ReviR Therapeutics, Inc.
150 North Hill Drive
Suite 19
Brisbane,
CA 94005

May 29th 2024

Re: TRAN1-16070 Application

Dear Independent Citizen's Oversight Committee,

We thank CIRM and the Grants Working Group for very favorable reviews and recommendation to fund our proposal, TRAN1-16070, **Genetic Therapy Targeting mHTT mRNA to Treat Huntington's Disease**.

ReviR Therapeutics is a California company committed to developing treatments for Huntington's Disease and we believe the proposal fits well with the goal of CIRM's Translational program. Huntington's Disease (HD) is a devastating, inherited, neurodegenerative disorder that is characterized by progressive motor, cognitive, and psychiatric symptoms that develop over 15–20 years with no effective therapies. Nationwide ~ 40,000 people have been diagnosed with HD and another ~ 150,000 have a 50 percent risk of developing the disease. We are eager to move our therapeutic candidate to the clinic as quickly and safely as possible and obtaining support from CIRM on this TRAN cycle will be instrumental to help us achieve this goal.

In this letter we would like to highlight support for our application from HD patient foundations and we would like to take the opportunity to provide additional clarity on points highlighted in the unanimously positive reviews by the Grants Working Group panel.

Application Number: **TRAN1-16070**
GWG score: **87 (recommended for funding)**
DEI score: **8**

Unwavering Support from HD Patient Foundations

We are extremely grateful to have support for our proposal and organization from several HD patient foundations including The **Huntington's Disease Society of America (HDSA)**, a non-profit organization dedicated to improving the lives of everyone affected by Huntington's disease and the **CHDI Foundation**, a nonprofit biomedical research organization committed to facilitate the development of therapeutics that offer meaningful clinical benefits to Huntington's disease patients. Please find below a letter from Mrs. Therese Crutcher-Marin, a California resident who

believes her public comment on the importance of HD research and therapeutic development will be best conveyed by submitting a letter. Mrs. Crutcher-Marin is President for HDSA San Francisco Bay Area Chapter, author, HD advocate, blogger, and retired healthcare professional. We are also pleased to have support from Dr. Robert Pacifici, PhD, Chief Scientific Officer CHDI Management, Inc. who will be calling into the Application Review Subcommittee meeting on May 30th to voice support for our application. By engaging with patient foundations and engaging with the HD community, ReviR Therapeutics understands the challenges HD patients and families are facing and are working diligently to develop transformative therapeutics for HD. We believe it is in reach, and we have developed the technologies that will be a game changer for people with HD. CIRM funding for our TRAN1 application will help us achieve this important goal of transforming the treatment of Huntington's Disease, in California and around the world.

Response to Reviewers

We are delighted reviewers unanimously recognize the high impact of our work and recommend funding of our TRAN1 application. We have carefully examined the concerns raised and provide additional clarification below.

> *1. There remains a major risk related to the candidate's efficacy. It is unclear if this will work in a relevant pre-clinical model, either an organoid system or a mouse model of HD (such as the BACHD mouse model). The applicant should generate some initial pre-clinical data in a clinically relevant model demonstrating that their candidate can actually mediate phenotypic correction of HD.*

Response:
We appreciate the reviewer's suggestions and have indeed considered the possibility that our candidate may not work in a relevant preclinical model. While we have confirmed that our candidate will not work in rodents containing only the rodent HTT gene sequence, we are delighted to confirm our candidate works in the fully humanized BACHD mouse model of HD, thereby re-disking our candidate's efficiency testing in preclinical models. Furthermore, we are pleased to report our candidate works in human preclinical models such as HD patient iPSCs and iPSC-derived neurons (as shown in Figure 3 of the submitted proposal). We have no reason to believe that it will not work in HD patient iPSC-derived organoid systems. However, as part of the proposal we will prioritize generating data using organoid systems to determine the candidate's efficacy at an early stage.

> *2. An attractive proposal is to conduct a study to support a machine learning/AI approach to interspecies splicing risk assessment that will support selection of informative animal species for toxicology studies.*

Response:
We agree with the reviewer on the potential benefits of integrating a machine learning/AI approach to interspecies splicing risk assessment. Indeed, since our inception ReviR Therapeutics has employed AI approaches to accelerate our drug discovery efforts. Our approach leverages in-house genomic and transcriptomic data to enhance the predictive accuracy of our splicing risk assessments across species. We are using our AI platform to train machine learning models to understand splicing events that may take place in species and/or cell types where we do not have a full transcriptomic profile. In addition, we have hired a computational biologist at our Brisbane California site who is currently working full time on developing predictive models to identify the most informative animal species for our toxicology studies. Implementing this strategy will not only optimize our selection of animal models for toxicity studies but also streamline our preclinical

study designs, ensuring they are both efficient and effective.

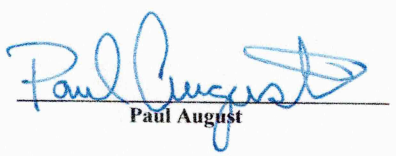
> *3. Due to the lack of specificity for mHTT RNA, the FDA likely will ask for a broader preclinical assessment of toxicity and safety as part of the final GLP studies. The proposal focuses on neural and CNS tissues and includes heart, liver, and muscle assessments. It may be wise to broaden the spectrum of non-neural tissues early during the grant-supported studies in case of unexpected toxicities in other organs (e.g., pancreas, thymus, lymph nodes, spleen, etc). Such an approach could be considered as an addition to the planned rodent toxicity screen.*

Response:
We appreciate the reviewer's suggestion to broaden the spectrum of non-neural tissues in our preclinical assessments. In response to this critique, we will expand our toxicity studies to include additional non-neural organs such as the pancreas, thymus, lymph nodes, and spleen. This will be incorporated into our initial rodent toxicity screens to ensure comprehensive safety profiling. By doing so, we aim to proactively address any potential organ-specific toxicities that may arise, thus aligning with FDA expectations for a thorough safety evaluation. This broader assessment will help mitigate risks and support a robust IND submission.

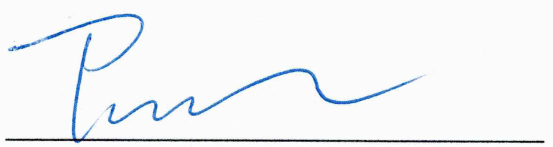
We hope that our answer to these comments will satisfy the board's concerns and propel our proposal across the line into the funded category.

Finally, we would like to thank CIRM and the ARS for giving us the opportunity to address the reviewer comments and for considering our responses. Based on the information provided in this letter and the unwavering support for our proposal from HD patient foundations, we hope the ARS will reconsider funding our proposal.

Sincerely,



Paul August, Ph.D.
CSO, ReviR Therapeutics
Cell: +1-617-230-6382
Email: paul.r.august@revirtx.com



Peng Yue, Ph.D.
CEO and Co-founder, ReviR Therapeutics
Cell: +1-650-866-1826
Email: peng.yue@revirtx.com

May 14, 2024

Paul August
CSO, ReviR Therapeutics
600 Gateway Blvd, Suite 100A South San Francisco, CA 94080

Attention: Dr. Paul August

RE: Support for ReviR Therapeutics CIRM application

Dear Mr. August,

My name is Therese Crutcher-Marin and I'm the President of Huntington's Disease Society of America San Francisco Bay Area Chapter, an author, Huntington's disease advocate, blogger and a retired healthcare professional.

I'm writing in support of ReviR Therapeutic's application to secure funding for Huntington's Disease (HD) research. The funding from CIRM will help move ReviR forward in developing a CURE for HD. The combination of the oral treatments ReviR is working on could have transformative effects in HD patients and stop disease progression in HD.

Huntington's disease has affected my husbands' family for five (5) generations. For 24 years, I watched and cared for my three (3) sisters-in-law, my friends, on their long HD journey and my family lived with the stress of my husbands' unknown gene status. The mother of these four (4) siblings was placed in Napa State Hospital and because her chorea was uncontrollable, she was restrained, and she strangled to death. I call HD the cruelest disease on the planet because it slowly steals everything from a person.

I believe research is critical as it provides for HD patients and their families renewed **hope** by knowing organizations are developing effective therapeutics and conducting clinical trials. A successful drug, a CURE, will stop the suffering of HD patients and their families. Stopping the progression of HD will lower their tension, allow them to work and live longer, fix dinner for their family, enjoy their children, watch their grandchildren grow up, live normal lives and enjoy the highest quality to their lives.

The state of California has the highest number of at-risk and symptomatic patients in the country. A few of the effects rendered would be: California's disability claims would be lowered and Medicare application for young people would be reduced. The CIRM funding is critical to support ReviR efforts to advance their programs to the clinic as soon as possible. My family considers CIRM's approval of ReviR's application as a gift to all HD families in California.

Thank you for your commitment to the HD community.

Sincerely,

Therese Crutcher-Marin
President for HDSA San Francisco Bay Area Chapter

HDSA San Francisco Bay Area Chapter
P.O. Box 1599
Cupertino, CA 95015