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To: Independent Citizens Oversight Committee (ICOC)
Application Review Subcommittee (ARS)
California Institute for Regenerative Medicine (CIRM)

Re: DISC2-13442 "**Microgel-encapsulated iPSC-derived notochordal cells to treat intervertebral disc degeneration and low back pain**"

Dear Independent Citizen Oversight Committee (ICOC) Members:

I would greatly appreciate your consideration of our Quest (DISC2) application, on which we received a median score of **83** from the Grants Working Group (GWG).

This project advances a new approach for stem cell treatment for intervertebral disc degeneration and low back pain and is a direct continuation of our completed proof-of-concept study funded under **CIRM's Inception (DISC1)** program. The results of that study were published in ***Theranostics*** in 2019 (PMCID: PMC6831475).

Significance: Disc degeneration is an unmet medical need that will affect nearly 80% of adults at some point in their adult lifetime. All fourteen of the Grants Working Group panelists who scored our application voted "Yes" on the first review criterion: "Is this proposal of significance and impact?" Historically, CIRM has funded very few projects that aim to address disc degeneration and accompanying low back pain.

Potency Data: According to the Grants Working Group (GWG) Minority Report, GWG panelists who scored 85 or above felt that the preliminary data in the proposal showed sufficient proof-of-concept to support further studies, while the other half (scoring 80 to 84) felt that more preliminary data were needed in the application. In specific, while all reviewers support our efforts *(as evidenced by the range of scores, 80-86)* to generate **potency data** with our proposed product **in its final formulation** as laid out in our ***Project Plan***, half the panel felt these data should be included as preliminary data in the application, and half the panel felt these data should be generated in the project.

We observe that applications in this Quest review that have scored 85 or above are very near the endpoint of Quest (DISC2) – readiness for translational activities. Our application has reviewers' support for proof-of-concept and includes all activities that will bring this project to the selection of the therapeutic candidate and getting it ready for TRAN1 application.

Project Plan: While all 14 panelists voted "Yes" on four of the five review criteria, five voted "No" on criterion 3: "Is the project well planned and designed?" These votes were accompanied with manageable advice unrelated to providing more preliminary data in the application. According to CIRM staff (as documented in the Minority Report), the actual scoring was driven by the question of **adequate preliminary data** rather than the project-related advice provided by the GWG under criterion 3. As a

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result, while we are grateful and attentive to this advice, we feel that adjusting the proposal accordingly will not change our score.

DEI: Finally, we wanted to address a reviewers' comments under criterion 5 (Diversity, Equity, and Inclusion). Again, *all panelists voted "Yes" on whether we met the criterion*. One panelist did note that our planned studies for further demonstration of disease modifying activity in an animal model will use female (not male) pigs. To clarify, our studies for Quest (DISC2) use a female animal model due to *(i)* practical constraints associated with working with male pigs and (ii) the high prevalence of disc degeneration in women (PMID: 18602869). Moreover, iii) limiting the study population to female pigs adds to the study's statistical power to demonstrate disease modifying activity. If our Quest studies demonstrate disease modifying activity as we hope, we will incorporate both sexes and all affected ages in future translational and preclinical studies.

In summary, we hope that the significance of the problem, the proof-of-concept, the Project Plan, the multidisciplinary team we assembled for this proposal, the relatively limited representation of back pain research in the CIRM portfolio and extremely positive feedback from some of the reviewers will garner your support for this application at this time.

Thank you for considering our request!

Sincerely,

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