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RE: "Key Tools for Spermatogonial Stem Cell Therapy" (DISC2-12580)

Dear ICOC/Application Review Subcommittee members,

Our grant application received a score of "80," which I understand is slightly below the "85" threshold recommended for funding. I am writing this letter to make a plea for why I believe our application deserves funding.

I want to thank the Reviewers for their many positive comments. With regard to their concerns, I consider them to be easily addressable; e.g., by providing alternative plans and using appropriate statistical approaches to analyze the data we obtain.

The reason why I am asking for funding this round (rather than waiting to revise for the next application round) is the immediate need to develop an approach for providing fertility through spermatogonial stem cells (**SSCs**).

In principal, SSC therapy could provide fertility for any of the >100 million men worldwide who are infertile (or sub-fertile). However, **the immediate target group for this therapy are men rendered infertile as a result of chemotherapy treatment as a child.** Typically, these children received chemotherapy to treat their cancer.

The good news is that chemotherapy is able to cure >70% of children with cancer. The bad news is the chemotherapy often renders the children infertile. If they are not yet adolescent, it is not possible to bank their sperm prior to chemotherapy because spermatogenesis does not initiate until adolescence.

Thus, it is critical to develop approaches to allow fertility for these cancer survivors. **The approach we are perfecting in our grant application is to inject purified SSCs into the testes of these cancer survivors.** Because the SSCs are stem cells, they should repopulate the testes of these cancer survivors and differentiate to form sperm (this is feasible, as it has been achieved in many other mammals, including non-human primates).

The reason why it is urgent that the experiments proposed in our application are performed as soon as possible is our collaborator, Dr. Kyle Orwig (U. Pittsburgh), has recently received approval to treat human male infertile patients using *whole testes biopsies* containing SSCs. Kyle Orwig is the director of a national fertility preservation program that cryopreserves testes biopsies from pre-pubescent boys that receive chemotherapy (https://www.upmc.com/media/news/032119-orwig-fertility-science). Thus, soon, his group should have data on the success of engrafting SSCs in humans, as well as their ability to generate sperm and permit fertility.

Our proposal is designed to take this one step further – to treat male infertile patients with *purified SSCs* (rather than unfractionated testicular cells) so as to greatly increase the number of SSCs injected into cancer survivors, and thereby increase the chance they can father children. I believe the detailed plan in my CIRM application provides the groundwork to implement this in the clinic.

The sooner the plans outlined in my CIRM proposal can be done, the sooner we can move forward with clinical trials (through CIRM). To achieve this goal, it is my plan to continue to collaborate with Dr. Kyle Orwig, along with my long-term collaborator, Mike Hsieh (Urology Dept., UCSD).

It is realistic that the purified SSC therapy approach will be used to treat infertility patients very soon, particularly since Kyle Orwig's group plans to soon get results with injection of non-purified SSCs into human infertile patients.

Sincerely yours,

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