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**Re: Quest proposal DISC2-10120 entitled "Microenvironment for hiPSC-derived pacemaking cardiomyocytes"**

Dear ICOC members,

I would like to thank the committee for again recommending our revised proposal DISC2-10120 for funding (score: 90 for February 2017 and 85 for September 2016 submission). I am writing this letter to address the two bullet points—but really a single concern—on the cost effectiveness of our envisioned therapy raised by the reviewers.

*"Concerns:*

- *It is unlikely that this approach will be a cost effective considering expenses required to manufacture these pacemakers for each patient.*
- *Use of iPSCs as opposed to more cost-effective immunomatched ESCs is not well justified."*

Based on our estimated cost for the GMP facility, trained personnel, and reagents at UC Davis, the generation of GMP grade hiPSC-derived pacemaking cardiomyocytes, from reprogramming of hiPSCs, to culture, and finally differentiation to ~5000 pacemaking cardiomyocytes needed for a functional biopacemaker (*Nat Biotechnol* 35: 56-68, 2017), would cost ~$140k, but over 85% of the cost is attributed to the reprogramming process. With improvements in reprogramming efficiency and automation, this cost is expected to decrease in the future and become comparable to the current costs of implanting electronic pacemakers, which is ~$80k per transplant (assuming no complications). However, given that no replacement of battery or parts is needed with a biopacemaker, the transplantation of these cells would require only a one-time operation instead of repeated procedures every 5-10 years needed for implanted electronic pacemakers for the life time of the patient. Hence, there is a significant cumulative cost savings, especially for patients that live more than 15-20 years after the procedure. In addition to its cost effectiveness, biopacemakers can also improve the quality of life for recipients, who will endure less pain and suffering by avoiding multiple operations. These patients can also lead a more active lifestyle since biopacemakers are more responsive to dynamic changes in physiological activities.

Regarding the use of hiPSCs instead of hESCs, since cardiac differentiation and maturation protocols have proven to be interchangeable for hESCs and hiPSCs with minor variations, the cost for hiPSC-derived products would be comparable to that of hESCs but without triggering ethical concerns. More importantly, our proposed proof-of-concept study could easily be translated to hESCs regardless of the eventual direction of the regenerative field in

using autologous hiPSCs, immunomatched hiPSCs, or immunomatched hESCs. With the latest transplantation work on retinal epithelial cells in patients with macular degeneration, the field seems to be headed towards the generation of these cells from super donor hiPSC lines. Therefore, the derivation of pacemaking cardiomyocytes from banked super donor hiPSC lines for generating biopacemakers is also a likely scenario.

We hope that we have sufficiently addressed the reviewers' concerns. Since our proposal submission, our manuscript on differential biomechanical and biochemical properties between the pacemaking and contractile microenvironment is under minor revision for publication and our work on cardiogenesis of hiPSCs via small molecules has been completed with a manuscript in preparation for submission. We are making great progress in our research. Funding of this proposed work will allow us to merge our microenvironment and small molecule research to make a significant impact in advancing the development of biopacemakers. Thank you for considering our proposal for funding so we may continue our exciting research.

Sincerely,

Deborah K. Lieu, Ph.D.