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January 20, 2025

To: CIRM ICOC

RE: CLIN2-17081 CIRM Application - Phase 1b/2a Study Of The Safety And Tolerability Of Human Neural Stem Cells For Huntington's Disease (REGEN4HD)

I am writing as an expert in Huntington's disease to address the review associated with CLIN2-17081. As an independent clinician-scientist, I would like to highlight that some of the key arguments presented against funding this project are fundamentally flawed.

I have recently been elected as one of the few international members of the US National Academy of Sciences in recognition of my contributions and expertise in Huntington's disease. Additionally, I am an elected Fellow of the Royal Society in London, honoured for my significant contributions to understanding Huntington's disease biology which are underpinning clinical studies of novel therapeutics for the disease. Over the course of my career, I have led numerous innovative clinical trials in Huntington's disease and am very familiar with the landscape of this field and am consequently very well placed to comment on Dr Thompson's proposal. I also was sent the proposal to review, but I received the email whilst on holiday and then could not meet the very tight timelines (a few days) by the time I came back from leave and saw the email.

I have significant concerns about the peer reviews you have received for the application. I have outlined these below.

1) Reviewer Comments relating to fetal cell trials:
"Surprisingly, the applicants have also omitted to discuss a phase 2 cell replacement trial that was conducted in ~50 early stage (as they propose to target) randomized patients, of which most were transplanted. This trial, which used human fetal tissue, showed no significant differences between groups for the mean motor score while ~30 adverse events were also reported (1/3 of which were related to the transplantation procedure). The main conclusion was that there were no clinical benefits of cell replacement in HD patients (Bachoud-Lévi et al. 2020). This large-scale trial adds to the previous 6 or 7 open labelled studies conducted across the world and in which similar negative results were obtained.

The clinical rationale is equally sound. Unfortunately, the clinical precedent for fetal transplants (early and more recent) is not favourable, putting some degree of pressure on this particular candidate cell therapy. There are reasons to expect better outcomes from this trial given the more extensive characterization of the cell product, manufacturing consistency, etc. The proposal ignores negative data with fetal cell transplants and encouraging data for IT gene therapy products."

My response:
It is unclear why there is this emphasis on older fetal cell work. I have summarised the key rebuttal bullet points on the arguments given by the reviewers.

- Original studies were not powered for efficacy

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- Variability in the transplanted fetal tissue or cells versus well-defined hNSCs.
- Lack of consistent graft durability
- Relatively advanced stage of the disease at the time of engraftment
- Immunosuppression regimen used may not have been efficacious
- The hNSCs are not just geared to cell replacement but are also targeted to provide neuroprotection to host tissue through increasing trophic support, reducing aggregates and preventing aberrant gene expression.

2) Comments relating to preliminary Data:

"Based on all previous failed clinical trials, the preliminary data that are provided by the applicant (in particular the rather minimal behavioural recovery shown in both HD mouse models) and the new emerging gene therapies targeting the gene product, the rationale for going forward with such work in humans is questionable, especially given the associated risks with the extremely invasive nature of the procedure, the complexity of the care management following surgery (including regimens of immunosuppressive treatment) and the high probability that benefits, if any, may be anecdotal.
The most significant improvement was observed in clasping, with a 50% improvement at 4 weeks post-implant. At the same time point, animals demonstrated an improvement (~20%) were seen in pole test and a grip strength. In the second mouse model, the results of only one test (running wheel) are shown in the grant and while the open field is mentioned, there are no other results reported. Is it therefore difficult to conclude on the efficacy of the cell candidate to improve HD-phenotypes of these mice."

My response:

This is not an accurate description of the mouse data. For the first model, which is a very rapidly progressing model of HD, it is very difficult to see any rescue at all. The fact there is even 20-50% rescue depending on the assay is significant and of high impact. For the second model, the running wheel is the most robust behaviour in these animals, and it showed complete rescue to normal levels (e.g. no progression at that age). Mouse behaviour does not ensure a positive outcome in humans, therefore the multiple other readouts – e.g. electrophysiology, electron microscopy showing connections and restoration of gene expression changes in the host tissue from the presence of the transplants is compelling.

Importantly, no Huntingtin lowering trials would be in existence if they relied on full rescue of murine phenotypes. The rescue seen with the mouse studies as part of the preclinical package are as good or better than that seen with other therapies currently being tested in Huntington's disease.

I feel strongly that this study is of great importance to the Huntington's disease field.

Yours sincerely,

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