The Brain Repair Group
Cardiff School of Biosciences

Museum Avenue
PO Box 911
Cardiff CF10 3US
Wales UK

Tel + 44 29 20876654
Email Rosserae@cf.ac.uk
http://www.cf.ac.uk/biosi/

Dear CIRM Independent Citizens' Oversight Committee

I am writing to you because I am very concerned that some important aspects of the reviewers' comments for the recent CIRM CLIN2-17081 application (**Phase 1b/2a Study Of The Safety And Tolerability Of Human Neural Stem Cells For Huntington's Disease: REGEN4HD**) are not factually correct.

First, I would like to give you some background on my credentials to explain why I think I am well placed to express these views. I am an expert in advanced therapies for Huntington's disease, in particular cell therapies. I led a fetal tissue trial in the UK and have written many reviews on the fetal tissue studies. I have collaborated with Professor Bachoud-Levi (whose studies were cited by the reviewers) to help interpret her fetal tissue trial results, and we have co-written opinion pieces on this work. In parallel, I have worked for many years on stem cell therapies, and we are currently attempting to take our own hESC-derived cell product through to a first-in-man study, in discussion with the UK Cell and Gene catapult and MHRA. In addition, I am an expert in Huntington's disease more broadly, and chaired the European Huntington's disease network (EHDN) from October 2018 until this October. I founded the EHDN Advanced therapies working group and co-founded Stem Cells for HD (SC4HD). I have been CI and PI for a substantial number of clinical trials, including the UniQure trial, which was also mentioned in the reviews.

My points are as follows:

1. The results of the human fetal tissue clinical studies are cited as a key reason for turning down the application, but many of the statements made with reference to these studies are incorrect or misleading.

"*… the clinical precedent for fetal transplants (early and more recent) is not favorable, putting some degree of pressure on this particular candidate cell therapy"; and "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".*

In my view this is a flawed argument, because none of the fetal tissue studies are sufficiently powered to give a clear answer and do not represent anything approaching a definitive trial. The main reason for this is that fetal tissue cannot be cryopreserved and so must be transplanted within a window of a few days. This means that coordinating tissue collection and neurosurgery is extremely difficult and thus most studies were very small, and all were underpowered. Indeed, these factors resulted in the MIG-HD trial taking >13 years to complete and is why the field turned to stem cell solutions.

First of all, there are three studies that have provided some proof-of-principle evidence that grafts can improve function in Huntington's, with the most convincing being the Creteil pilot trial (Bachoud-Lévi Lancet. 2000;356:1975-1979 and Bachoud-Lévi Lancet Neurol. 2006;5:303-309). These are reviewed in Bachoud-Lévi 2021 (Stem Cells. 39(2):144-155).

The reviewers cite the MIG-HD trial (Bachoud Levi 2020) as providing evidence of non-efficacy of fetal cell transplants. This trial was a little larger but was still underpowered. Critically, it was also deeply flawed in a number of ways and thus cannot be interpreted as providing evidence either way. The flaws are discussed in detail in Bachoud-Lévi 2021 (Stem Cells. 39(2):144-155), but in brief, a key problem was that very few grafts appeared to have survived at all, as suggested by the almost total lack of increase in post-operative raclopride binding (also see the supplementary data in Bachoud-Levi 2020). This is likely to be due to poor tissue collection processes and almost complete lack of quality control. We are currently working with Prof Bachoud-Levi (who has provided us with her data) to analyse this further. However, the key issue is that if the grafts have not survived or are inadequate, as they seem to have been in this study, the study cannot be taken as proof that transplantation does not work in HD.

There are various other factual errors which are important, for example one reviewer suggest that transplanted cells would not survive in the HD brain *"the fate of any cell type would be similar given the very aggressive nature of the pathology (marked brain atrophy),"* but this is not the case - clinical studies show that grafts can survive long term in people with HD.

2. The reviewers give the impression that gene therapy studies are on the brink of being successful, with the implication that cell therapy should be deprioritized

"However, UniQure has very recently released preliminary results reporting that patients receiving the highest dose of their candidate drug showed 80% slowing of disease progression and statistically significant lowering of CSF neurofilament light protein compared to baseline levels. While developing efficient treatments for patients with HD remains an unmet medical need, gene therapy may show the most promise we haven't seen in years".

Whilst many (including myself) are hopeful about this approach, it is important to note that (i) this is an early-stage study (ii) these are interim results reported in a press release ie not published data, (iii) this is likely to be a partial treatment at best (iv) it is likely to be extremely expensive.

Having been in this field for many years, it is clear that it would be highly premature at this stage to assume that we have "a winner" and to stop looking more broadly for potential therapies. Moreover, in the long term it is very unlikely that HD will be treated using a single therapy; the history of MS tells us that a suite of therapies is a more likely scenario. Finally, a cell therapy would be compatible with a gene therapy such as the UniQure product and may provide important added value.

3. The reviewers suggest that the preclinical behavioural data was insufficient.
"…the rather minimal behavioral recovery shown in both HD mouse models"

I strongly disagree that the mouse data represents minimal improvement. The studies in the application reported improvements over a range of test – which is a considerably higher bar than used in the preclinical Parkinson's disease cell transplant studies, where there was reliance on a single outcome measure (amphetamine or apomorphine rotation).

I would like to kindly request that consideration is given to whether these (in my view highly misleading comments) should prevent this application to move forward. I would be happy to provide further comment if helpful.

Kind regards,

Anne Rosser MA, Phd, MB BChir, FRCP