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RE: PC1-08128: Embryonic Stem Cell-Derived Chondroprogenitor Cells to Repair Osteochondral Defects

Dear CIRM Independent Citizens Oversight Committee,

This is a sincere request to consider our application "Embryonic Stem Cell-Derived Chondroprogenitor Cells to Repair Osteochondral Defects" for funding.

We received an Early Translational Research Award from CIRM In 2009 to begin translating our basic science discoveries in the use of pluripotent stem cells for orthopaedic applications. We generated several pluripotent cell lines and compared them against adult cells from various sources. We demonstrated very convincing proof of concept leading to our development candidate: an embryonic stem cell-based progenitor cell suspended in a chondrogenic hydrogel that was very successful in repairing osteochondral defects (a major factor leading to osteoarthritis).

To continue this initial work that was funded by CIRM, Scripps Health provided bridge funding over the past 2 years. We also received funding from my colleagues in the Division of Orthopaedics who believe that our approach has the potential to transform the current standard of care. In addition, we received philanthropic support from numerous patients and advocates who have donated to our research program. Of our two largest patient donors to date, one had bilateral knee replacements, and the other, a hip replacement. Their main motivation was to contribute to any science that could prevent the need for joint replacement.

The RFA for the Preclinical Development Awards committed a total of $40 million for up to 8 awards; less than half of which will be required to fund the present applications ranked in Tier 1. Our application met every eligibility criterion in the RFA. More importantly, we also qualified for highest priority based on following criteria: a prior Early Translational Research Award from CIRM, identification of a clear development candidate with compelling evidence of efficacy, demonstrated readiness to proceed to a pre-IND application, and a commitment of co-funding of 25% (we received a commitment of 50%). We have filed 4 relevant patents generated from this CIRM-funded technology, one of which has already been allowed by the USPTO.

Our median score was 75 indicating that at least half the reviewers recommended the application for funding. A concern raised by one reviewer was that we did not compare our therapy with competing therapies. We compared our development candidate against adult chondrocytes (clinically available therapy), against adult bone marrow-derived mesenchymal stem cells (in development), and against induced pluripotent stem cells (potential for development). As a universal control we also compared the results of our development candidate against a surgical procedure simulating microfracture (the present standard of care). To date none of these therapies have been effective in preventing the progression or reducing the severity of osteoarthritis. As we indicated in our application, our development candidate

(a combination of ESC-derived cells and hydrogel scaffold) was significantly superior to all of these treatments.

The majority of reviewers agreed that the application addressed a clear unmet need; while a minority felt the unmet need was moderate. Osteoarthritis and osteochondral defects are not life-threatening disease. However, the ensuing pain and disability has a profound impact on quality of life and mental health. My younger sister had crippling osteoarthritis and underwent numerous treatments for 7 years before finally undergoing bilateral knee replacements 2 months ago. I have been collecting a long list of patients that have contacted me in person, by phone, or by email wishing to be considered for enrollment in a stem cell-based clinical trial when available. In addition to the medical consequences, the economic burden of arthritis is staggering, over $200B in the US alone. Again, to date no therapy has shown to be effective in preventing the progression or reducing the severity of osteoarthritis.

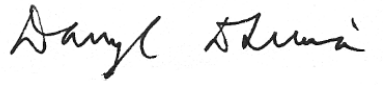
Our investigative team is comprised of translational scientists, physicians with expertise in multi-center clinical trials, which includes four adult knee reconstruction surgeons, stem cell biologists, three members of the FDA Cellular, Tissue and Gene Therapies Advisory Committee, a rheumatologist, a musculoskeletal radiologist, a biostatistician, and a biomechanist.

As a measure of our feasibility, reviewers believed that we might be ready to submit a pre-IND application even before our projected timeline. I have been very careful in conducting and proposing experiments to reduce any risk and equally cautious in estimating the timeline. Our proposed activities were based in part on our informal discussions with the FDA regarding our readiness for a pre-IND application. Our leadership team includes three co-investigators that are members of the FDA Cellular, Tissue and Gene Therapies Advisory Committee. We also proposed to contract with Parexel International to provide critical regulatory consulting services including Gap Analysis, and support for Pre-pre-IND Meeting, and Pre-IND Meeting.

We proposed in the application to work closely with CIRM staff to establish important milestones and identify criteria for success. If any of the proposed activities are not essential for a pre-IND we will work with CIRM to revise the scope and budget if necessary. Scripps Health also believes in the potential for our stem cell-based therapy and has committed to contributing 50% to the CIRM-funded portion. It is especially important to us to be able to take advantage of the offer from Scripps Health which would greatly accelerate our progress to the clinic.

We greatly appreciate your consideration for funding this application for the Preclinical Development Award. We will be happy to provide any additional information if needed.

Sincerely,



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