**Project 14352 – Grant Feedback**

Dear Authors,

Thank you for the opportunity to work with you on the revision of your grant proposal. I have reviewed the provided file, and overall found it to be a clear proposal. In an effort to provide you with the most helpful feedback possible, I have included comments in the text when I noticed specific points/issues that I felt would benefit from further clarification or that were relatively minor. In addition, I have provided any more general input I have on the different sections of your proposal below. I hope you find this input helpful, and I wish you luck on your application! Please reach out if you have any questions or if we can provide any additional help.

Best Regards,

Ryan Molony, Ph.D.

**General Feedback**

* While the grant is understandable in its current form, I found that there were many passages that may benefit from some further English language editing to improve the overall flow and clarity of the text. I have marked some instances of this in the text, but have not provided exhaustive input on this point as this was not the focus of the present review. This is a service that I or other ALE experts can perform, on request.
* With respect to the actual formatting of the text, I would recommend justifying the text rather than left-aligning it, as this tends to give a cleaner appearance. I would also suggest avoiding the indented subsections that are used starting with Section 3 of the grant, as they are a bit inconsistent and needlessly constrain the space for the text.
* I see that your Figures are not currently included in the grant. When you do incorporate them, I strongly recommend incorporating some throughout the text to highlight key data or to provide schematic overviews of the models and systems you are discussing. I know that the ISF formatting guidelines recommend placing preliminary data at the end of the proposal, but including at least some figures earlier in the text can be extremely beneficial, particularly when it can aid readers in their understanding of the topic(s) in question.
* No Abstract was provided for review, so please let us know if you would like any assistance with this portion of your proposal.

**Section 1: Scientific Background**

* Overall, this section provides an effective overview of the pathology of TMJ disorders and touches on important challenges to addressing these issues.
* I think the section may benefit from a bit of an extended discussion of current/previously published translational efforts, with a focus on the limitations of these strategies or the challenges they have faced to further help set up the proposal. I have marked the paragraph where I think these additions would be helpful with a comment.
* If you have relevant publications in this space, it would be worth specifically calling these out in the background section. Something along the lines of “We have shown that…” or “We and others have found…”.
* Given that you introduce hyaluronic acid as an advantageous material in the following sections, it may be worth introducing it in the background and discussing its advantages. Similarly, you may want to offer a bit more of a detailed breakdown for each of the components that will be used in your study, highlighting their useful properties (i.e. k-carrageenan, hydrogels, HAMECs).
* I would suggest ending the background section with a stronger sentence about the promise of the proposed approach as a means of extending more effective individualized treatment options to patients in need.

**Section 2: Research Objectives**

* While your Aim titles for Aims 2/3 are fairly straightforward, the title for Aim 1 is a bit too long and involved - I suggest trimming it down to a single line that captures just the most important aspect of this Aim.
* For each Aim, I suggest restructuring the paragraph to provide a 1-sentence overview of the challenges to be addressed in the grant, followed by 2-3 sentences detailing what precisely you will do in that Aim to address these challenges. You can also include a final sentence indicating the expected outcomes for each Aim.
* Be sure to use the future tense when discussing what will be performed in your project, as the present tense is currently used in some cases.
* Am I correct in understanding that all three of your Aims are essentially dependent on one another, working through the progressive development of this TMJ system? Reviewers often express concerns when Aims are all interdependent, since this means that if Aim 1 encounters issues it can disrupt the entirety of the project. It may be worth more clearly detailing which Aims will build on the results of which other Aims.

**Section 3: Significance and Innovation**

* For this section, I suggest building from the specific significance of your grant to discussing the broader potential of your TMJ system, in particular with respect to the potential it can provide to patients, re-emphasizing the debilitating effects that TMJ disorders cause for patients and highlighting how your system may, in the long term, alleviate these effects.
* With respect to innovation, it is worth specifically highlighting the novelty of your grant, using phrases like “for the first time, our system will…” or similar text to indicate which aspects of this project have not been performed previously. It is important to demonstrate that you effort stands apart from other work in the field and to emphasize the unique aspects of this work.

**Section 4: Research Plan**

**4.1 – Working Hypothesis**

* The phrasing of this section is a bit unusual. You currently present your “hypothesis”, but in actuality, it is presented as more of an Aim. Consider reformulating it as something along the lines of “We hypothesize that by combining appropriate polymers and injectable biomaterials capable of mimicking the native cellular microenvironment, we will be able to successfully fabricate a biomimetic TMJ system comprised of bone-supported articular surfaces and an articular disc that can…” ending with some statement about the expected performance of this platform. You can then start the following sentence with “To test this hypothesis, we will design…”
* You allude to your experience with different materials and systems, but you should more explicitly detail this experience in prior sections.

**4.2 – Design and Methods**

* Reviewers may not be familiar with all aspects of your utilized system. Be sure to define all acronyms that are not extremely common (including PDMS and PCL), and consider indicating why particular materials and cell types will be used, noting their advantageous characteristics.
* For Aim 1 you discuss what will be done, but don’t provide much information on how you will analyze the outcomes associated with these experiments. More detail on that side of this would be extremely beneficial, demonstrating that you have a comprehensive plan to characterize the different aspects of your system and to modulate it as appropriate. If you plan to test a range of conditions, I would recommend providing greater detail on that front as well (i.e. concentrations of particular compounds, different numbers of cells to be added, different testing time points, etc.).
* Be sure to use the future tense when discussing planned experiments.
* Is Aim 2 using the same system detailed in Aim 1, or is this a distinct system? More clarification on this front is needed. If it is the same system, some clearer demarcation between Aims 1 and 2 is needed, as they currently seem to contain substantial overlap in terms of the general techniques being employed such that they could easily be combined into a single Aim.
* Aim 2 does provide more detail than Aim 1, but it would still benefit from further details on specific experimental parameters to demonstrate that you have a specific, detailed plan for achieving your goals.
* If I understand Aim 3 correctly, you plan to work with both implants and explants? The specifics of how explants will be established/maintained are not clear, nor is there clear enough delineation between which experiments will be performed *in vivo* and which will be performed *ex vivo.*

**4.3 – Preliminary Results**

* For section 4.3.1 – it is not clear what has actually been performed to date, as the text is very general on this front. Be a bit more specific regarding what you have completed to date with respect to the design of your TMJ system.
* For section 4.3.4 it is not clear – do you have experience with the mouse model in question, or are you detailing the experiences of others? Be more specific regarding your experiences.

**4.4 – Facilities and Infrastructure**

* No specific feedback beyond the comments already included in the text – be sure to update the placeholder/missing text.

**4.5 – Expected Results, potential pitfalls, and alternative approaches**

* You say that your device should be biocompatible with minimal cytotoxicity. Is there any risk of unforeseen issues on this front?
* Are there any potential challenges to the implementation of your rat model system?