UT SOUTHWESTERN
MEDICAL CENTER

Department of Pediatrics

January 22, 2024

To: California Institute for Regenerative Medicine (CIRM)

RE: Support for Elpida Therapeutics' appeal regarding CRIM application CLN2-15607

To whom it may concern,

I strongly support Elpida Therapeutic's appeal for their recently reviewed and rejected CIRM application to initiate a Phase III study to test intrathecal administration of AAV9/AP4M1 (MELPIDA) as a gene therapy treatment for Spastic Paraplegia type 50 (SPG50).

I'm writing from the perspective of the laboratory that I lead, which designed the AAV9/AP4M1 vector, and led all the in vivo preclinical pharmacology and toxicology studies that supported the original CTA and IND applications for this gene therapy treatment.

A major criticism noted by the scientific members of the review committee, which appeared to be score-driving, centered around skepticism that the preclinical data inadequately predicted a benefit to patients, due to the limited number of cells transduced within the CNS. For example, in response to the criteria addressing if the rationale is sound, the response included "The vector biodistribution in mice, rats and NHPs suggest that somewhere between 1 in 10,000 to maybe at best 1 in 100 cells will express the corrective transgene. So, 99% to 99.99% of the CNS neurons will be uncorrected." This conclusion was made incorrectly based on graphs that quantify RNAscope data (in situ hybridization to visualize expressed transgene mRNA), in which the metric of quantification was "% positive area". Rather than interpreting this data correctly according to the y axis label as "% positive area", the reviewers incorrectly interpreted the data as the percentage of cells transduced. In situ staining of RNA in tissue sections (RNAscope) appears as punctate foci subcellularly localized within cells and does not fill the cell volume, so the raw quantification of "% positive area" is always a low number even if a large percentage of the total cells express the transgene. This RNAscope data was meant to confirm the expression of the transgene and provide a general qualitative visualization of the spatial distribution of transduction, and should not be used as a metric of the number of cells transduced. The biodistribution data provided from rats and NHPs showing ~10% of cells receiving the vector DNA is a more accurate and quantitative measure of the number of cells targeted. All of the preclinical data in the CIRM application was pulled from our peer-reviewed publication (Chen X et al., JCI, 2023). My overall sense is that this misunderstanding of the preclinical data clouded the reviewers' view of the overall program as a fatal and impassable flaw, leading to the low score and decision to reject. If the application was reviewed with this correct understanding of the preclinical data, I have confidence that the strong merits of the program could be given greater consideration, leading to a different review outcome.

I also want to emphasize that the published preclinical data for SPG50 supporting the use of AAV9 to treat a CNS disorder does not stand alone. In rodent and large animal models of similar monogenic CNS disorders, when we achieved similar biodistribution by intra-CSF administration of AAV9, we've seen substantial efficacy for Giant Axonal Neuropathy (GAN), Rett Syndrome, CLN7 Batten disease, Charcot-Marie Tooth disease type 4J, Leigh syndrome, Krabbe disease, and Aspartylglucosaminuria, among others (Bailey RM et al, MTMCD, 2018; Sinnett SE et al, Brain, 2021; Chen X et al, JCI, 2022; Presa M

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et al, JCI, 2021; Ling Q et al, MTMCD, 2021; Bradbury AM et al, JCI, 2020; and Chen X et al, Mol Ther, 2021). To be clear, all of these saw meaningful preclinical efficacy even when a minority of cells (i.e., ~10%) where transduced across the brain, and across these studies that used high doses of AAV9, we've seen consistent biodistribution results across mice, rats, dogs, and NHPs. Since 2015, seven of these treatments based on intra-CSF delivery of AAV9 have expanded into human clinical trials. Across the field, there are over 2 dozen clinical trials using this approach (recently reviewed by Chen X et al, Hum Gene Ther, 2023). Broadly speaking, the potential for intra-CSF administration of AAV9 to broadly target the CNS and enable a meaningful benefit has thus been demonstrated by numerous academic laboratories and companies. The preclinical data that my laboratory generated for SPG50 is consistent with the data generated by those numerous other precedents, so I am confident that the preclinical data for this program strongly predicts a meaningful benefit to patients.

Sincerely,

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