Review of Beseiso Proposal

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2023-11-08

Overview

The applicant provides a compelling case for the importance of research on transcription start site switching. It is an underexplored topic and the possible implications are important to understanding biology and health and disease processes.

The applicant chooses to explore the canonical example of epithelial to mesenchymal transition (EMT) in breast cancer, which I especially like given the high burden imposed by breast cancer.

The applicant proposes the research while studying for a Ph.D. at the University of Michigan. The applicant presumably has a strong biology background. U of Michigan offers world-class resources for biology research.

Factor 1: Importance of the Research (Significance, Innovation), scored 1-9

Overall, I think this research is quite important. I'm honestly a little surprised that it hasn't been done before. The applicant has some nice ideas, but I felt that more detail in the proposal would have nicely emphasized this point.

The applicant writes:

> In addition, knowledge of these 5' UTR regulatory elements can facilitate the prediction of protein output from the mRNA sequence

I felt like this idea was not well explained. It is, in my opinion, a really important consideration. For example, how exactly would the 5' UTR regulatory elements' identities or structures enable prediction of protein outputs?

The applicant could have said more about prior limitations about construction of genomewide TSS switching sites. Doing so likely would have made me even more enthusiastic about the research. Why has this research not been done before?

> I will identify 5 UTR isoforms with significant differences in translational potential.

The above sentence is an example of a sentence that seems to contain a really important idea, yet I feel that it is not conveyed precisely or completely. For example, what is the meaning of "translational potential"? How do you know if you have "significant differences" in translational potential?

Factor 2: Rigor and Feasibility (Approach), scored 1-9

Overall, I feel like the applicant's approach is feasible. I would have been more enthusiastic about this proposal if the applicant had provided more information about the rigor of prior research. Additionally, the applicant doesn't adequately describe some concepts in the proposal, which isn't reassuring.

I do worry a little about the proposed timeline. Can the applicant really complete the proposed research in 2 years? Maybe, but I am unsure about this.

The timeline table might benefit from more detail. Also, I feel like the applicant might want to justify the 2-year timeline. What has the applicant done, or what skills does the applicant already have, that might justify an apparently short timeline?

Given the diverse data that require analysis in this proposal, I would have appreciated discussion of the applicant's computational and data analytic skills. Does the applicant have the skills to complete the proposed analyses? And, if not, does the applicant have resources to learn the necessary skills?

For example, the applicant writes:

> Significance in RRSs between isoforms will be determined with a Bonferroni-corrected two-tailed t test

However, the applicant doesn't justify the use of a t-test. I expected to see a mention of the assumptions needed for reasonable inferences from a t-test and a justification of why those assumptions are met in this setting.

In aim 2, the applicant writes:

> Since the shorter 5 UTR isoforms of the plasticity inducing proteins SNAIL and NANOG were reported to be preferentially translated in stressed breast cancer cells that mimic an EMT signature.

What exactly does the applicant mean by the terms "EMT signature" and "mimic"? I feel like these ideas could be quantitatively defined, but they are not.

Factor 3: Expertise and Resources (Investigator, Environment), to be evaluated as either sufficient for the proposed research or not (in which case reviewers must provide an explanation)

While the applicant's biosketch is unavailable, the applicant is a graduate trainee at the University of Michigan, so I expect that the applicant has a strong background in molecular biology. The applicant's experience in data analysis and computing is not discussed, which is a little concerning.

Given that the applicant is proposing research in a well funded and highly productive biology department at the University of Michigan, I expect that the research environment is excellent. The department's resources are world-class.

Thus, I believe that the expertise and resources probably are sufficient for the proposed research.

Overall Impact

Likely to be quite high, but attention to detail in the proposal might have made this clearer. A justification for what seems to me to be an accelerated timeline would have increased my enthusiasm.