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May 23, 2024

RE: TRAN1-16030

Dear Application Review Subcommittee,

I am writing to ask that our application to develop a gene therapy for a rare non-degenerative neurogenetic condition, Angelman syndrome (AS), be supported in this current funding cycle. We are eager to move our gene therapy to the clinic as quickly and safely as possible. Obtaining support from CIRM on this TRAN cycle would play an instrumental role in helping us realize this goal. This entire project to date has been funded by the Foundation for Angelman Syndrome Therapeutics (FAST), a patient advocacy group focused on supporting research toward transformative therapies, but bringing a program through the entire drug development pipeline needs additional financial support. The Foundation's collaboration with UCLA, with CIRM's support, could make this a reality, while also allowing this nondegenerative neurogenetic condition serve as a model for so many more newly recognized rare neurogenetic conditions.

Application Number: TRAN1-16030
Project Title: Evaluation of an ex vivo lentiviral gene therapy for the treatment of Angelman Syndrome
GWG score: 85 (recommended for funding)
DEI score: 9

We are part of a team at UCLA that specializes in developing ex-vivo gene therapy approaches to treat a multitude of disorders (for example, Adenosine Deaminase-deficient severe combined immunodeficiency, sickle-cell disease, X-linked chronic granulomatous disease). We have decades of experience in successfully bringing therapies to the clinic and this would be the first neurogenetic condition that we are eagerly supporting. We are coming to realize that our platform of ex-vivo gene replacement technology could have a profound impact on neurogenetic conditions like AS with the recent approvals for both metachromatic leukodystrophy and adrenoleukodystrophy supporting this vision.

Some very exciting proof-of-concept data has been generated in the Angelman syndrome mouse model, which was solely funded, since 2016, through the patient advocacy group, FAST, a California registered non-profit organization supporting the discovery and advancement of transformative therapeutics for this rare condition. What is most remarkable about this specific program is the comprehensive phenotype and electrophysiological correction that was observed in the AS mouse regardless of the age of treatment – this is frankly the most robust rescue that has been seen when considering all possible modalities in this well studied animal model, and was notably more extensive than that seen with AAV9 in-vivo gene therapy, antisense oligonucleotide therapy, zinc finger technology and CRISPR-gene editing. What is most promising is that the full phenotypic correction was similarly robust in the adult as it was in the newborn mice, which can be highly impactful in a population of individuals that have an estimated incidence of 1:15,000, or ~2,600 affected in California, ~25,000 in the United States and over ~500,000 worldwide. There are currently no approved therapies for this condition and the clinical unmet need is profound.

We, as the scientific team at UCLA, as well as our collaborators at the Foundation for Angelman Syndrome Therapeutics, would greatly appreciate your vote to fund this award and support our efforts to develop this therapy so that we can bring a potentially transformative treatment to patients who are urgently waiting.

Sincerely,

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Allyson Berent, DVM, DACVIM
Chief Science Officer, Foundation for Angelman Syndrome Therapeutics
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