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KAREN L. CHRISTMAN, PhD, FAHA
PROFESSOR, DEPARTMENT OF BIOENGINEERING
ASSOCIATE DEAN FOR FACULTY AFFAIRS & WELFARE, JACOBS SCHOOL OF ENGINEERING
SANFORD CONSORTIUM FOR REGENERATIVE MEDICINE, ROOM 2006
2880 TORREY PINES SCENIC DRIVE, LA JOLLA, CA 92037

TELEPHONE: (858) 822-7863
FAX: (858) 534-5722
EMAIL: christman@eng.ucsd.edu

July 23, 2020

Re: CIRM DISC2COVID19-12007 #2 application

Dear ICOC Members,

We would like to thank the CIRM Grants Review Working Group for their strong support of our application entitled "Pro-healing biomaterial for treating lung inflammation associated with COVID-19" with 14 votes supporting funding. Both myself and my clinical collaborator, Dr. Mark Hepokoski, who is currently treating COVID-19 patients in the ICU, are committed to bringing this novel biomaterial-based technology to patients to meet this urgent unmet clinical need. With CIRM's support we can quickly accelerate the translation of this technology into patients. Below we would like to respond to some of the questions and minor concerns identified by the reviewers as well as identify strengths of our application that warrant funding.

Response to remaining reviewer concerns/questions:

- This is the first pro-regenerative biomaterial to be delivered intravascularly and therefore is highly novel.
- We agree with the reviewers that Milestones 1 and 3 are the critical path milestones to enable clinical translation. We plan on first completing these milestones and secondarily completing Milestones 2 and 4 since our main goal is generating sufficient data to enable translational activities.
- We chose to use immediately available lung stem cell types for our *in vitro* studies given the rapid need to complete this work. Since the original submission, we have found a source of commercially available human alveolar epithelial cells, which include Type II cells, that we can use instead of the MSCs.
- We have performed power analyses using data in the literature. We chose to power the studies based on prioritized readouts of experimental ventilator induced lung injury related to inflammation, namely inflammatory cytokines in bronchoalveolar lavage fluid and inflammatory cell infiltration in the lung. Secondary measurements related to lung function are also sufficiently powered at n=10.
- In skeletal muscle, we have seen that a skeletal muscle extracellular matrix hydrogel better promotes regeneration in skeletal muscle compared to a lung extracellular matrix hydrogel and therefore think it will be important to examine a lung extracellular matrix hydrogel in our proposed studies to see if it maximizes lung regeneration. By the time this award starts we will already have a batch of the lung material and therefore we do not anticipate that adding this 1 additional group will slow our proposed studies or prevent us from meeting our timeline. We

are however acutely aware that using the cardiac material will lead to faster translation. We would therefore envision translating this first if it is effective in our proposed studies. The lung material could then be a second generation product if efficacy is deemed superior.

- In terms of patients, we envision targeting patients with moderate to severe disease who require mechanical ventilation. These patients contribute to the majority of COVID-19 deaths, and account for roughly 20% of patients hospitalized with COVID-19. We would treat patients immediately prior to the initiation of mechanical ventilation, which we will model in our pre-clinical studies. This strategy offers the unique opportunity to pre-treat against the second inflammatory insult caused by the ventilator, which is referred to as ventilator induced lung injury. Importantly, treatments focused on preventing ventilator induced lung injury remain the only proven therapies for acute respiratory distress syndrome.

Strengths of the technology and the proposal:

As the reviewers noted, this is "a unique project that could have a big impact," and "the path to translation is rapid and accessibility may be high." Indeed, we think a major strength of our approach is that it is based on our extracellular matrix hydrogel technology that has already been tested in patients in another clinical application, so we can rapidly translate this to patients upon success with our proposed studies. In addition, another major benefit is that our approach will be significantly cheaper (~1 to 2 orders of magnitude cheaper) than other traditional regenerative medicine approaches, which will enable greater patient access to this medical therapy.

Thank you for your consideration.

Sincerely,

Karen L. Christman, PhD
Professor of Bioengineering
Associate Dean for Faculty Affairs & Welfare
Jacobs School of Engineering
University of California, San Diego