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California Institute for Regenerative Medicine (CIRM)

1999 Harrison Street, Suite 1650
Oakland, CA 94612

Application Number: CLIN2-11775

Title: *Evaluation and Characterization of SARS-CoV-2 Antibody in Convalescent Volunteer Plasma Donors for Potential Therapeutic Use*

Principal Investigator: John A. Zaia

We are pleased with the recommendation from the Grants Working Group (GWG) that reviewed our proposal. The reviewers recognized that our project “*could provide advances in fundamental knowledge about antibodies in COVID-19 convalescent plasma (CCP), and may provide an important understanding of types of antibodies formed after COVID-19 infection*” and thought that “*this will help develop a new screening tool for the California public-health arsenal by identifying what patient and CCP donor factors predict clinical benefit.*” The GWG raised a few concerns which we address below:

1. The amount of coordination and infrastructure necessary to engage with treating physicians and donors was a concern for some reviewers.

Response:

a. How do we bring CA physicians on board?

We recognize that engagement with pulmonologists, infectious disease (ID)/ intensive care unit (ICU) specialists, and the blood collection community is critical to form the partnerships necessary to reach our goals. To that end:

- **We are registered with the National Convalescent COVID-19 Plasma Expanded Access Program (EAP).** Our website will be posted on the EAP website linking us to more than 150 sites in California that have already registered. We recognize that MDs have already declared their interest by linking to the EAP, and we will provide antibody and nasopharyngeal (NP) swab testing that they need for efficient donor qualification.
- **We have a method for engaging specific sites and the MDs who are treating COVID-19 patients and need access to donor testing.** For example, we have contacted a single group in Ventura County, that includes a communication system the reaches 150 MDs in 8 Dignity Health hospitals and a Kaiser Permanente hospital, has expressed their need for plasma antibody testing. Using our “Outreach Coordinator” and the Alpha Stem Cell Clinic Network we will extend this model to as many sites as possible throughout California.
- **We will leverage State and County Public Health departments** that oversee the NP swab testing and have recently been recognized as key to locating potential plasma donors

based on their records. We will seek-up this information and be available to provide the testing necessary to qualify these candidate donors.

- **We have a commitment from a large plasma collection group (Vitalant and Life Stream) to work with us in solving the 'intake' problem for plasma collection**, namely the qualification of the candidate donor. This group has committed to work with us in increasing the efficiency of donor qualification.

b. How do we facilitate plasma donor engagement in underserved communities?

The backbone of our infrastructure involves the CIRM Alpha Stem Cell Clinic (ASCC) Network through which we will engage key COVID-19 physicians at their sites. To reach underserved communities, we will use a multi-faceted approach.

- **To engage African-American communities**, we will leverage the connections established within the Alpha Stem Cell Clinic Network which has established relationships with companies, organizations/foundations, community pillars involved with underserved communities. In particular, we will harness our connections to the black communities via the ASCC Network Sickle Cell Disease. We have continued interactions with the founder of Axis Advocacy SCD, and initiated contacts related to this project with oneSCDvoice and the Secure-SCD Registry, Surveillance Epidemiology of Coronavirus (COVID-19). Working with the Center for Healthy Communities at UC Riverside, we will have contacts African-American communities in the Inland Empire. Among other interactions, we will also contact Verily, Optum Serve and myCovidMD® initiative that perform health services and COVID-19 testing in rural areas and in black/brown communities.
- **To engage with Native American Nations**, we are in the process of establishing communication with California physicians working for the Indian Health Service (IHS) and with the California Rural Indian Health Board, Inc. We recognize the importance of seeking the input of this group involved as the central focal point in California for planning advocacy and coordination in the Indian health field. Specifically, Dr. Daniela Bota, the UC Irvine ASCC Director, has agreed to be responsible for linking us to Native American communities in Riverside County with whom she has ongoing activity. On our team, we also have connections with Native American Nations via Dr. John Burnett from City of Hope, a citizen of the Muscogee (Creek) Nation (MCN), who is actively involved in an organized community of MCN citizens living in Southern California.
- **To engage with Latino Communities and Others**, we will work with our Center for Community Alliance for Research and Education that has a long-standing relationship with the Latino Communities. In addition, we work with Dr. D. Lo and J. McMullin from the Center for Healthy Communities at the UC Riverside (UCR). This Center is leader in community engagement efforts to help reduce health disparities in Riverside and San Bernardino counties, particularly among Latino communities that make up about 49% of inland Southern California population.

In regard to assisting the LGBTQ community, we have associations with Richard Zaldavir who is the Executive Director of The Wall — Las Memorias Project in Los Angeles, a community health and wellness organization dedicated to serving Latino, LGBTQ and other underserved populations. Their organization strongly supports people living with HIV/AIDS (PLWH) and Hepatitis C. We also extensive contacts with those caring for the PLWH community in the Palms Springs area. I personally have presented the proposed program at these HIV/COVID-19 sessions and have engaged ID/pulmonary physicians at Eisenhower Medical Center and at Desert Regional Medical Center.

These activities will be particularly labor-intensive at the beginning of the award period, and will be supported by the ASCC personnel, our Outreach Coordinator and the individuals mentioned above

to help identify new CCP doors. A Registered Nurse from our Alpha Stem Cell Clinic will follow-up with interested prospective donors, and our Outreach Coordinator, working with the Project Manager and the Principal Investigator, will engage with physicians and staff. In addition, due to the suspension of laboratory research activities at City of Hope, a Labor Pool was created to provide staffing support throughout the organization and to keep employees actively engaged in solving the problems presented by this epidemic. Help will be available from this talented Labor Pool.

2. The most compelling component of this application is the promise of clinical correlation. However, some reviewers were concerned by our plan for correlation with clinical data and the need to collect the dose of plasma infused to properly correlate antibody characteristics with outcome.

Response: Due to time constraints, we were not able to provide the case report forms (CRF) in our proposal. Since, we have developed a complete questionnaire that will capture all key plasma recipient/patient's characteristics (including gender, COVID-19 symptoms, co-morbidities, vital signs, and biomarkers), the dose of plasma infused, which will follow the Expanded Access protocol from the Mayo clinic using the dose specified (a full unit of COVID-19 convalescent plasma, or at least 200 mL), current supportive care and medication. In addition, we will collect adverse events and clinical outcome 7 and 28 days post-CCP infusion, or at the time of hospital discharge. To limit the burden of work on treating physicians, we will ask them to register a local support person (e.g. a nurse or research coordinator) we will contact directly if needed. Printed paper CRFs may be used and emailed to us.

As described in detail in the Section 9 of our clinical protocol, our endpoints of interest are:

- All-cause mortality at Day 28.
- Reporting of adverse reactions to CCP
- Duration of hospitalization (in days)
- Time to clinical improvement (in days): Clinical improvement is defined as disease improvement from Day 0 to 28 post-CCP infusion on a 7-point ordinal scale used in other COVID-19 studies.

The descriptive analysis of day-28 mortality of recipients will naturally be compared to reported data from other studies, but the main focus of our analysis will be to demonstrate whether the antibody content of donor plasma increases the odds of surviving past day 28. The statistical analysis plan has been vetted by COH. With this plan, we will examine donor antibody levels and how this relates to the duration of hospitalization and outcome. If donor plasma quality, as measured by SARS-CoV-2 antibody levels and neutralizing potency, has a statistically significant and positive impact on patient outcomes, this would be considered evidence of benefit of convalescent plasma, and further provide better guidance on donor selection and serum qualification.

In summary, we are confident we can accomplish the proposed research project. Our work will not only fill a knowledge gap in our understanding of the effect of COVID-19 convalescent plasma, but will also provide California citizens rapid access to plasma with known anti-COVID-19 properties.

Yours sincerely,



John A. Zaia, M.D.

Director, Center for Gene Therapy
Hematological Malignancy and Stem Cell Transplantation Institute
Beckman Research Institute