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September 25, 2023

CIRM ICOC members

Re: DISC2-15114
"Development of a VAV2 antisense oligonucleotide (ASO) treatment for ALS"
PI: Justin Ichida, PhD

Dear Committee members,

Thank you for reviewing our DISC2 application, "Development of a VAV2 antisense oligonucleotide (ASO) treatment for ALS." The proposed study aims to identify a development candidate ASO that suppresses VAV2. Our data and genetic evidence suggest this strategy could treat all forms of ALS, including sporadic ALS, for which there is high unmet need and a dearth of therapeutic targets.

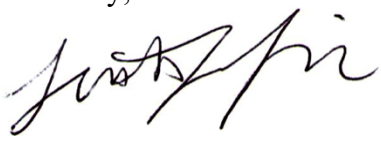
We thank the review committee for their insightful comments and I'm writing to address some of the key critiques. One important comment from one reviewer was that it would be better if suppressing VAV2 could address C9ORF72 ALS, since this is the most common known form of the disease. We believe the reviewer may have overlooked the data in Figure 3 of the proposal that shows that VAV2 suppression extends the survival of neurons from 3 different C9ORF72 ALS patients. Therefore, we anticipate that if it is efficacious in humans, VAV2 suppression should be able of treating C9ORF72 ALS patients.

A second comment raised concerns about known challenges of ASO therapeutic delivery for ALS and other brain conditions, and reviewers felt that these challenges were not adequately addressed in this proposal. This is an important concern, and we thank the reviewers for raising this issue. We have been encouraged by the recent approval of tofersen, and ASO for SOD1 ALS and will incorporate some of the additional studies Biogen/Ionis used to improve ASO safety. This includes testing inflammation in human peripheral blood mononuclear cells, since testing in rodents and NHPs may not fully predict human immune responses. In addition, we will perform longer and more in-depth rodent and NHP tox studies, and we will explicitly evaluate hydrocephalus in this models since this has plagued multiple clinical ASO studies in the CNS.

A third comment was that it would be important to better understand the mechanism of action for VAV2 suppression. We agree wholeheartedly and are actively working on this. We have recently made significant strides in understanding why VAV2 suppression protects ALS neurons against degeneration and will continue to invest in mechanistic experiments throughout development of the VAV2 ASO program.

Thank you very much for considering our DISC2 application for funding. We are also enclosing a letter of support from a member of the ALS patient community who feels this application merits funding do to its innovative approach, preliminary data, and the high unmet need. Please do not hesitate to reach out if further discussion would be helpful in your funding decision.

Sincerely,



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Sept 24, 2023

CIRM ICOC

Re: DISC2-15114, Development of a VAV2 antisense oligonucleotide (ASO) treatment for ALS

Dear Committee Members,

I am writing to provide my strongest support for Dr. Justin Ichida's DISC2 application, "Development of a VAV2 antisense oligonucleotide (ASO) treatment for ALS." In 2012, I lost my mother, Martha Olson-Fernandez, to ALS when she was just 49 years old. I was her primary caregiver for the last 6 months of her life. I remember the day I truly understood what "fatal" meant in the context of a disease. Up until that point, my family was in denial, treating symptoms like they would eventually go away, thinking that the NP001 trial at the Forbes Norris Center would work and we that had more time. We were in the parking lot at Martha's pulmonologist's office - she was experiencing an allergy attack on top of her minimal respiratory function, and physical inability to expel built up mucus and saliva. There was nothing our pulmonologist could do outside of provide the steroids they already had and give us swabs and a suction machine. It was helpless. Modern medicine had failed us and would continue to fail us for the next few months until her passing. Prior to her death, my mom and dad established the Martha Olson-Fernandez Foundation (MOFF). Martha's wish was for all funds to go to research so that future ALS patients did not have to experience what she went through.

I am currently CFO and Program Director at MOFF. Since 2012 we have invested over $900,000 in ALS research projects and ALS patient care initiatives. My sister, father and I have hosted golf tournaments, dinners, and hikes to ensure that people living with ALS feel supported in their journey and early-stage neuroscience projects do not die in a lab but are made more specific and selective until they become attractive to a biopharma company. MOFF's diversified philanthropic investment portfolio has funded research on C9of72, AAV and ASO therapies, ALS animal model development, ALS biomarker database initiatives, and microbiome studies. I have attended conferences, symposiums, and panel discussions over the past decade to search for promising programs to invest in. Through these efforts, my work with NEALS, and my MBA degree in pharmaceutical and healthcare business, I have a solid understanding of the ALS research landscape, how drug development works, and where funding should and should not be invested. I currently hold the title of Project Manager and Head of Patient Advocacy at Viracta Therapeutics, a company developing targeted therapies for viral driven malignancies. I will work for a company developing therapies for ALS in a few years but for now, I am learning from a therapeutic area that has had a head start on innovation in the scientific and clinical realms.

I believe that Dr. Ichida's innovative iPSC platform is uncovering new therapeutic targets with a high probability of disease-modifying activity given that it uses ALS patient-derived nerve cells. Dr. Ichida discovered VAV2 as a new target through a screen across the entire genome, suggesting it is one of the most potent ways to slow the degeneration of ALS patient nerve cells. In addition, there is genetic data that suggests that inactivating VAV2 may be protective against ALS, which further supports the disease relevance of this target. The preliminary data from Dr. Ichida's lab suggest early signs of efficacy in animal models, which is exciting and worth exploring further. Importantly, VAV2 has the potential to slow neurodegeneration for all forms of ALS, including the sporadic patient population, for which there is a very high unmet need.

Overall, I feel that the lines of evidence Dr. Ichida's lab has presented suggest this target is of very high importance and should be investigated further.

Lastly, I would like to add that MOFF previously funded work in Dr. Ichida's lab on PIKFYVE, an ASO program originally started in Dr. Ichida's lab which was recently licensed by Takeda and is expected to enter clinical trials next year. This shows that the Ichida lab has the experience and know-how to build early-stage therapeutic leads that can be transferred to industry partners for clinical development.

Thank you for your consideration of this application.

Sincerely,

Natalie Marie-Fernandez Hooks, MBA