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September 15, 2025

Application Review Subcommittee
California Institute for Regenerative Medicine
601 Gateway Blvd #400
South San Francisco, CA 94080

Subject: Letter in support of DISC0 proposal #17276

Dear Members of the Application Review Subcommittee,

We are grateful for the positive reviews of our proposal entitled “Modeling Rett Syndrome Neurological Disorder with Human Pluripotent Stem Cells to Develop in Cellulo Screening Platforms.” (DISC0 application #17276). We are writing to underscore the importance of this proposal and the potential impact for people with Rett syndrome.

Rett syndrome is a devastating disorder that robs affected individuals of neurological functions in every domain (social, cognitive, motor, balance, autonomic, moods, and more). It is especially devastating that the child loses these abilities after a period of apparent normal development. It is, however, uplifting and encouraging to note that in spite of this, we know that the brain in Rett is intact, but its synaptic function is suboptimal. Importantly, studies in mouse models have shown that the disorder is reversible in adult mice.

To date, there is no meaningful therapy for Rett syndrome. While there are two ongoing gene therapy clinical trials, the fact that these therapies only reach 10% of brain cells and in regions close to injection sites reveals the limitations of such therapies emphasizing the dire need to significantly improve today’s available therapies. Moreover, the expense and intense monitoring needed (due to potential serious complications associated with gene therapy) renders this treatment modality of limited access to patients and especially those without adequate health insurance. Thus, there is a dire need for alternative treatments including small molecule therapeutics that are much less costly and thus much more feasible to treat a much greater world-wide patient population with Rett.

Fortunately, about 65% of Rett patients have mutations that either affect the DNA binding of MeCP2 or its protein levels. Recent unpublished work from the Zoghbi lab has shown that enhancing the stability of a defective MeCP2 rescues all the molecular, physiological, and morphological phenotypes in human

iNeurons. This important proof-of-concept finding indicates that if a small molecule drug can be identified that would enhance the stability and/or levels of a mutant MeCP2, this could help the many patients with mutations that still make a protein (~ 65% of all mutations). We are therefore excited about the proposed approach of screening for small molecules that can stabilize MeCP2 or enhance its activity. Our unique single molecule tracking approach of mutant MeCP2 in living human iNeurons will not only allow us to detect enhanced MeCP2 levels but, importantly, will also assess the key molecular function of MeCP2 which is its ability to bind DNA.

The mutations we selected are excellent representatives of missense mutations affecting humans as they alter both protein levels and DNA-binding. Importantly, human and mouse data show that enhancing their levels overcomes the DNA-binding deficits.

Rett syndrome is one of thousands of neurodevelopmental disorders affecting children worldwide, but it is one of the four most common causes of this class and has been paradigmatic in revealing reversibility and establishing the breadth of genotype phenotype relationships. Thus, the proposed research which relies on screening with ESC derived cells, will not only help Rett syndrome patients, but will also inform other disorders caused by haploinsufficiency of protein (2/3 of NDD disorders) whose levels can be enhanced using small molecule drug intervention strategies.

We thank you for your support of this proposal.

Sincerely,

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