Written comments by the applicant to the ICOC

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Project Title: Generation of expandable, self-renewing muscle stem cells for Duchenne Muscular Dystrophy

We would like to thank CIRM for the opportunity of providing comments on our proposal. We are enthusiastic to see that the reviewers considered the application highly relevant to address an unmet need for the development of Duchenne Muscular Dystrophy (DMD) disease modeling and therapeutics. We have appreciated the constructive reviewers' comments; at the same time we would like to take the opportunity to clarify some of the issues raised by the reviewers.

One concern relates to the limited high-risk high-reward nature of the proposal. We would like to emphasize that approaches for the efficient derivation of muscle stem cells (MuSC) from human iPS cells are currently lacking, with available strategies being able to only generate "committed" muscle progenitor cells, which have obvious limitations in term of self-renewal function and therefore applications for tissue repair. This is a major bottleneck that prevents the use of DMD iPS-derived muscle progenitors for reliable disease modeling as well as cell replacement therapies and that we have decided to address with our proposal. We are particularly aware of the importance of this bottleneck, as we and others have shown that DMD MuSC exhibit severe defects in self-renewal and tissue repair function and contribute to disease progression (Sacco et al, Cell 2010; 143(7):1059-71; Dumont et al. Nature Medicine 2015; 21(12):1455-63). Thus, we would like to emphasize that our approach, which integrates developmental signals together with treatments that promote MuSC expansion, if successful will actually be highly rewarding in term of resolving a long-standing issue in regenerative medicine. While we acknowledge that mouse models is the next step for in vivo treatments, before extension to larger animal models for pre-clinical studies, we also reiterate the importance of addressing the first basic essential issue.

A second concern was the yield of iPS-derived MuSC for tissue repair in DMD. One goal of this inception award, beyond in vitro disease modeling, is to assess the tissue repair function of human iPS-derived MuSC in mouse models. Cell replacement therapies for muscle diseases still face major challenges, one of which is cell migration within and across multiple muscle groups affected, thus even though low number of MuSC may be sufficient for tissue repair, when transplanted MuSC are retained close to the injection site, thus limiting their impact on tissue maintenance. For these reasons, strategies aimed at increasing the yield of generation of human iPS-derived MuSC would overcome this limitation.

For the last critique, on our ability to carry out the proposed studies, we would like to emphasize that we have extensive expertise in multiple aspects of skeletal muscle biology, ranging from skeletal muscle development (Tierney et al, Cell Reports 2016; 14(8):1940-52), to MuSC-mediated muscle tissue repair (Sacco et al, Nature 2008; 456(7221):502-6; Sacco et al, Cell 2010; 143(7):1059-71; Tierney et al, Nature Medicine 2014; 20(10):1182-6), generation of muscle cells from ES and iPS cells (Puri and Mercola, Genes Dev, 2012; 26(24):2673-83; Albini et al, Cell Reports 2013; 3(3):661-70; Albini and Puri, J Vis Expt, 2014; (88):e51243; Hwang et al, PloS One 2013; 8(8):e72023), as well as preclinical and clinical studies (Consalvi et al, Molecular Medicine 2013; 19:79-87; Bettica et al, Neuromuscular Disorders, 2016; 26(10):643-649).

We would like to emphasize that DMD is a pediatric lethal disease for which no cure is available to patients, thus there is a major need to develop novel strategies to accelerate stem cell treatments. Our approach integrates exposure of human iPS cells to developmental signals in conjunction with STAT3 pharmacological inhibitors already in preclinical and clinical studies, which will accelerate the transition to the clinic. Finally, the impact of the proposed project will extend beyond DMD to other muscle degenerative disorders, as it would serve as an ideal platform to study the early stages of myogenesis and how each disease affects tissue maintenance in patients.