Dear CIRM Board

Over the past 18 months, our efforts to secure a CLIN2 grant have faced repeated and systemic obstacles. The challenges we've encountered, particularly regarding a lack of expertise in gene therapy and rare diseases among the CIRM scientific review teams, jeopardize a critical program with transformative potential for both patients and the field of medicine.

To provide context, CureSPG50, the foundation I founded, first submitted SPG50 to the BGTC program four years ago. It was selected as one of the top eight programs for its scientific rigor and high probability of success. Despite this recognition, it was disqualified due to its advanced stage of development. Subsequently, we were introduced to Dr. Creasey and CIRM, who mentioned they could support our program, thereby, reinstating SPG50 to the BGTC/FNIH programs. This led to the founding of Elpida – a California-based biotech company-and a collaboration aimed at advancing SPG50 and other promising programs.

Since Elpida's acceptance into the BGTC program in May 2023, we have worked closely with BGTC/FNIH/NCATS, CIRM, and other stakeholders to move SPG50 forward. CIRM itself has publicly highlighted our work on numerous occasions, including presentations at UCLA and rare disease meetings, as well as an October 2024 CIRM blog post where Terry and CIRM emphasized the vital (and critical) role of CIRM's funding for innovative therapies, such as those for the rare disease community.

Yet despite this alignment of goals and public support, we have repeatedly encountered unwarranted and poorly substantiated barriers in the grant review process. Notably:

1. **Critical Errors in the 2023 Review Process**: A reviewer's misinterpretation of biodistribution data, which we clarified in January 2024, highlights a concerning lack of scientific rigor in the review. Rather than addressing this through open communications or clarifications prior to voting or listening to the appeal during the voting, the CIRM process forced us into a resubmission.
2. **Delays Due to Internal CIRM Decisions**: The closure of the CLIN2 program, coupled with the increased timelines between the submission and review caused by new CIRM policies, delayed the evaluation of our July 2024 submission until December 2024. These delays further hindered progress on a program addressing an urgent unmet need.
3. **Biased and Inadequate Review**. Despite using the additional time to refine and strengthen our application-garnering support and input from senior NIH directors, the BGTC chairperson, and a Phase III trial design vetted by the FDA – the latest review demonstrated a glaring lack of understanding of gene therapy, AAV technology, and rare diseases, especially in the context of neurodegenerative disease. The dismissive tone and lack of due diligence were not only unprofessional but also deeply disrespectful to the significant efforts invested in preparing the proposal.

These issues raise serious concerns about the review process's capacity to fairly and accurately evaluate transformative programs like ours.

Below, I highlight the most egregious of these reviewer remarks and explain the reasoning behind my concerns:

Comment #1:
"There are ethical concerns with this submission as beyond 'failing to work.' There is a high likelihood of worsening or accelerating bad outcomes for the recipients AND it may preclude them from receiving other more efficacious products in the future."

Response #1:
This program targets an ultra-rare neurodevelopmental and neurodegenerative disease for which no other therapies exist. To date, four subjects have received treatment in Ph1/2 trials in the US and Canada. The FDA, as adjudicators of the ethical process, approved an IND and the ongoing trial. In addition, permitted approval of the treatment of pre-symptomatic infants (>4months old) given the scientific merit and rationale. The phase 3 trial was designed based on preliminary data of safety and efficacy, in collaboration with the FDA and subject matter experts in both gene therapy and SPG50 disease. All communication was provided in detail in our application.

The ethical concerns raised in this comment also appear to reflect a lack of familiarity with the realities of rare diseases and gene therapy. For these children, there is no alternative therapy in development, making this program their only hope.

We respectfully request that reviewers with expertise in gene therapy and rare diseases evaluate this application to ensure a fair and accurate assessment.

Comment #2:
"It is unclear that this revised protocol is feasible. The patient population is small, the control group is not truly matched, and the number of cells modified is likely inadequate to lead to modifications in disease outcome. As previously stated, there are ethical concerns with allowing this project to move forward as the outcomes may be worse rather than better for these patients. With these factors, this project should not be funded."

Response #2:
This program addresses an ultra-rare disease with a very small patient population, making traditional trial designs challenging. Despite these limitations, we have collaborated extensively with the FDA and leading experts to create a feasible Phase III protocol that meets regulatory standards and likelihood of meeting the primary and secondary endpoints. The trial design incorporates robust measures to assess safety and efficacy, and the preliminary results show promising signs of potential benefit.

The concerns raised appear to overlook the realities of rare disease research and the lack of alternative therapies for these patients. This program represents the only potential treatment for this population. We urge that reviewers with expertise in rare diseases and gene therapy evaluate the application to ensure objective and appropriate review.

Comment #3:

The trial is designed as phase 3, involving children, matched by age and highest level of motor function at baseline, with consideration of the presence of seizures. While serum and CSF biomarkers are proposed, no data has been provided. It is an open-label trial, and it is

unclear how blinding can be implemented. The matching is not very convincing, as it includes other forms of spastic paraplegia.

Response #3:
The trial design, including the blinding plan, was developed in close collaboration with the FDA and was clearly detailed in our submission. These concerns could have been addressed during the allocated question-and-answer session, but they seem to stem from a lack of understanding of the underlying biology of the disease. The AP4 complex is composed of four genes (SPG47, 50, 51, and 52), and dysfunction in any of these genes results in the same phenotype due to the inability to produce the AP4 protein.

This innovative trial design avoids a placebo control while ensuring rigor and fairness, a solution discussed and endorsed by the FDA as appropriate for this rare disease. We respectfully suggest that reviewers with expertise in rare diseases and gene therapy evaluate this application to ensure a fair and accurate review.

Our Request:
We respectfully ask that CIRM seek input from leading experts in rare diseases, such as Dr. Richard Finkel (St. Jude Hospital) or Dr. Barry Byrne (University of Florida), to provide guidance on our program and support a re-evaluation of our application.

We are confident that these renowned leaders in the field will recognize our program as a model for effectively designing and executing rare disease initiatives, setting a precedent for future programs to build upon.

These children are far too important to abandon, and I believe that both CIRM leadership and the board share this sentiment.

Thank you for your time and continued support.

Sincerely,

Terry Pirovolakis
Founder