LETTER to CIRM BOARD ADDRESSING SCIENTIFIC REVIEW for TRAN1-12907
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Regencor's proposal to perform IND-enabling studies of FSTL1 for cardiac regeneration received a score of 83. There were 11 reviewers who scored the application. There was 100% positive assessment on 4 of the 5 key questions (significance, rationale, feasibility, and service of underserved communities). Reviewers were split evenly on the 5th question (experimental design). This is to clarify the specific points raised.

Significance
100% of reviewers agreed that the proposal has the necessary significance and potential for impact. Perceived strengths include very solid preliminary data in small and large animal models and their assessment that "this therapy is unlike any other currently being studied in clinical trials".

Rationale
100% of reviewers found the rationale to be sound and that "the applicants included many studies in order to submit an INTERACT to the FDA".

Feasibility
100% of reviewers consider the study to have particular strengths in "preliminary studies, planned work for INTERACT, and appropriate grade material".

Serving the needs of underserved communities
100% of reviewers view the proposal as definitely beneficial for underserved communities, including policies accounting for diversity and major benefits for the Medicare patient population.

Approach
Reviewers raised two major points on the approach to optimize efficiency, both useful in anticipation of their perceived FDA requests: 1) the number of animals used for the study and 2) blood and non-cardiac histology sample collection for safety evaluation.

RESPONSE: We agree with these points. We would very likely have reached the same conclusions during the award term as we participate in the required IQVIA partnering and following the FDA INTERACT recommendations.

> Regarding number of animals: We originally proposed to study 10 different dosage regimens. Reviewers stated that the pilot dosage groups should be smaller, in order to subsequently provide more statistical power to evaluate a fixed dose. This is indeed a better design, and we will follow the recommendation.
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> Regarding collection of material for safety evaluation: All toxicology analysis will be performed according to IQVIA and INTERACT recommendations. The original proposal included the collection of blood samples at 5 experimental points that will be used for pharmacokinetic studies. We planned a separate complete safety/toxicology arm. The reviewers felt that the experimental animals could be used for the safety/toxicology arm, resulting in a reduced number of animals needed, and to expand histological safety studies to include non-cardiac tissue samples. We will follow these recommendations.

One reviewer rightly stated that the inclusion of an obese, diabetic cohort, which we added to show efficacy of the treatment in the presence of the most common comorbidities of MI patients in the US, would not be necessary for FDA approval. We included this experiment to show that Regencor is highly motivated to deliver treatment to diverse and community-based patient populations, in particular to underserved communities in which these comorbidities are so prevalent. Since we were not asking for CIRM funding to do these experiments, we kindly request that this point not be used against the merit of our application.

Together, we are thankful for the Reviewers' comments. They are helpful in advance of the discussions with the regulatory authorities that will occur during these proposed studies and will facilitate the planned Interact meeting with FDA. With these modifications, all Reviewers criticisms will have been incorporated into the proposal. We respectfully request the ICOC consider awarding funding to help advance the development of this breakthrough first-in-class regenerative cardiac therapy, a highly unmet medical need in California and world-wide.