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Dear Joan,

In response to your question about Professor Gage's proposal I'm happy to share the following thoughts that developed both from reviewing his proposal for the ICOC as well as in discussion directly with him.

You asked if the work could be accomplished with the reduced level of funding being recommended. In short yes, but it is clear to me that the work would move faster with more funding. In fact, I asked him this same question. In fairness, Professor Gage is quite grateful for the opportunity to work with CIRM staff and me as Chair of the GWG, but he was concerned that he does not wish to be viewed as ungrateful if he were to ask for more support.

Because he has reduced his workforce for this project from 5.4 FTE to only 2.2 FTE's it is logical that the pace would be accelerated with more staff. When I asked for more specifics he mentioned that another $200,000 in direct costs spread over the three years would allow him to more advantageously staff the project. I agree based on the complexity of the science.

I would give him every reason not to fail; the question is too important and extends well beyond PD.

Here are some points to consider:

A. The Science.

• A **clever use** of patient specific (human) iPSC's to test novel compounds; yes, one could use other cells, but it would be shooting blindly in my opinion.

• **A timely analysis of the role of inflammation as a cause, or part of a cascade** in PD. There has been an undercurrent of the importance of inflammation since I first started studying PD in the '70's; some are still skeptical as seen in one of the reviews, but at least five reviews in the literature this year focus on inflammation in PD. In these experts view there is no question about inflammation as a contributing factor.

• The **concern** of one reviewer that **inflammation might help stimulate** regeneration **is not valid;** if so, there would be no PD or other degenerative disorders of the nervous system. It's not a functional mechanism for CNS repair. While there is some evidence that inflammation can lead to axonal sprouting, particularly in the peripheral nervous system this has not been shown for nigrostriatal dopaminergic neurons that degenerate in PD.

B. The Scientists

• **Professor Gage has assembled a world-class team** that includes clinical investigators. In fact the work will go from Bedside to Bench back to Bedside as they search for effective analogues of the dopamine transcription factors that can lead to a blunting or repression of the inflammatory response.

• I have know Professor Gage for many years and have engaged in scientific dialogue with him frequently. **I have never witnessed such a passion to succeed** as I did in my conversations with him over this project. I've been around a long enough time to know when someone is genuine and his passion is real. His dedication is a welcome addition to the PD research field. And it is much needed, as there are an unusually small number of PD researchers in California.

C. The Opportunity

• CIRM has a **unique opportunity** to advance PD research using a clever and meaningful approach by testing novel drugs candidates on patient specific cells of the central nervous system. As I have heard others articulate, "the clock is ticking".

• We heard at the last ICOC meeting that CIRM has been advised to "be proactive" and "**not to be afraid to make mistakes".** I agree fully. This is an opportunity to be proactive. There is risk involved in even the most carefully justified proposal, but this team can be counted on to mitigate risk and move aggressively, and effectively.

• **Again, I would give them every opportunity not to fail.**

Sorry I can't be with the ICOC again to be able to answer any questions you might have, but we have surgeries planned all this week on our NIH grant on tract reconstruction for PD. I can be reached on my cell (303.521.4621).

Best wishes,

John Sladek
Chair,
Grants Working Group