Response Form for the Final Performance Review Report*

1. Name of Grantee: Pittsburgh Tissue Engineering Initiative

2. Year of Grant: 2010 Formula Grant

A. For the overall grant, briefly describe your grant oversight process. How will you ensure that future health research grants and projects are completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) are submitted to the Department in accordance with Grant Agreements? If any of the research projects contained in the grant received an "unfavorable" rating, please describe how you will ensure the Principal Investigator is more closely monitored (or not funded) when conducting future formula funded health research.

PTEI provides grant oversight to all Formula Grants in the following manner. Weekly update meetings are conducted between the PI (Dr. Rick Koepsel) and the Grant Coordinator (Dr. Alan Russell) to ensure progress of milestones. The Annual and Final Progress Reports are submitted to PTEI two weeks prior to the State's submission deadline to allow for review, comments, and questions, by the Program Manager and the Grant Coordinator. Once reports are finalized and approved they are submitted in accordance with the Grant agreement. If the project receives an unfavorable rating, the Grant Coordinator meets with the PI to address the comments and craft the appropriate response. PTEI will then continue to closely monitor the progress of the project.

In addition, PTEI monitors the grant through the review of invoices from the subcontractor, the University of Pittsburgh, along with a review of its own internal administrative expenses. PTEI is invoiced monthly for expenses of the previous month by the subcontractor. Once received, the invoice is coded by the Grants Coordinator and checked against the original budget for variances. If no variances have occurred that need follow up, the invoice is submitted for additional review to the Senior Research Administrator and the Controller. Once these approvals have been obtained, the invoice is prepared for payment. Using this information the audit report is prepared and submitted accordingly.

* Please note that for grants ending on or after July 1, 2007, grantees' Final Performance Review Reports, Response Forms, and Final Progress Reports ***will be made publicly available on the CURE Program's Web site.***

Project Number: 1086701
Project Title: Acrylic-Bisphosphonate Polymer Mediated Cell Binding to Collagen-Hydroxyapatite Scaffolds
Investigator: Koepsel, Richard R.

B. Briefly describe your plans to address <u>each</u> specific weakness and recommendation in Section B using the following format. As you prepare your response please be aware that the Final Performance Review Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

Reviewer Comment on Specific Weakness and Recommendation (*Copy and paste from the report the reviewers' comments listed under Section B - Specific Weaknesses and Recommendations)*:

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

<u>Reviewer 1:</u>

1. It is apparent that the funds and time necessary for the aims of the strategic plan (proposed) were not sufficient. In particular, it was noted that the first aim (characterization of the material) was not completed. Consider revising or limiting the number of time-intensive aims to match the scope/funding of the project. The completed work was certainly proportional to the time and funding provided. This research could easily be scaled to an R01 mechanism or equivalent.

2. Consider coordination of research with commercial aims. Even if the PI has no interest in the commercialization aspects, the institution may wish to create an agreement with the PI and visiting scholars for further development and protection of the research. Note that these agreements should be in place before the research is submitted for peer-reviewed publication.

3. During the annual progress report, the deviation from the original aims could have been reported. In particular, the move from a 'material characterization' study to the more polymer/scaffold binding study emphasis of the second aim was perfectly valid, but not well described. In addition, the last statement, "what remains is to test the cell binding on the scaffolds synthesized for the project to test the materials *in vivo*," needs much greater description. Are these studies planned for your laboratory? Are they intended for the visiting scientists to continue?

<u>Reviewer 2:</u>

1. Given what was stated in the research strategy, the PI should have evaluated the fibers for material properties and stability. Knowing these two parameters is critical in order to ensure that the project has any clinical significance.

2. There is a lack of publications. I understand the budget limitation, but the funding obtained from this project plus the co-funding from DoD should have allowed the PI to obtain critically needed data to produce at least one manuscript for publication.

3. There is no disclosure as a result of the work performed. It is recommended that the PI talk to his technology office to determine if there is intellectual property that needs to be protected as a result of this work.

Reviewer 3:

1. No peer-reviewed publications resulted from the project. The researchers should communicate their results to the scientific community.

2. No license or patent was submitted/filed. It will be helpful for the researchers to look into the potential of protecting the intellectually property and commercialization of the technology.

3. Several objectives in the strategic research plan were not achieved. It will be helpful to give some explanations.

4. Some changes made in the research protocols were not explained clearly. It will be helpful to provide some detailed justifications.

5. No detailed future plan was proposed for this research project. It will be helpful to provide some details for how the researchers will use the data/results from the current project to continue/expand the research.

Response (*Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts*):

General response: I would like to thank the reviewers for their comments which were, on the whole, well taken and quite helpful. The reviewers all seem to have found the same weaknesses in the project and have all made similar recommendations. This being the case I would like to answer generally and cover the common areas of concern.

I would like to say that the weaknesses as presented by the reviewers were not unexpected.

Deviation from protocol/non-completion of Aim 1; I agree with the reviewers that pointed out that the deviations from the proposed protocol were not well explained. An upfront explanation is therefore required here. Fundamentally, pretty pictures aside, the materials we made were nowhere near our expectations. Far from being nice fabric with all the features this would imply, the electrospinning produced a material that was far from the "mat" of fabric that we were looking for. At best it was sparse, thin, very brittle, and was mostly soluble in water and culture media. It was, in other words, not useable for the proposed purposes. We had hopes of finding a formulation that would fix these problems but we did not. We probably gave up too early because a paper was published this year by another group (Wei Song, David C Markel, SunxiWang, Tong Shi, Guangzhao Mao, and Weiping Ren. Electrospun polyvinyl alcohol–collagen–hydroxyapatite nanofibers: a biomimetic extracellular matrix for osteoblastic cells. Nanotechnology 23 (2012) 115101 (15pp) doi:10.1088/0957-4484/23/11/115101) that made materials very similar to what we were attempting. They also showed growth of cell on the

material, although not polymer modified cells. Interestingly they did not attempt to make fabric like materials but instead electrospun thin accumulations of fibers onto glass slides on which they grew cells. Notably their pictures looked similar to ours but they were able to add a second polymer (polyvinyl alcohol) that made their fibers insoluble. Had we thought of this, Aim 1 might have been achievable.

IP, disclosure, commercialization; We did provide Pitt with information about the materials we were developing and their decision was to defer application for patent coverage until more substantive results were obtained. Commercialization is not off the table but it is difficult to negotiate without IP coverage.

Publications; We have continued work with the cell binding polymers used in the project. I am finally convinced that they are acting as we expected. We have two manuscripts in preparation for submission to top journals.

Continued interaction with the visitors from Kazakhstan; Since the end of the project we have moved the lab from Pitt to Carnegie Mellon University. We have also hosted a visit from one of the Kazakh researchers to learn techniques to continue our collaboration in her home institution. We expect to continue the collaboration and are working on funding arrangements with them. The future work will center on the cell binding polymers.

C. If the research project received an "unfavorable" rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive "unfavorable" ratings.

Response: N/A

D. Additional comments in response to the Final Performance Review Report (OPTIONAL):

Response: N/A