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~ Via Electronic Submission ~

April 24, 2023

The Independent Citizens Oversight Committee and Application Review Subcommittee
California Institute for Regenerative Medicine (CIRM)

Application Number: TRAN1-14710
Project Title: AAV Gene Therapy for Treating Congenital Hereditary Endothelial Dystrophy (CHED) associated with Biallelic *SLC4A11* Mutations
PI Name: Anthony J. Aldave, MD
Co-PI Names: Matthew L. Hirsch, PhD; Wenlin Zhang, MD, PhD; Brian C. Gilger, DVM, MS

Dear Application Review Subcommittee:

We thank the Grants Working Group for their critical review of our **TRAN1** application submitted on December 12, 2022, under the Memorandum of Understanding (MOU) between CIRM and the Foundation for the National Institutes of Health (FNIH) (Stem Cell Agency Joins Consortium Developing Gene Therapies for Rare Diseases). This application submission followed the invited submission of a full clinical trial proposal entitled *Phase I/II Safety and Efficacy Study of AAV-SLC4A11 Vector to Treat Congenital Hereditary Endothelial Dystrophy (CHED)* to the Foundation for the National Institutes of Health (FNIH) Accelerating Medicines Partnership® (AMP®) Bespoke Gene Therapy Consortium (BGTC) clinical program 2022-BGTC-005 on October 31, 2022. The FNIH AMP® BGTC program is a public-private partnership involving CIRM, eleven NIH Institutes, Centers, and cross-Institute initiatives, the U.S. Food and Drug Administration (FDA), twenty-four pharmaceutical and biotech companies, non-profit organizations, and patient advocates (the full list of AMP® BGTC partners can be found on the AMP® BGTC program website). The BGTC is dedicated to making gene therapy a reality for people with rare genetic diseases affecting populations too small to be viable from the current commercial perspective. The goal of the BGTC is to evaluate methodologies to streamline the process of AAV gene therapy clinical trial initiation for pediatric and adult monogenic disease, in the process generating a standard operational playbook for developing gene therapies for rare genetic diseases. This playbook, to be established and piloted using up to six clinical trial test cases from the BGTC clinical program, will include streamlined templates, master regulatory files, and uniform manufacturing processes to create a pathway toward the commercial viability and sustainability of gene therapies for rare diseases. This playbook is also projected to have substantial positive impact on the larger field of gene therapy, especially as the field moves into the era of genome editing. For example, BGTC has developed standard evaluation criteria for selecting manufacturers of AAV vectors and a minimum set of Critical Quality Attributes (CQA) for product testing. Such standardized approaches will be incorporated into the BGTC playbook, becoming a public resource

describing best practices in gene therapy clinical trial initiation.

After rigorous scientific and technical review by a world-class team of ocular gene therapy experts, our application to the AMP® BGTC was judged to be highly meritorious. The BGTC Steering Committee voted on February 23, 2023, to include *Phase I/II Safety and Efficacy Study of AAV-SLC4A11 Vector to Treat Congenital Hereditary Endothelial Dystrophy (CHED)* in its pipeline of manufacturing, pre-clinical testing, and clinical trials for bespoke gene therapies, contingent upon approval of funding by CIRM, due to UCLA being a California-based organization. A letter from Philip J. Brooks, Ph.D. Co-Chair, BGTC was sent to CIRM on March 15, 2023, stating "we hope that CHED will be one of those trials (participating in BGTC clinical program)".The support letter also states "…if approved by CIRM, the CHED project would benefit from the expertise and resources of the BGTC, including the BGTC Coordinating Center (an NIH-led hub for clinical trial management), BGTC manufacturing and preclinical testing partners, and gene therapy subject matter experts in AAV biology, trial design and conduct, product manufacturing and testing, preclinical study design and execution, regulatory submissions, and IND approval."

The six clinical trials selected for funding in BGTC clinical program will be supported by consortium partners, including Contract Manufacturing Organizations (CMOs) and other manufacturing entities to produce the GMP vector to be used in IND-enabling Good Laboratory Practice (GLP) toxicity studies and in the human clinical trials. By creating the AMP® BGTC, which was referenced in the White House Bold Goals for US Biotechnology and Biomanufacturing (Opportunities for Public-Private Collaboration, page 47), the NIH, FDA and numerous private sector organizations have committed to working with a range of federal, industrial, academic, and advocacy organizations to address the unmet medical need in rare or ultra-rare diseases, a population of patients where no standard business case can be made for commercial therapeutic development.

We believe that the decision by the AMP® BGTC Steering Committee to support the manufacturing, pre-clinical testing, IND approval and clinical trial of the AAV-SLC4A11 vector to treat CHED through the provision of the aforementioned expertise and resources addresses the primary concerns in the Grants Working Group's Review Summary, namely product characterization and regulatory consultation, as summarized in the Minority Report:

> While the majority wanted to see the project plan revised with fuller characterization of the product and more input from FDA or a regulatory consultant, reviewers who scored 85 or higher found the project meritorious despite weaknesses in the current project plans.

We look forward to partnering with CIRM and the FNIH AMP® BGTC to achieve our CIRM TRAN1 Project Objective of performing the requisite assays and studies in preparation for a pre-IND meeting with the FDA and the goal of the BGTC, to streamline the process of AAV gene therapy clinical trial initiation for pediatric and adult monogenic diseases.

Sincerely,

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