CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

MEMORANDUM

Date: March 11, 2013

From: Alan Trounson, PhD
CIRM President

To: Independent Citizen's Oversight Committee

Subject: Extraordinary Petition for Application ID1-06560

Enclosed is a petition letter from Dr. Evan Snyder of Sanford Burnham Medical Research Institute, an applicant for funding under RFA 12-03, CIRM hiPSC Derivation Awards. This letter was received at CIRM on March 11, 2013 and we are forwarding it pursuant to the ICOC Policy Governing Extraordinary Petitions for ICOC Consideration of Applications for Funding.

POINTS OF CONCERN IN THE REVIEW OF THE SANFORD-BURNHAM MEDICAL RESEARCH INSTITUTE's (SBMRI's) APPLICATION (ID1-06560) FOR CIRM hiPSC INITIATIVE RFA 12-03

The proposal from SBMRI (ID1-06560) ranked 2nd in the State among all applications to become the hiPSC "Deriver", only 4.6 points below the "winning" proposal. Therefore, any errors or misconceptions by the Grants Working Group (GWG) or by CIRM Program would significantly – and adversely -- impact our rank. I feel the need to raise some areas of concern and inaccuracy during both the proposal's initial review as well as the post-review assessments by Program (during which priority rankings were generated). These biases and errors, I fear, serve to create the unappealing perception that CIRM **(a)** "leap-frogged" over a proposal deemed scientifically more meritorious to ones that were judged as weaker; **(b)** revealed an unjustified bias against academic institutions (based on a misunderstanding of what indirect costs/overhead actually cover), despite the fact that the success rate of such academic entities has typically been greater and the costs substantially less than in most commercial entities; **(c)** seemed to bypass -- yet again and unjustifiably -- Southern California for the siting of a state-wide entity.

Hence, my motivation for bringing out the following points:

- There were scientific errors in assessing what amounted to minor portions of our proposal yet which, given the closeness in score of the top 2 application (only 4.6 point separation), may have been sufficient to hurt our rank.
    - We were criticized for indicating that, our *back-up* cell source (fibroblasts were our primary source), would be "transformed" lymphocytes. In fact, we stated that our secondary source would be nucleated peripheral blood cells, principally lymphocytes. As is well-known, lymphocytes need to be proliferative to be reprogrammed. At the time – and as is well-accepted in the literature – promoting proliferation via EBV is an established and safe technique that does *not* "transform" the cells. In addition, we provided data, not acknowledged by the GWG, that all genes carried by EBV are silenced after reprogramming and have no adverse effects, simply promoting proliferation. Nevertheless, in this fast moving field, while promoting lymphocyte proliferation was, at the time of submission, best achieved via EBV (and many patient banks actually archive starting cells in that fashion, e.g, the NIH-supported Rutgers bank for mental disorders), since submission, the field (including our group) has been able to promote the proliferation of lymphocytes *without* EBV, with mitogens alone, and reprogram those; EBV-mediated proliferation was indicated as being used *"only if necessary"* in order to use *peripheral blood lymphocytes* from valuable patients in whom no other cell source was obtainable. It is no longer necessary. As stated in the original proposal, "peripheral blood lymphocytes", induced to proliferate by the safest available means, remains our back-up starting cell type.
    - While the non-integrating episomal reprogramming technique is well-practiced, efficient, and cost-effective, the study section – as did we and the field – acknowledged that it does not entirely eliminate the risk of transgene integration. Nevertheless, we described in exquisite detail – supported by data -- how clones with possible integration are screened out in our SOPs. We indicated that hiPSC clones that contain vector integration are identified at passage (P) 6-8 and subsequently discarded based on a PCR-based technique. We cited – and provided the detailed SOP -- for how qRT-PCR is employed to determine the episomal DNA copy number in each cell; that our studies have shown this assay capable of distinguishing integration-free colonies at P5; that all clones with <0.1 copy/genome at P5 have no integrated episomes. We indicated that only integration-free clones will be preserved and further characterized and that, based on our extensive experience, 3 integration-free clones can be efficiently and readily identified when 10 clones are initially picked, quite feasible given our nearly-automated techniques. These procedures were detailed explicitly in the proposal multiple times but were seemingly ignored by the GWG prompting them to raise concerns that are not accurate. In addition we cited the Sendai virus as our back-up reprogramming technique, a newer strategy with no risk of integration.

- There were a number of administrative issues for which we were inaccurately and/or inappropriately criticized.
    - We were criticized for not having enough space to perform this work. We were contacted on the phone by the GWG specifically to ask whether we could allocate more space to the project, and I indicated that it was absolutely possible. Space is *not* a limiting factor in our Institute, I indicated, and would not require our requesting additional funds (as a commercial entity might need to do when leasing space). I indicated that dedicated lab space and personnel would be available for this project separate from and non-overlapping with the current Core functions. Apparently this discussion never made it into the GWG's deliberations and inevitably lowered our score.
    - It was cited that the culture method we described might need to be altered slightly to be compatible with the method used by the designated Repository. It was rightfully acknowledged by the GWG that this was *not* a major hurdle, particularly since the Repository was not identified at the time of submission. It should be emphasized that we have grown our hiPSCs under multiple conditions based on the needs of our users/customers with no difficulty. Furthermore, the RFA explicitly indicated that, once the Deriver and Repository were identified, that a period of time would then be devoted to coordinating the SOPs of the respective entities. We took that statement at face value in good faith.
    - I, as the Program Director (PD), was criticized for devoting only 25% effort. This was the amount of time stipulated by the RFA. Assuming that CIRM and their advisors had determined this to be the adequate amount of effort required for monitoring the progress of this project, I affirmed that degree of commitment in good faith. I could have devoted more effort -- and am still prepared to do so – if it were made clear that 25% would actually be judged as insufficient, and that the recommendations of the RFA were disingenuous and misleading. However, my experience in directing our successful Core to date indicates that CIRM was, indeed, accurate in deeming 25% effort on the part of the PD as sufficient for *supervision*. One must remember that there will be, under the PD in the organizational chart, as stated in the application, managers and technicians devoting 100% effort to this project. It is a bit presumptuous for the GWG to second-guess the quality and impact of my time (a full one-quarter of my professional activity), and to assume that, as the PD, I cannot lead this effort with the same success I have done for our Stem Cell Core and other aspects of hiPSC-generation. Therefore this concern represents *pure speculation* on the part of the GWG and of CIRM Program, is not valid, and should not carry the weight it appears to have been accorded. The hiPSC-service of our institution has become a major focus of my effort.
    - Reviewers expressed concern that the proposed data management software (as described in the application and through follow-up information from us) would not be adequate for tracking the life cycle of the primary tissue cells through the hiPSC cell line. The reality is that we presently track many primary samples, having generated as many as >300 hiPSCs to date – both from users bringing material for reprogramming as well as material obtained by us for reprogramming. Again, this concern represents pure speculation and is not valid.
- The bias against academic institutions is not fair, accurate, or justified and is certainly an unappealing position for CIRM to stake out. It was expressed as follows in the final recommendations: *"…reviewers observed that applicants from academic institutions requested funds for facilities and indirect costs that were significantly higher than other applicants. This reduced the enthusiasm for such proposals, as less of the total funds would be devoted to direct project costs. Reviewers were also concerned about potential licensing issues related to hiPSC derivation technology…".* It should be noted that the funds requested for indirect costs by academic institutions is off-set by the much diminished money devoted to salary and personnel as well as the *additional services for the project* that derive from these indirect costs, e.g., administrative, secretarial, data analysis, legal, regulatory, intellectual property, information/data processing, custodial, phone/fax/internet, and Core services. In other words, academic institutions are simply above-board in declaring what functions these indirect costs cover. Commercial entities simply add the cost of these functions to their "direct" "per cell line" costs. So the difference between commercial and academic entities in terms of funds devoted to the project is, at worst, not substantively different. In reality, our academic institution generates lines substantially more *inexpensively* than any entity in the world because

our labor costs are so low, our efficiency and automation so high, our real estate requires no additional support, and we have no need to generate any profit margin. With regard to "freedom-to-operate" vis-à-vis licensing, we asserted, and provided written signed documents that affirmed, that, in fact, we have complete freedom to operate. Furthermore, as a non-profit entity, we will probably have *fewer* restrictions to providing material to potential users than would a for-profit commercial entity. Hence, the issue of being an "academic institution" is a red-herring yet, inevitably, reduced our final score.

- The RFA did *not* require that the Deriver partner with a Repository *before* the submission of the application, be located in the same part of the State or in the same building – and gave no indication that such a situation would be viewed more favorably if it were pre-arranged. We could have – and certainly still can – partner with a Repository in the Southern California area. In reality, transporting frozen cells (what the RFA requested) within the State, is not a significant limitation, and CIRM was correct in *not* requiring such a partnership in the original RFA. It is disingenuous to revise the requirements of the RFA post-hoc. A similar requirement could just as well be imposed on the "Collectors", probably with greater justification since those starting cells are optimally *not* frozen and should be transported with little delay.

In short, our scientifically strong application is receiving no support in favor of less scientifically-regarded proposals for specious reasons. Furthermore, the end-result of an unjustified bias against academic institutions coupled with a post-hoc requirement that the Deriver and Repository be in the same building, provides yet another situation in which CIRM appears to ignore Southern California for a state-wide function. To reward adequately meritorious proposals, to preserve the appearance of fairness, and to insure that hiPSC derivation be quite near the multiple cell "Collectors" statewide, I would propose, counter to CIRM's initial plans, that the ICOC endorse the creation of a *Northern* California Deriver and Repository and a *Southern* California Deriver and Repository, perhaps splitting equally the task of generating hiPSC from 3000 samples as well as the ear-marked funds (e.g., $8MM to each Deriver). The two groups can coordinate their SOPs.