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Dear CIRM ICOC Board,

I am writing this letter to encourage the ICOC to move DISC0-15764 from tier 2 to tier 1 and to fund in the current cycle. This application is entitled "Modeling Arealization to Understand Etiology of Neurodevelopment Disorders". It is urgent to fund this proposal in this cycle because this project seeks to provide critical improvements in current human brain organoid models to enable accurate studies of neurodevelopmental disorders. Without these improvements, our ability to identify and test treatments for neurodevelopmental disorders which impact 4.6% of California children (as per the CDC) will remain severely limited.

This study will test data driven improvements in organoid models to make them more resemble the development that occurs in the human brain, enabling more accurate studies of neurodevelopmental disorders. The progress from this application would directly help patients by creating improved tools to study neurodevelopmental disorder etiology and in which to test novel treatments. I understand neurological disease is a current priority of CIRM - consistent with this, reviewers noted "*The project plan and timeline demonstrate an **urgency that is commensurate with CIRM's mission.***"

I would like to thank the reviewers for their positive comments and criticisms. Of the criticisms about the project, all are **already addressed** in the application. In the rationale section, one reviewer says that cells with guide activation do not show more PFC identity, when in Figure 3 (page 9) we show that the PFC cells are wholly from guide activated cells (and not overlapping populations as indicated). The reviewers note that in Aim 1 we are testing transcription factors (TFs) from the PFC and claim we use the same factors as readout; in fact, we plan to use a sequencing-based readout that would be unbiased in measuring effect (page 13). Another review suggests we should use VPR because it is superior to VP64 for CRISPR activation, however in our system we tested and saw that VP64 produced a stronger effect (page 9). One comment indicates that given the small number of (TFs) tested we should try a cDNA overexpression approach; this is in fact our approach in Aim 1B (page 14) and the screen in Aim 1A is used to identify and prioritize these candidates with single-cell readouts that are cost prohibitive to screen with individual overexpression experiments. Finally, the last comment notes that we should do some pilot work to measure lentiviral silencing, which we have completed and is shown in Figure 6 (page 12). **No critiques are offered for Aim 2**, and a number of positive comments including "*Overall, the project is well designed,*" "*it is invaluable data for the field of stem cell neurobiology*" and "*The project addresses a major bottleneck... The project will open doors for multiple laboratories with different interests.*"

Additionally, the nature of the critiques is such that I am confident if any further clarification is required, I can work directly with program officers to ensure all reviewer concerns are addressed during the execution of the project.

Given this positive response to the application and limited technical criticisms, I would encourage the ICOC to fund this research *in the current round of applications* because it will have a major impact to patients who urgently need new treatments, the field of neurobiology, and the taxpayers of California. Thank you for your consideration.

I will be present at the meeting and am happy to answer any follow up questions.

Sincerely,

A handwritten signature in cursive script that reads "Aparna Bhaduri".

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