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Re: Review of our QUEST proposal DISC2-09542 entitled "Multipotent Cardiovascular Progenitor Regeneration of the Myocardium after Myocardial Infarction"

Dear Members of the ICOC,

I am honored to provide information in support of our QUEST proposal. As you know, myocardial infarction or heart attack is a major cause of heart failure and a tremendous burden on society. Death and damage to heart muscle cells from ischemic injury is estimated by The World Health Organization to cause of over 13% of all human mortality.

There is no curative therapy. Therefore, achieving therapeutic cardiac regeneration has been one of the biggest challenges and potential rewards of regenerative medicine.

Our proposal is to test the ability of iPSC-derived cardiac progenitor cells to rebuild the heart muscle after myocardial infarction, a major cause of cell death. I would like to make two points about our proposal that distinguish it from all other cell therapies for heart regeneration:

> The first point is that nearly all experimental cardiac regenerative therapies to date, and all CIRM-funded studies, have focused on either non-cardiac progenitors or terminally differentiated cardiomyocytes. As emphasized by the GWG reviewers, our proposal will use true cardiac progenitors that are similar to those in the fetus that build the heart in the first place. Unlike all other progenitors yet tested, these cells are robust, can be biobanked easily, and make heart muscle cells as well as the vasculature needed to supply blood to regenerated tissue. The distinction between true progenitors and non-cardiac progenitors is important. Non-cardiac progenitors used in prior studies, including cardiosphere cells and mesenchymal stem cells, do not efficiently make heart muscle cells or even persist in the heart long term. Rather, their clinical benefit seems to come from the factors they secrete. The other cells under evaluation are terminally differentiated cardiomyocytes, such as iPSC-derived cardiomyocytes. Although these cells do make new muscle, they are very fragile so there is substantial death after injection, and they do not make vasculature.
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> The second point is that we propose a delivery method that is straightforward to implement clinically. We propose to deliver the cells via intracoronary injection using a specially developed catheter that is already on the market. Most heart attack victims already undergo intracoronary catheterization to open blocked coronary arteries or place stents, and the procedure does not require specialized training or facilities. Moreover, intracoronary injection has successfully delivered a range of cell types to the hearts of experimental animals and humans, documenting feasibility. Since the delivery modality is

straightforward, our proposed therapy could be performed at a large number of hospitals to benefit the large patient population.

As Reviewers noted, we've assembled an experienced team that is highly skilled in all the technologies needed execute an innovative program and translate the results to clinical application.

Thanks very much for your consideration.

On behalf of the co-investigators:

Eric Ahrens, PhD (UCSD)
Alexandre R. Colas, PhD (Sanford Burnham-Prebys Medical Research Institute)
Nabil Dib, MD (UCSD and Dignity Health)
Pilar Ruiz-Lozano, PhD (Stanford)
Phil C. Yang, MD (Stanford)

Yours sincerely,

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