March 22nd, 2023

Application and Review Subcommittee (ARS)/
Independent Citizens Oversight Committee (ICOC)
California Institute for Regenerative Medicine

Re: DISC0-14566 "*Immune cloaking of human stem cell-derived insulin producing cells for curative cell therapy without immunosuppression"*

Dear Members of the Committee,

We appreciate the overall positive review of our grant submission and are naturally disappointed that we so narrowly missed the funding cutoff. We would like to report that in the time since submission, two key steps that were raised as concerns by the reviewers have been **successfully completed**:

- Generation of an hESC cell line with the target gene knocked out
- Successful differentiation of the modified hESC cell line into pancreatic islet cells

The reviewers rightfully pointed out that these two aspects of the original proposal were potentially challenging at the time of submission - one, successful knock out of our gene candidate in human stem cells, and two, the capability of such engineered knockout stem cells to undergo successful differentiation into insulin-producing cells. In the time since the original submission, both these goals have been successfully achieved, and we thought it would be prudent to update the committee on the progress that has been made since our submission. We are working nimbly and with urgency to move our work towards impacting patient lives as quickly as possible.

Our DISC0 application focuses on understanding the mechanisms surrounding immune-rejection of cell transplants that could cure insulin dependence in patients living with type 1 diabetes – specifically, how elimination of one gene can reduce rejection of allogeneic cell grafts and increase graft longevity. Successful immune-evasion is a roadblock that needs to be solved to move away from systemic immunosuppression for allogeneic cell grafts – as a patient-led company, with patients in senior leadership and as advisors to the company, we are focused on identifying strategies to suppress rejection without administering strong immunosuppressive drugs – a deal breaker for many people involved in Minutia.

We have successfully differentiated stem cells into insulin-producing cells and demonstrated function in vivo. We have assembled a strong team to be able to query the outcomes of the genetic manipulation we propose – with decades of experience in stem cell biology, immunology, and transplantation biology. We believe this to be a unique amalgamation of experiences that needs to come together to solve a pressing problem of graft rejection today.

Below are some comments from the review that support our application-
- Based on a sound scientific rationale
- The applicants present solid data supporting their hypothesis
- The experimental layout is appropriately planned and designed to give meaningful results
- If successful, this project will have a big impact on stem cell therapy
- The applicant team is well rounded and has assembled a fantastic group of consultants

As stated in the Minority Report that accompanied the GWG's assessment, "the majority of the 15 panelists indicated that the proposal addressed a significant need, had the potential for impact, and was based on a sound rationale." Overall, we are excited to note that our application has been received

well by the GWG, with several reviewers recommending it for funding. The reviewers state that our project has the potential to change the impact of stem cell therapy in general – raising the possibility of collaborating with other groups to develop cell replacement therapies for diseases other than diabetes.

Considering the new data and the enthusiastic support of several reviewers, we would like to request that the ARS/ICOC committee reconsider our DISC0 application for funding.

Sincerely,

Katy Digovich

Katy Digovich
CEO
Minutia