MEMORANDUM

Date: July 20, 2012

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application DR2-05739

Enclosed is a petition letter from Dr. Henry Klassen of University of California Irvine, an applicant for funding under RFA 10-05, CIRM Disease Team Therapy Development Research Awards. This letter was received at CIRM on July 18, 2012 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

Henry Klassen, MD, PhD Extraordinary Petition: DT2 17 July 2012

Due to our early attainment of ET2 milestones, Dr. Trounson suggested that we submit a DT2 application, yet the conundrum is that the reviewers had no real way of gauging the extraordinary rate of our progress. Since January we have already satisfied all concerns raised and are effectively 6 months into our DT2 timeline. We have GMP product in hand and trials scheduled for 2013. Our major challenge is simply coordinating the funding to meet the accelerating timeline.

Below is the review summary, with our responses in **blue**, overlooked facts from **DT2 Application** in **red**, and affirmations in **green**. Our **ET2 Year 1 Report** was filed prior to notice of review**.** Note: Pages cited are the #s at bottom of page (not position in PDF).

EXECUTIVE SUMMARY The goal of this proposal …The applicant hypothesizes that transplanted RPE [Correction: hRPCs] could, by differentiating, regenerate lost photoreceptors [Clarification: rescue of host photoreceptors is primary mechanism].

Significance and Impact

1) There is an unmet need for the treatment of RP and this work, if successful, is likely to be of high impact. **Thank you.**

2) The preliminary data presented indicate that this approach has promise and suggest that RPCs may present an important therapeutic intervention in RP. **Thank you.**

3) Based on the data provided it is difficult to draw a clear conclusion as to how this is superior to other approaches using cell transplants. [Clarification: we know of no other effective cell-based treatment for RP, **Pg 7-16, Fig 7,8,10**]. More broadly, our method is advantageous vs. other stem cell-based "retinal interventions" due to lack of surgery, pan-retinal effect, and positive initial results in humans (above). It differs fundamentally from RPE-based approaches and would be largely complementary for AMD.

4a) The proposed method and site of delivery of RPCs is surgically simple and relatively safe from the standpoint of risks such as anesthesia and infection, **Thank you**

4b) although there are other serious risks with this approach such as a greater likelihood of an immune response. Such concerns are general to posterior ocular interventions (vitreous, retina), not specific to our cells. The dreaded complication of proliferative vitreoretinopathy (PVR) is associated with any posterior ocular trauma, including surgery, and caused by ectopic fibroblasts and especially **RPE** cells. We are not transplanting RPE and have never seen PVR associated with neural-type progenitors in research going back over a decade. Likewise, our data show that the key issue is that RPCs don't express MHC class II and are well tolerated as allografts to both the vitreous and subretinal space. That said, immune suppression can be used, either proactively or PRN, as deemed appropriate by our world class clinical team of Drs. Kuppermann, Boyer, and Chew, plus expert advisors including John Heckenlively, MD.

Rationale

1) The applicant has presented compelling non-clinical data in multiple species. Three human clinical case reports performed outside the USA are consistent with the non-clinical data. **Thank you**.

2a) It was clear that RPC-mediated photoreceptor rescue (rather than regeneration) was the predominant effect; **Agreed.**

2b) no guidelines are provided as to how long they expect this (the effect) to last. [No: **Pg 16, Fig 10**, clearly shows at least 33 weeks of sustained improvement in visual acuity in 3 humans. We also included duration of effect studies in rats (**Pg 18 "2.2"**).] More significant is the fact that there was evidence of clinical efficacy at all. We can speculate that the dramatic improvement seen in patients will have limits and could ease

with time. RP is a progressive disease, yet studies indicate a semi-permanent impact on the course of photoreceptor loss in favor of the treated eye, even with donor cell attrition. Patients should be better off having been treated and might never progress to complete blindness. Also, as noted below, re-treatment may be feasible with intravitreal injections (but would be highly problematic with sub-macular surgery).
3) The scientific rationale is clear and strong. **Thank you.**
4) The 2-tier clinical strategy proposed is not rational. This concern has been satisfied. We now have 3 GMP banks of human RPCs for trials (**ET2 Year 1 Report, Pg xii**). (The rationale of the early tier was to expedite the replication of dramatic offshore clinical success in an FDA-approved trial, using hRPCs already in house at the time).

Therapeutic Development Readiness

1) The applicant proposes to use "GTP" RPCs initially and then switch to "GMP" RPCs; the FDA may consider them to be two different products. A single therapeutic candidate should therefore be chosen (GTP vs GMP). Done. We now have ample GMP product.
2) It seems they have not selected their lead candidate yet as required by the RFA, so there is a question of readiness. Done. We have GMP product and we are ready.
3) The cells aren't optimized, which calls into question the feasibility of the timeline. Done. Cells are optimized and manufactured. We continue to outpace the timeline.
4) They need to first understand the cells and finish the optimization before doing any other safety studies. Done. This concern has been satisfied, as above.

Feasibility of the Project Plan

1) The proposed 2-tier clinical plan …FDA .. consider them two different products. This concern has been satisfied. We have already transitioned to GMP product (**ET2 Yr 1, Pg xii**). We have the data referred to as well (see **ET2 Yr 1, Pg viii-ix**).
2) Reviewers expressed concern about lack of immunosuppression in proposed clinical trial. The applicant has not provided enough evidence that there is lack of graft rejection; … can occur in the eye without evidence of inflammation … claim of no rejection is unsubstantiated. Immune rejection may be an issue, especially in … re-treating. Immunosuppression is entirely feasible and can be used in trials, as deemed appropriate by our clinical team and expert advisors. Although we do not see classical acute rejection, chronic rejection of the type described above in the setting of **RPE** transplantation (Zhang and Bok, 1998, IOVS) is important to keep in mind, yet a far lesser threat to vision than the disease of RP itself.
We agree with respect to re-treatment, which we did not propose here. Re-treatment is an exciting prospect (favoring our method) and will need dedicated allograft studies, which we are anticipating. Our DT2 proposal is focused on a single treatment paradigm to formally establish safety and efficacy of intravitreal hRPCs in RP.
3) Focusing only on the GMP RPC, the development plan outlined by the applicant appears comprehensive … for a … persisting cellular therapy product. **Thank you.**
4) It does not seem the applicant intends to perform safety studies with the GTP RPC, but only for GMP RPC. It is unclear why... [No, see: **Pg 11-12, Fig. 4-6**] Safety studies in GTP cells are being done (**ET2** grant), as above, with 9 mo. tox imminent (see below).
5) Adventitious virus testing will be performed on the master cell bank only if requested by FDA. The responsible action would be to perform this testing regardless of FDA input. [Adventitious testing is routine (**Pg 8**)]. We are contracting with CRO for *in vivo* testing.
6) The applicant will need to do tumorigenicity studies, but the proposed timeline does not reflect this. [No, see **Pg 21** Timeline, Tumor CRL = burnt orange colored bar: 11 months were allotted for *in vivo* tumorigenicity studies (vs. 9 mo. expected per FDA)]. *In vivo* tumorigenicity studies on GTP cells to conclude imminently. Third party tumorigenicity studies for GMP cells have IACUC approval at UCD and will begin shortly under auspices of Prof. Jan Nolta (UCD). This is >6 months ahead of schedule.

7) Clinical trial monitoring procedures are not described. [No, see: Clinical Protocol Synopsis, Data and Safety Monitoring Plan (DSMP) and Stopping Rules, **Pg 27-28**]
8) The applicant proposes to identify candidate potency markers using a proteomics approach. Reviewers were concerned that this sounds like a very large project in itself and may not be completed during the grant funding period. Done. We have completed proteomics on secretome and identified top candidate potency markers using this and other means (see **ET2 Yr 1 Pg vii-ix**). Proteomic data was prepared, but omitted from report due to page limit. Additional validation of candidates continues according to plan.

Principal Investigator (PI) and Development Team

1) The PI and development team are excellent and a strength of the proposal. **Thanks!**
2) The GMP manufacturing facility appears to be qualified. **Thank you.**
3) The clinical investigators are excellent as are the clinical sites. **Thank you.**
4) The entity responsible for clinical trial monitoring is not described. [No, see: **Pg 27-28**, letters of support from DSMB members Jacque Duncan, Michael Gorin, David Musch]

Collaborations, Resources and Environment

1) Resources and environment: Outstanding **Thank you.**

Budget a) significant budgetary discrepancy between the two clinical sites … not justified adequately b) budget for the toxicology subcontract not justified adequately c) The project seems over-resourced. All to be addressed to CIRM's complete satisfaction.

CONFIDENTIAL INFORMATION TO PI

1) For the purposes of CIRM funding, a single therapeutic candidate should be chosen (GTP vs GMP). GMP RPC is recommended. Done. GMP made (**ET2 Yr 1, Pg xii**).
2) Intravitreal delivery of allogeneic RPCs is surgically simple and relatively safe from the standpoint of risks such as anesthesia and infection, although there are other serious risks such as a greater likelihood of an immune response. The applicant should take into consideration the fact that the vitreous cavity does not have the same immuno-suppressive qualities as the subretinal space. Immunosuppression is a very straight forward addition to the clinical protocol, if determined to be prudent by our clinical team and expert outside advisors (see discussion above, including topic of re-treatment).
3) The reviewers were of the opinion that the applicant will need to do dose finding studies in animals. We already have, including function (see **ET2 Yr 1, Pg x**).
4) The applicant may want to evaluate the toxicity and efficacy of repeat-dosing in animal models, to support future clinical development. Agreed. This is all planned. Note that hRPC product is a xenograft in animals, so immune sensitization studies require use of a dedicated allo-transplantation paradigm, which we have previously developed.
5) Systemic toxicology studies will apparently only be pursued if migration of the hRPCs is detected in short term studies. This may be a mistake .. cell migration may be missed and .. systemic toxicity .. manifest itself independent of cell migration.. Agreed. For GMP cells we are doing full toxicology at 1 and 9 months under auspices of Prof. Jan Nolta.
6) No direct evidence … to support notion that cells injected by intravitreous approach … migrate to the retina … not clear … if integration is critical for the therapeutic effect. What we see is that integration is not required (also see **ET2 Yr 1, Pg xi**). This means clinical efficacy is much easier to achieve, mechanistically, since trophic factors diffuse from the vitreous to the entire retina. Critically, it is also known that trophic rescue of photoreceptors persists much longer than the peptide factors (and/or cells) that induce it (e.g., Faktorovich et al.,1990, Nature; Klassen et al., 2001, Exp. Neurol.) so that long term efficacy is obtained even in the setting of xenografts (see **ET2 Yr 1, Pg x**), which can exhibit erratic survival times (patients of course get allografts).
Note also that migration and integration of neural-type progenitors from vitreous into the retina is a well documented phenomenon known to occur in rats (e.g., Takahashi et al., 1998, MCN; Young et al.. 2000, MCN) and pigs (Klassen et al., 2008, Clo. Stem Cells).