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RE: Responses to the Review of CIRM Proposal DISC2COVID19-11838

Dear Board Members of ICOC,

I am writing this letter to respond to the review and comments on our CIRM proposal entitled: "Biomaterial vaccine to enhance the formation of SARS-CoV-2-specific T memory stem cells" (DISC2COVID19-11838) submitted on April 21, 2020. We hope that ICOC can consider our responses when making funding decision. The proposal has a score of 82, and we believe that it merits funding consideration as detailed below.

The objective of this discovery project is to develop an injectable biomaterial platform that can induce T memory stem cells (TMSCs) and boost immunoactivation to vaccines against SARS-CoV-2, which will help protect the elderly population. We appreciate the insightful comments from the Application Review Committee on this proposal and the **unanimous** support on the significance and impact of the project as exemplified in the comments: "A very interesting proposal using a very unique approach and if successful may have wide application." "The immunological approach is promising and could help patients including the elderly." "The concept is intriguing and could have a high impact." "Novel approach potentially high-risk high-reward."

The major concerns are the **feasibility** of product development. While it is recognized that this is "unique approach that should be supported", "Biggest concern is complexity of the construct, ultimate manufacturability." We also appreciate the perspectives on this **discovery-stage project**: "It's a challenge but worth the risk for a small investment." "There is a lot of work to get to a final approval, but I feel this needs to be attempted."

We would like to respond to the review with the following points.

(**1**) The susceptibility of the elderly population to COVID-19 and other infectious diseases present unmet needs and there is a lack of effective therapy. This Discovery project may be one of the earliest efforts to address the challenge and improve the immunity of elderly population, which will have broad impact on healthcare.

(**2**) We have assembled a team including expertise on stem cell engineering, biomaterials, immunoengineering and virology, and have all materials and reagents for the proposed studies, including COVID-19 virus culture and recombinant Spike protein. We have developed the drug delivery platform and demonstrated the modulation effects on T cells. This project, if funded, should move quickly to the development and demonstrate the potential and pathway to the preclinical trials and the clinic applications.

(**3**) Although the drug delivery platform includes several components, a part of the project will be devoted to the understanding the effects of these components, reduce the complexity, and develop a simplified cocktail for further development of therapeutics.

(**4**) Almost all components in our drug delivery platform have been used in clinical trials or approved by FDA in clinical applications. Therefore, the regulatory path is clear and feasible. This non-cellular approach is not necessarily more difficult than cellular approaches for clinical translation. Some technical details can be found in Appendix.

Our team appreciate your attention on this response and your kind consideration. Please feel free to contact us if you need further information. I will call in and make myself available to answer any questions during the ICOC meeting tomorrow.

Sincerely,

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Appendix. Feasibility for FDA Regulatory Pathways

The following components are a part of our drug delivery platform. As demonstrated below, these components have been approved for clinical trials or therapies.

Artificial Antigen Presenting Cells (aAPCs): Novartis's Kymriah™ T cell suspension, the first commercially available T cell therapy, was approved by the FDA in 2017 for treatment of pediatric acute lymphoblastic leukemia. This product developed utilizing Gibco™ CTS™ Dynabeads™ CD3/CD28 which were first used for isolation, activation, and expansion of T cells. However, the non-degradable nature of Dynabeads due to presence of magnetic polystyrene limit its in body applications.

Currently, there are several clinical trials (phase 1) in progress developing cell-based pathogen-specific aAPC (e.g., NCT04299724). Our aAPCs will be developed based on GMP-grade and FDA approved alginate to facilitate clinical translation of these particles. Here, we are utilizing the the same recombinant human CD3/CD28 antibodies as approved for use in CAR-T cell therapy by Novartis. Production of particles is highly scalable, and we published several reports on them recently. So, we anticipate no issue moving forward to clinical trial in several months.

Cytokines: Here we will use cytokines with proved clinical or preclinical outcomes. Recombinant human Interleukin-2, Interleukin-7, and Interleukin-17 will be provided by the BRB Preclinical Repository of the National Cancer Institute, Frederick, MD, USA. These cytokines are available in bulk and we expect no issue moving toward clinical trials with these cytokines.

Hydrogel Delivery System: Various 2D or 3D biomaterials can be used as a subdermal delivery platform. Specifically, there are a few reports on the use of biomaterials for localized delivery of vaccines. Delivering vaccination agents through biomaterials can provide their protection and enable better control of the local concentration of immunogens in order to elicit stronger immunization at a lower dose. Here we proposed alginate (approved by FDA for other applications) as an injectable platform for delivery of our vaccine. This formulation can form temporary "artificial lymph nodes" to provide required antigens and activation cues to promote the formation of T memory stem cells. We have worked with these materials before and we are confident that we can develop high-throughput and scalable manufacturing of these materials in GMP-compatible fashion.