Parkinson's Institute
and Clinical Center

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Independent Citizens' Oversight Committee
California Institute for Regenerative Medicine
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Subject: Consideration for funding of DISC2 08953 application

Dear ICOC members;

I am writing this letter to update the ICOC members on an exciting newly published paper that demonstrates the feasibility of the approach we propose in our DISC2 08953 entitled: "CRISPR/dCas9 mutant targeting SNCA promoter for downregulation of alpha-synuclein expression as a novel therapeutic approach for Parkinson's disease". We believe this new publication and the additional information in this letter should be sufficient to recommend our proposal for funding.

The new paper published on June 24th, 2016 by Heman-Ackah and colleagues from Oxford University (doi:10.1038/srep28420), while our application was under review, describes the successful use of CRISPRi/small guide RNA constructs to achieve an ~50% knockdown of alpha-synuclein in human iPSC-derived neurons. This new data demonstrates the soundness and feasibility of our approach. I have strong expertise in gene editing (see manuscript using zinc-finger gene editing in a genetic Parkinson's stem cell model which was recognized by the editor of Nature Genetics as a benchmark paper, Sanders et al 2014, doi: 10.1016/j.nbd.2013.10.013). The inventor of CRISPR interference, Dr. Stanley Qi, Stanford University, supports this application and will advise us and share reagents (see letter in grant application). While we have not yet published on the specific use of CRISPR interference, we have the necessary skills and insights to perform the proposed study. Perhaps most importantly, this new data will 1) allow us to accelerate the project and move more rapidly into *in vivo* studies (Milestone 3) and 2) allow us to build on these findings to test additional constructs that might achieve greater than a 50% knockdown as reported in the paper.

The reviewers were also concerned about reaching the clinical goals. Although not discussed in the proposal, we would like to share with the committee that the Parkinson's Institute and Clinical Center team has led bench-to-bedside translation for academic studies and in partnership with pharmaceutical companies in industry-sponsored clinical trials over 25 years. With the hire of Dr. Carrolee Barlow, MD, PhD, as the CEO of the Institute, we have added substantial expertise in the area of therapeutic development. Dr. Barlow has experience in drug development including early stage preclinical development through clinical development, including filing of INDs and NDA's for drug approval. Dr. Barlow has worked to establish a team of internal and external preclinical and clinical therapeutic experts needed for regulatory grade studies. These capabilities are complemented by our strong understanding of Parkinson's and an ability to interface with regulatory agencies to ensure that new preclinical and clinical studies will meet FDA standards for a product development path.

Lastly, the GWG panel asked whether the *spread of the virus and appropriate dosing requirements in human* would be a concern. Viral vectors are the most powerful tools we have to introduce therapeutic interventions at the genetic level. Our co-investigator Prof. Deniz Kirik, Lund University, Sweden,

selected by CIRM scientific staff as an expert in gene therapy, is adding these skills for translation of these methods into human. A clear objective of the DISC2 application is to advance to clinical trials within a short time frame using small animal studies as biological proof of concept. Once we demonstrate that the CRISPRi intervention is viable in small animal models, we will use published data that we and others have collected both in larger animal species as well as in small clinical trials that have been completed and published to address the virus spread. Most importantly, we can control and adapt the expression level of the constructs in the brain, define its duration and terminate as and when needed (see e.g., Cederfjall et al., 2015, PMID: 25592335 for a recent animal study from Prof. Kirik's group on this topic).

Taken together, I hope we have provided valuable new data that will allow the ICOC to move the proposal into the Tier 1 category for funding.

Sincerely,

Birgitt Schuele, MD
Principal Investigator