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July 24, 2020

The Independent Citizen's Oversight Committee (ICOC)
The California Institute for Regenerative Medicine (CIRM)
1999 Harrison Street, Suite 1650
Oakland, CA 94612

Application: DISC2COVID19-12020
Project Title: Battling COVID-19 Using HSC-Engineered Off-The-Shelf iNKT Cells
PI Name: Lili Yang, Ph.D.

Dear Members of the ICOC and Board,

We are respectfully writing to you regarding our application, that will be reviewed at the meeting of the Application Review Subcommittee (ARS) on Friday, July 24th, 2020.

First we would like to thank the Grants Working Group (GWG) for their critical review of our research proposal, which received ***a median/mean score of 86/86 that was the highest*** from the most recent round of COVID-19 applications. ***The GWG recommendation is "Exceptional merit and warrants funding, if funds are available"***.

Some Highlights of GWG Review Comments

- "This is a potentially highly impactful proposal."
- "The proposed technology will address unmet medical need if successful. There is no approved highly effective treatment for COVID-19."
- "Excellent revision from the initial submission. The authors did a great job addressing the earlier concerns. It is impressive that they were able to quickly generate data in response to the prior CIRM review."
- "The scientific rationale is sound. Addition of preliminary data strengthens the proposal."
- "The project is well planned and designed."
- "The proposal is well thought out and highly feasible."
- "The team is qualified and can perform the work."

While we understand that the remaining budget in the COVID-19 program may not be sufficient to fund all recommended applications, we would like to take this opportunity to emphasize important aspects of our proposal and ask for the ICOC's consideration to fund this project. In particular, ***this project has several unique features making it especially suitable for CIRM's Special Call for COVID-19 Projects Program***.

Unmet Medical Need

Our project is directly in line with the ***CIRM mission to accelerate stem cell treatments to patients with unmet medical needs; in this case, COVID-19 pandemic***. As of Wednesday, July 23th 2020, the COVID-19 pandemic is responsible for over ***15.3M cases and 626K deaths worldwide*****.** There are over ***4.1M cases and 146K deaths in the US*****,** including over ***424K cases and 8K deaths in California***; the numbers are still counting. With the continued new cases worldwide especially in California, there are increasing concerns that COVID-19 may stay/recur for an extended period, and that a vaccine may not be immediately available or adequate to end the COVID-19 pandemic. Our application fulfills CIRM's ***Special Call for innovative approaches that utilize stem and/or progenitor cells.***

An "Off-The-Shelf" Cell Therapy Applicable to All Patients Without Age/Gender/Race Limitation

COVID-19 has had ***a disproportionate impact on people related to age/gender/race***; these differences may also affect the application of many COVID-19 treatments/vaccines. For example, ***vaccines may not benefit an aged population due to their weakened immune system***; however, patients who are over 60 years of age with underlying conditions are at the highest risk for severe COVID-19, which is associated with a 75% risk for mechanical ventilation and 50% risk of death. Many adoptive cell therapies can only be performed in a "patient-by-patient" autologous manner, and/or are limited to a genetic match (e.g., HLA) between highly selective donors and recipients. In sharp contrast, ***our proposed stem cell-engineered "off-the-shelf" iNKT cell therapy can potentially be used to treat ALL COVID-19 patients without age/gender/race limitations***. We also have devised a plan to incorporate underserved populations in our study and have designed strategies to ensure the delivery of this therapy to all patient populations, as described in the "Impact of Study on Underserved Populations" section of our DISC2COVID19-12020 proposal.

Feasibility & Immediate Deliverable

- **Previously Developed & Off-The-Shelf:** The stem cell-engineered "off-the-shelf" iNKT cell product proposed in our project has been ***previously developed for treating cancer***, partly supported by a CIRM DISC2-11157 award, and ***is now under commercial development by a biotech company, Appia Bio***. ***An IND filing is projected in 2021 Q2***.
- **Repurpose Off-The-Shelf iNKT Cell Therapy for COVID-19:** In the current DISC2COVID19-12020 project, we aim to ***repurpose*** this "off-the-shelf" iNKT cell therapy for treating COVID-19. Since the precedent cancer therapy development has accomplished a large part of the product development and established necessary materials/methods, the current project only needs to focus on the COVID-19 specific study, making the project highly feasible.
- **Clear Deliverable in 6 Months:** We expect to be able to ***initiate work on the funded project within 30 days*** of approval, and ***achieve a clear deliverable within 6 months*** of project initiation (Milestone 1; ***production of off-the-shelf iNKT cells***).

Potential to Address COVID-19 Pandemic and Beyond

If successful, our proposed stem cell-engineered "off-the-shelf" iNKT cell therapy has the potential to ***save the lives of COVID-19 patients and thereby addressing the unmet medical need of battling COVID-19 pandemic.*** Moreover, iNKT cells are powerful innate immune cells that evolve to combat various acute virus infections in regardless of virus types and sub-strains. We will initially focus on treating COVID-19; but ***once established, the stem cell-engineered "off-the-shelf" iNKT cell therapy can be readily applied to treat future emerging viral diseases and thereby has a significant impact on modern medicine and human health***.

Regarding some specific concerns from the GWG review:

- ***Heterogeneity of the cell product*** (CD8 flow and MHC I expression): If needed, this can be readily addressed by incorporating a Magnetic-Activated Cell Sorting (MACS) step in manufacture to purify $CD8^{+}MHC\text{-}I^{-}$ cells. MACS is a well-developed technique that is available commercially.
- ***Safety of the cell product*** *(*high dose and cytokine release/storm side effect):
  - The front-running NK and iNKT cell therapy COVID-19 clinical trials will indicate safety and instruct clinical trial design of our proposed new "off-the-shelf" iNKT cell product.
  - The precedent cancer therapy clinical trials testing the same cell product will provide important information about the therapeutic dose and safety of the cell product.
  - Cytokine release/storm syndrome (CRS) side-effect is a common concern for all adoptive cell therapies. The fast-evolving CAR-T cell therapy has accumulated valuable clinical experiences on managing CRS (e.g., anti-IL-6 antibody treatment), that can be adopted for our proposed iNKT cell therapy for treating COVID-19.
  - Moreover, we have incorporated an sr39TK suicide gene "safety switch" in our cell product. In a safety need, administrating ganciclovir (GCV) into patients can quickly deplete these therapeutic cells.
- ***Accomplishment of all proposed work*** (budget and timescale): Our proposal is indeed ambitious, in an attempt to address the unprecedented COVID-19 pandemic crisis. As recognized by the GWG review, ***we are a qualified and highly motivated research team***. Also, ***the UCLA BSCRC has committed a $150K matching fund*** to support this project once it is funded by CIRM. With the combined support, we are confident we will accomplish the project.

We are happy to discuss this further and will present at the ARS meeting on July 24th, 2020.

Sincerely yours,

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