Responses to Panel 1 Review – CLIN2COVID19-11823 Application

Michael A. Matthay MD – PI - May 14, 2020s

I have listed the main concerns below and my responses.

1. **Key concern is that COVID-19 patients may not enroll in the trial** - We have now enrolled 11 CVOID-19 patients with ARDS at UCSF (Zuckerberg San Francisco General Hospital and UCSF Medical Center Hospital) since March 9, 2020. Thus, this provides direct evidence that we are enrolling well and rapidly COVID-19 ARDS patients in this trial in San Francisco. We anticipate enrolling additional COVID-19 ARDS patients at UC Davis if this application is funded. The main stimulus for this application was to enroll more COVID-19 ARDS patients in California by adding a major site in northern California, UC Davis Medical Center in Sacramento, CA
2. **Currently no supportive data of positive outcomes in lung diseases** – This is not correct. We published the results of our multicenter NIH Phase 2a trial in *Lancet Resp Med* 2018 trial (40 patients treated with MSCs and 20 patients with placebo). The primary endpoint was safety and there were no safety issues. Secondary endpoints including clinical and biologic indices. There was a statistically significant decline in Angiopoietin-2 in the plasma of the MSC-treated patients which is a biomarker and mediator of lung and systemic vascular injury. Also, a secondary post-hoc analysis showed a trend for improvement in lung function as measured by the oxygenation index in the patients who received high viability MSCs. Therefore, we were funded by the DoD and NIH to now carry out the current randomized, blinded phase 2 randomized, blinded and placebo-controlled efficacy trial with the primary endpoint focused on improvement in respiratory function.
3. **The approach is not unique –** Cell based therapy for ARDS is new and just beginning to be tested, it was a cornerstone of our UCSF Alpha Stem Cell Application three years ago. Therapy with cell-based therapy for acute respiratory failure from ARDS from viral and bacterial pneumonia has been pioneered by our research group at UCSF since our initial pre-clinical studies in 2007, and our translation to safety clinical trials. In all modesty, we have led the field in this area and have also assisted other investigators in both academics and industry to implement MSC based strategies. One reviewer did say "Excellent team and 15 years of planning has moved into this project."
4. **The rationale is weak** – This is not true. In fact, in the critique another reviewer said "the rationale seems good." There is substantial pre-clinical data that MSC therapy can decrease lung injury from bacterial and viral pneumonia and hasten lung repair. Our group and other investigators have reported several pathways by which MSCs can reduce inflammation in the lung. For example, we first reported that MSCs can reprogram lung macrophages to become more pro-resolving (M2-like macrophages) and also our group discovered that MSCs have anti-bacterial properties in both mice and in the human lung. (Matthay M, Pati S, Lee JW. MSC for Therapeutic Effects in Organ Dysfunction. *Stem Cells* 35:316-324, 2017 and Laffey and Matthay. Cell based therapy

for ARDS:Biology and Potential Therapeutic Value, *Amer J Resp Crit Care Med* 196:266-273, 2017)

5. **Unclear if a signal will be seen in 20 patients** – The reviewer did not appreciate that the additional 20 patients at UC Davis will be part of the larger multi-center trial of 120 patients. We will not analyze the 20 patients in the trial alone at UC Davis – that would not be an adequate sample. But the 120 patients does provide an adequate sample to test the hypothesis that MSCs will reduce respiratory failure in ARDS. A secondary endpoint is to reduce mortality.
6. **The trial design does not seem optimized for COVID-19 patients.** – We do not agree. We have proof from March 2020 through May 13, 2020 that we have in fact enrolled 11 patients with COVID-19 ARDS in San Francisco at UCSF Medical Center and Zuckerberg San Francisco General Hospital. We have enrolled an additional 2 patients with ARDS from non-COVID-19 ARDS. No one can predict the number of patients in California or other states who will develop ARDS from COVID-19 in the next few months and years, but there will not be an effective vaccine available for the entire population for at least 1-2 years so with this trial we will be in an excellent position to enroll patients in both Sacramento at UC Davis and in San Francisco at our UCSF hospitals. We will prioritize enrolling COVID-19 positive patients at UC Davis as we have done in San Francisco. Our scientific officer from the Department of Defense, Sandy Snyder, has been very enthusiastic about our trial enrolling to date so many COVID-19 ARDS patients.
7. **The endpoints for the trial will not result in a product** - We respectfully disagree. If the MSCs are effective in this phase 2 trial, we will proceed to a larger phase 3 trial and there will be ample opportunity for MSC production from both industry and NIH cell production sites.
8. **The trial has had difficulty enrolling nationwide –** This is not true. The trial just opened at UCSF in January 2020 and has just opened at U. Texas Houston in late April 2020 and they have enrolled one patient already. We expect Oregon Health Science Center to open this week and U. Washington Harborview Hospital and Vanderbilt University Medical Center will open in June 2020. Also, our prior NIH/NHLBI supported phase 2a safety trial enrolled very well in California (UCSF and Stanford University Medical Centers) and nationally (Ohio State University in Columbus, Massachusetts General Hospital in Boston, University of Pittsburgh Medical Center).
9. **Dr. Matthay has supported academic and industry projects** – Dr. Matthay is committed to both academic and industry-based trials. He provided the blueprint for the phase 1 and 2a safety trials for Athersys (Multistem therapy) in Cleveland, Ohio to help them test their MSC product (Multistem). He is also advising them on their plans for phase 2 and 3 work, although he has no financial interest with this company and has not been paid any consulting fees. He believes that a partnership between academia and industry is needed to advance the field of novel therapeutics for COVID-19 related diseases which is what Francis Collins, MD the Head of the NIH has recommended. This theme also fits well with the CIRM mission of bring both academic and industry resources to test new therapeutics for challenging medical diseases. Dr. Matthay's vision is that interactions between academics and industry should be bi-directional and with this approach, new therapies will be more rapidly and effectively identified. A good recent

example is the partnership between NIH and NIAID and Gilead to test an effective new agent for COVID-19, remdesivir.

10. **Underserved populations** – As explained in our CLIN2 application, UC Davis serves a population that includes underserved patients, and therefore adding UC Davis as a clinical site will serve the CIRM mission well. Also, please note that our UCSF Alpha Stem Cell application was focused on underserved patients in the East Bay (Sickle Cell Disease) and in San Francisco (Zuckerberg San Francisco General Hospital).
11. **Collaboration and links with the Alpha Stem Cell Clinic at UC Davis and UCSF** – This application will further deepen the collaborations between UCSF and UC Davis, both Alpha Stem Cell Clinic sites. It will also give more evidence that CIRM is devoted to testing promising therapies for serious medical disorders, in this case ARDS and the devastating COVID-19 pandemic.
12. **Personnel Coordination between UCSF and UC Davis**. The proposed site PI at UC Davis is Rachael Callcut, MD, MAS, Associate Professor, who worked with Dr. Matthay closely on the clinical protocol for this MSC trial at UCSF and was the site PI at Zuckerberg San Francisco General Hospital before she moved to UC Davis in March 2020. Dr. Callcut is a very bright, highly motivated and talented physician-scientist. Furthermore, she will work closely with Dr. Tim Albertson, the Chair of Medicine as a Co-Site PI. Dr. Albertson and Dr. Matthay have worked together on clinical trials for ARDS and Sepsis for 15 years as part of the NIH/NHLBI ARDS and PETAL networks.

Respectfully submitted,

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