenic indications, such as age-related macular degeneration, glaucoma, and diabetic retinopathy. Preclinical and early-stage clinical studies of gene therapies for AMD are in progress (Rodrigues GA, *Pharm Res.* 2019;36[29]), but significant work is needed to reach the clinical stage.

-Further preclinical study of CRISPR and other gene editing tools in ocular contexts (Tsai YT, *Ophthalmology* 2018;125[9]).

-Exploration of the use of induced pluripotent stem cells and bone marrow-derived stem cells for ocular therapeutic approaches (Yazdanyar A, *Experimental Eye Research* 2019; 190).

The Society is also supportive of the additional federal funding to the NEI that would be necessary for the translation of scientific discovery into human medicine. Thank you for considering these comments.