

**Response Form for the Final Performance Review Report—
Allegheny-Singer Research Institute 2008F***

1. Name of Grantee: Allegheny-Singer Research Institute
2. Year of Grant: 2008 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.

The Allegheny-Singer Research Institute Office of Grants and Contracts is responsible for distributing, collecting, reviewing, and submitting all reports for this program. If any problems arise, the Office of Grants and Contracts will contact the appropriate administrator in the Pennsylvania Department of Health.

We are pleased that the overall grant received a favorable score. The investigator for the one project which received an unfavorable rating (Project #0862304) is no longer with this institution.

For each research project contained in the grant, please provide a response to items B-D as listed on the following page(s). When submitting your response please include the responses for all projects in one document. The report cannot be submitted as a ZIP file, because the Department’s exchange server will remove it from the email. If the report exceeds 2MB, please contact the Health Research Program for transmittal procedures: 717-783-2548.

* 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: 0862301
Project Title: Analysis of Ulnar Collateral Ligament Reconstruction
Investigator: DeMeo, Patrick J

B. Briefly describe your plans to address each 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 1:

- 1. The strain data in Specific Aim 1 is good and promising, but it seems quite disconnected from the work done in Specific Aim 2. I was excited and hoping we'd get a modeled simulation of ligament strains over a range of motion as well as forces to compare to the experimental work. (I envisioned plots of the experimental work with FE simulated curves with which to contrast.)*

It is a bit ambitious for the funding, but as presented, it seems like the approach for Aim 2 went in a different direction. It would be beneficial to see a simple FE model of two bones and a ligament, simulated over a range of motion with contact at the joint.

Response:

The experiment and the finite element (FE) model began in parallel with the approval of the funding, and the project's timeline envisioned concurrent completion of both aims. The two parallel aspects of the work involved very different levels of laboratory resources. The opportunity to use 6 of the DOF robots required more management by the laboratory director, because a minimum of three people were needed for each test day. The finite element project, on the other hand, was the primary responsibility of a single member of the research staff and management was not as important in the project's daily progress. The concurrent conclusion of the two tracks could have happened had the research team stayed intact for the duration of the project.

The Reviewer is partially correct in her/his insight concerning the altered direction of the approach to Aim 2. The first step in the finite element model was the creation of the appropriate geometric model of the ulna and humerus. The geometric modeling was completed and the work concerning the hole placement in the medial epicondyle in mUCL repair began as a useful companion investigation while waiting for more extensive experimental data for input to the FE model. While waiting for the strain data, the well-trained and experienced FE modeler answered the questions about the effect of hole placement, and after, left the institution. An appropriate FE model of the mUCL requires relatively sophisticated understanding of FE modeling because of the nonlinear tissue behavior. At the time of the original analyst's departure, no one in the laboratory had the skills to complete that part of project, whether or not the experimental data were available. The laboratory is in the process of training another analyst who can complete the work if funding becomes available.

- 2. The lack of models presented for the relationship between the force applied by the robot and the forces in layers of the ligament, is a large weakness. It cannot be assumed that the force applied to the arm at a lever is constant at the far end.*

Response:

The research team agrees with the Reviewer that the lack of modeling is a major weakness. The FE model was to have made predictions about the distribution of the strains and resulting stresses in the ligament. These predictions remain part of future work and form a major component in the steps to achievement of a means to prevent damage and of a comprehensive analysis of overuse.

Reviewer 2:

- 1. With regard to the elbow flexion simulation, the use of a single muscle does not appear very physiological. The investigators should perform simulations with additional muscles actuated, including antagonists. Even if these simulations are not exactly physiological, they will allow a determination of the sensitivity of ligament strains on the muscle activation pattern. These additional tests would provide corrections and/or improve confidence in the current findings.*

Response:

The use of the elbow simulator ensures essentially identical performance of all tests. The actuation with a single muscle ensures that each specimen had force input that was only at a level needed to produce flexion/extension. Testing in this manner has been shown (Duck, Dunning Armstrong et. al.) to produce consistent results. Consistency was the goal in the tests. In retrospect, however, the researchers would have tested the specimens under more than one condition of loading to determine that no difference arose.

- 2. If ligament specimens are still available from the physiological strain testing and ligament force testing, these ligaments should be analyzed for stress-free resting length. Using true stress-free lengths (and subsection lengths) will allow the elongation measurements to be converted to actual strain measurements. This could be done with physical measurements (calipers, as proposed) or with optical measurements with a calibration frame in the images. This would provide information about regional strain in the ligaments and should improve the confidence in the interpretation of the physiological strain measurements.*

Response:

The specimens were retained with the intent of performing a load to failure test in tension. Their use for determination of a rest length is another possibility. In any case, the lengths will be recorded again while unloaded, in a manner similar to that suggested by the Reviewer.

Subsequent tests with the 6 DOF robot have shown that the net force across the elbow, when all the tissue except the anterior band of the mUCL has been removed, show that there is very little force, if indeed any force, transmitted by the anterior band during passive flexion/extension. More work is clearly warranted.

- 3. With regard to ligament force testing, there are two possible improvements that could be made. One improvement would be to match robotic simulator kinematics to those of the elbow simulator. In this case, the in situ forces would then be known for an in situ active elbow flexion, instead of the current passive elbow flexion. The second improvement approach would be to do the actual bone-ligament-bone tension testing. This would allow strains from the active elbow flexion simulator to be used to calculate the corresponding ligament forces. Either approach would provide more useful and relevant data.*

Response:

The research team agrees completely with the Reviewer. Although the first suggestion has several technical challenges related to programming the robot, the research team has started the process with tracking the finite helical axis during flexion/extension. An article currently in review at the Journal of Biomechanics, "Elbow Helical Axes of Motion are not the same in Physiologic and Kinetic Joint Simulators," answers the question whether the physiologic and robotic simulators produce the same motion. Continued work is envisioned. The second suggestion is one reason why the specimens have been retained. Tensile testing with forces in a variety of directions in the flexion/extension plane is planned.

- 4. The validation of the ligament reconstruction finite element models should be improved. First of all, the validation experiments should be performed on the same specimen used to construct the finite element model. The model loading conditions are not provided in detail, but were apparently to replicate multiple muscle forces. The main point, besides a specimen-specific validation, is that the loading conditions in the experiment precisely match those in the model. Also, the registration of the strain gauge locations, with model locations/data, is important so that the data will properly correspond; then clear quantitative comparisons can be made to determine if the model meets the 10% validation criteria. The measures to be validated should be clearly stated, as many investigators tend not to perform clear and thorough quantitative validations. Also, thorough quantitative validation of a model is generally difficult to achieve.*

Response:

The research team again completely agrees with the Reviewer. The use of the same specimen is the right way to compare the computational and experimental results. The research team had no experience with applying strain gages to bone when the experiment began, so that the experimental testing was first performed for development of the techniques. The results included in the report are from this practice, because that was available at the time of the report. The location of the strain gages was not considered to be as important as the general ability to apply the gages and perform the test. The team agrees, however, that final model validation is best completed with more complete information than was available at the time of the report.

- 5. The investigators should submit a manuscript on the in situ ligament strain data from the elbow simulator. Based on this strain data, once clearly summarized, they should submit grant proposals to continue this work and provide more definitive data on research questions.*

Response:

The research team appreciates the encouragement from the Reviewer. A series of articles is underway with plans for grant submissions.

Reviewer 3:

- 1. As the investigators continue to use their elbow simulator to study biomechanics of pathology and treatment, they may want to consider expanding their scope to include conditions that affect more people. For example, epicondylitis affects both athletes and workers. Focusing on conditions of working populations makes this kind of research more relevant to large populations of people.*

Response:

The research team can always use additional suggestions about use of the simulator. A project concerning radial head replacement has been anticipated, and a comparison of two lateral ulnar collateral repairs has also been planned. Each project requires funding and the Laboratory continues to seek the necessary support for more work. While the team is fortunate to have funding elsewhere, they would prefer more work with the elbow. Even though the number of patients in need of optimal ulnar collateral reconstruction is not as large as that number of patients with other elbow pathologies, the work on the medial ulnar collateral may find funding because of the financial impact.

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: Not applicable.

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

Response: None.

Project Number: 0862303

Project Title: A High Fidelity Rat Model of Pulmonary Arterial Hypertension

Investigator: Passineau, Michael J.

B. Briefly describe your plans to address each 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 1:

- 1. The PI should publish a study utilizing the PAH model to demonstrate that the model is fully established at CVI. This will increase the competitiveness for future extramural funding in the area of pulmonary hypertension by the PI and other researchers at the CVI.*

Response:

We agree with the reviewer's recommendation. However, since the project's stated goal was to replicate a previously-published model, a publication can only result subsequent to this project, not as a result of it (although we did extend the model, our novel results were not enough to warrant publication on their own). As reported, two external grants in PH were obtained by the PI in 2010, directly following this project period and the research performed during this project established the preliminary data and credibility needed to obtain these competitive external awards. In one of these grants, the PAH model is being utilized, and these studies will be published when complete.

Reviewer 2:

- 1. To expand the scope of the project, to include the development of specific methodological and/or experimental hypotheses, and test as the model is developed.*

Response:

We have done so, both in the ongoing externally funded awards mentioned (Entelligence and Gilead Scholars Awards) as well as through continued internally-funded development of the model.

- 2. To incorporate the development of a multidisciplinary research group aimed at utilizing this model and other pertinent models in pulmonary hypertension research.*

Response:

In addition to this left pneumonectomy/monocrotaline model, we have successfully established the chronic hypoxia model of PAH and have recruited an additional scientist (Dr. Kelly Shields) to our multidisciplinary group. As evidence of this multidisciplinary approach, Dr. Shields is studying the role of perivascular adipose in the rat model of PAH, and has recently been awarded a competitive external research grant to continue her work.

- 3. To develop an organized training program for technicians and research fellows to expand the scope of research in this model and in pulmonary hypertension. An extension of this recommendation would include the creation of a pulmonary hypertension modeling core to serve as a "hub" for a research program in pulmonary hypertension.*

Response:

We agree with the reviewer's recommendation, but the modest size of our research group does not yet justify a training program of this scope.

- 4. To prioritize the characterization of the experimental model based on accepted endpoints, namely pulmonary catheterization and pulmonary vascular histology. The development of accessory tools, such as microCT, should be not prioritized at the expense of these standard methods.*

Response:

The reviewer's recommendation speaks to a valid criticism that this study chose to prioritize novel destructive metrics over conventional destructive metrics of PAH. In short, we demonstrated the development of PAH with a non-destructive metric (echocardiography) rather than the destructive methods of conventional catheterization and histology. While novel, echo is nearly as definitive, and allowed us to redirect our analysis to a more novel destructive metric (microCT). It should be noted that the scope of budget of this project were limited, and thus this choice was necessary. With that being said, we are adding conventional metrics to our ongoing research in PAH.

- 5. To develop a specific plan of development of models of pulmonary hypertension into competitive grant applications.*

Response:

Since this project ended, the CVI has been awarded three competitive grant applications to study PAH in rats using two different models, including the model developed in this project.

Reviewer 3:

- 1. The grantees must use more animals and establish routine hemodynamic measurements.*

Response:

We agree that conventional (destructive) hemodynamic measurements are important, but our lack of in favor of angiographic methods reflects novel expansion of the model in our hands.

- 2. Lung and heart histology are essential and none have been provided.*

Response:

These metrics are valuable, but are incompatible with microCT. High frequency echocardiography has non-invasively confirmed many of the salient findings of histology, specifically right ventricular hypertrophy and pulmonary artery thickening.

3. *Overall quantitative data—with the exception of data reflecting survival of the rats—are needed.*

Response:

Echocardiography data are quantitative and we are developing an analysis method for our microCT findings, which are inherently quantitative.

Generic Recommendations for Allegheny-Singer Research Institute

Reviewer 3:

Due to the lack of progress, I would recommend to reset milestones and discontinue funding if no publishable data are forthcoming.

Response:

The issue of publishable data was addressed in our response to Reviewer 1. The proposal, as written, did not produce enough novel data to warrant publication, but has rather served as the foundation for subsequent studies, both externally and internally funded.

ADDITIONAL COMMENTS

Reviewer 3:

There is yet to be a robust model or published data. The incomplete tool kit does not promise definitive data or future studies.

Response:

We respectfully disagree. This project has formed the basis of 5 applications for external funding for future studies, 3 of which have been successful.

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: Not Applicable

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

Response: None.

Project Number: 0862304
Project Title: Myofibroblast Inhibition in Dupuytren's Contracture
Investigator: Satish, Latha

B. Briefly describe your plans to address each 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 1:

1. *Quantitative experiments on cAMP levels should be carried out as proposed in the application. Use of forskolin to increase cAMP levels should be quantified.*

Response: We realized that direct quantification of cAMP, while supportive and useful, was not in itself ultimately very important to advancing our understanding of the physiology of these cells. Because we were able to significantly alter the expression of multiple gene products using forskolin, known for decades as a stimulator of cAMP pathways, we had strong evidence that these were involved in the regulation of the gene products of interest that we assayed. Further, in other fibrotic systems we have directly assayed for cGMP (a similar cyclic nucleotide) and found no clear correlation between measured levels and the expression/activity of factors known to be involved in the synthesis/degradation of the cyclic nucleotide, and suspected that the same might obtain here. Thus, given the limitations in time and support for the project, we determined on reflection, that this was likely not the most important aim to pursue, and adapted our research plans accordingly.

2. *Experiments should be carried out in parallel with the control and involved fibroblasts. All RT-PCR experiments should be accompanied by parallel western blotting as was proposed in the application. Reproducibility of results from experiment to experiment should be analyzed.*

Response: We agree with the Reviewer, and in our continuing work this level of experimentation has in fact been carried out. Rather than reproduce these results here, we direct the Reviewer to the published manuscript:

Satish L, Gallo PH, Baratz ME, Johnson S, Kathju S. Reversal of TGF- β 1 stimulation of α -smooth muscle actin and extracellular matrix components by cyclic AMP in Dupuytren's-derived fibroblasts. BMC Musculoskelet Disord. 2011 May 25;12:113.

This manuscript is published in an open access journal with free online access to the public.

3. *Contraction, migration and proliferation experiments should be carried out as proposed in the application.*

Response: We are in the process of completing these experiments, some of which are now being gathered into a second manuscript.

Reviewer 2:

1. *The PI proposed to do a number of experiments that were critical to address hypotheses that were not done, most importantly to measure levels of cAMP. The second was to overexpress AC6. Neither were done.*

Response: As per our response to Reviewer 1, re-consideration of our ultimate goals and the means at hand to pursue them suggested that direct measurement of cAMP was of secondary importance. We are still in the process of generating and successfully overexpressing adenoviral vectors carrying AC6. This has been delayed by our change in institutions.

2. *The PI found increased expression of AC6 in DD cord fibroblasts and uninvolved palmar fascia compared with carpal tunnel control fibroblasts. Anticipated AC6 would have been decreased in DD cord and PF fibroblasts. The opposite result was found. The PI needs to address this finding. This needs to be compared with measured levels of cAMP.*

Response: We agree that this was an unexpected finding, but believe that our finding that forskolin can successfully differentially impact gene expression in Dupuytren's cells versus carpal tunnel (or palmar fascia) cells speaks more to the significance of our approach. Possible reasons why the apparently increased AC6 may not directly reflect the level of cAMP-pathway activation are: variations in other adenylyl cyclase enzymes and/or their inhibitors, variations in other downstream effector molecules such as protein kinase A or cyclic-AMP response element binding proteins (CREBs), variations in enzymes that consume or degrade cAMP etc. Thus, even with apparently elevated levels of AC6 already, further elevation to tilt the balance towards more cAMP synthesis may still be useful in modulating Dupuytren's fibroblast physiology to our purposes.

3. *The PI only examined DD fibroblasts from cord tissue and not from nodule tissue. As the PI described in the Background section, differences have been found between these two cells and nodule cells appear to be more myofibroblastic. The PI needs to obtain and examine DD nodule fibroblasts.*

Response: We agree that it would be interesting to examine fibroblasts from DD nodules as well. However, we have chosen to focus on cells from cords, because it is typically at this point in disease progression that the disease becomes clinically significant and requires surgical intervention. Thus, in terms of limiting disease recurrence, we believe this is the most relevant cell population, and also the most practical to work with, since DD nodules themselves are only rarely operated, as typically they are not yet causing any contracture symptoms.

4. *For the most part, the specific aims proposed have already been done on other types of fibroblasts, like cardiac and lung. Little new with regard to fibroblast-myofibroblast differentiation, will be discovered with these specific aims. The PI needs to design specific aims that will test underlying mechanisms by which changes in cAMP levels can alter fibroblast-myofibroblast differentiation. Such findings may provide new therapeutic interventions for DD disease.*

Response: We appreciate the Reviewer's suggestion, and are continuing to develop our thinking in how to limit the progression/recurrence of Dupuytren's in this regard. We submit that it is still

useful to know that the abnormal physiology of Dupuytren's cord fibroblasts is still responsive to cAMP-mediated stimuli, and that this may yet prove to be one means of blunting the fibrosis of Dupuytren's specifically in addition to playing a role in cardiac and lung physiology.

Reviewer 3:

1. *The grantee did not adhere to the specific aims as written: performance of preliminary data points (Figures 1, 2, 3, and 10 from question #17, Final Progress Report). It is recommended that the grantee recognize when preliminary data are needed, and include in the first aim. An alternate recommendation would be to perform these experiments ahead of time. A third recommendation would be to have done one preliminary experiment at a time followed by a specific aim. For example, assay the alpha-smooth muscle actin in the cells; then follow up by testing the effect of forskolin and related aims. Only after completing the next preliminary experiment, move on to TGF-beta preliminary experiments, etc. This weakness may be related to the lack of anticipated work load.*

Response: We agree that the proposed study proved in the end to be ambitious, and we were therefore forced to prioritize our efforts. We will be better prepared in future to match our study aims and goals with a more practical outlook in terms of the experimentation required.

2. *The grantee did not adhere to the specific aims: inclusion of outside experiments (Figures 6B and 7 from question #17, Final Progress Report). In addition to the preliminary experiments performed, the grantee produced data on fibronectin and CTGF, not included in the specific aims as written. The recommendation is that the grantee periodically read the grant proposal and ask whether the aims are being met. One way of doing this is to have a chart, PowerPoint slide, or worksheet of the specific aims and required experiments listed; then, every time there is a lab meeting (or set a weekly alarm), produce the document and determine what experiments have been done and what have yet to be done. This weakness may also be related to the lack of following instructions on question #17.*

Response: We appreciate the Reviewer's recommendation, and will institute a better system into the lab for periodically reviewing progress as s/he suggests.

3. *Weakness:*
The grantee did not adhere to the instructions provided for question #17, Progress in Achieving Goals, Objectives, and Aims, in the Final Progress Report. As written, the material for question #17 read as a rough-draft manuscript for a journal article, not a progress report for a grant. It is difficult to determine why most of the work expected was not done because no information is given in this regard.

Recommendation:

Provide information to enable the reviewer to make a qualified recommendation. There is no page limit for question #17. The grantee could simply cut and paste the specific aims from the text of the proposal and answer the questions whether the aims had been met, and if not, why they were not met.

Response: We again appreciate the Reviewer's recommendation, and hope that our responses here have been at least somewhat clarifying in this regard.

4. *Weakness:*

The grantee's expectation of the amount of work to be done apparently exceeded the ability to do the work. A conservative estimate lists 30 discrete units of experimental methodology, each requiring multiple cell lines and replicate experiments. For example, in Specific Aim 1 the grantee stated that adenylate cyclase activity would be measured by RT-PCR; this was considered an experimental unit. The grantee was able to complete one of these units (the adenylyl cyclase RT-PCR), and partially performed four other units (forskolin effect on basal alpha-sma; forskolin effect on TGF-b treatment; RT-PCR for Col1A1; RT-PCR for Col3A1), leaving the other 25 or so units unreported (most of Specific Aim 1A, more than half of Specific Aim 1B, half of Specific Aim 2A, all of Specific Aim 2B). Without provided details of why the work was not performed, the reviewer assumes that too much work was promised.

Response: Once again, we agree that the Reviewer has identified a relevant issue, and will in future endeavor to match our proposal to a more practical experimental course.

5. *Weakness:*

There was lack of progress toward external funding leverage.

Recommendation:

Become aware of grant opportunities. There is probably a grant helper on your campus who could help find grants that would be appropriate for this research. For example, the grantee listed an R21 but no details were provided. This study would likely be appropriate for the National Institute of Aging, or the NIGMS. The team members on study sections are posted at the NIH website, so the grantee can find the best fit for this study by finding study section members whose work focuses on scars, fibroses, wound healing or aging. In addition, since students were employed on this study, the grantee is taking advantage of a research aspect that is a primary component of grants from the National Science Foundation (REUs) and the NIH AREA Grants (R15).

Response: We appreciate the Reviewer's thoughtful and helpful comments, and are pleased to report that a proposal based on this research was formulated and submitted to the NIH as an R21 grant entitled: "Myofibroblast Inhibition in Dupuytren's Contracture." This proposal was reviewed by the Musculoskeletal Tissue Engineering study section and was awarded a score of 46, although it was not ultimately funded. Nonetheless, we take this as evidence that the NIH also found some merit to these studies, and we will continue to refine our approaches as above and continue to seek funding to address this important disease.

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.

The steps that we will take in future include:

Better matching our stated objectives in the proposal with what is experimentally practical in the time period available and with the resources available.

Perform a periodic review of progress to ensure that original Aims will be fulfilled as much as possible.

Better reporting of the progress of the project so that, in instances where original Aims are downgraded or discarded, the specific rationale for this decision is clear.

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

We regret that the Reviewers arrived at an “unfavorable” rating but wish to emphasize that significant progress in the project was indeed achieved:

1. We have a better understanding of the ability of cAMP pathway-stimulation to modulate Dupuytren’s fibroblast physiology, and are making progress towards experimentally manipulating this in both in vitro and in vivo model systems.
2. As evidence of productivity from this grant, we have published a peer reviewed manuscript on results generated by these studies and again cite the reference below. This manuscript is freely accessible to the public in a respected open access journal:

Satish L, Gallo PH, Baratz ME, Johnson S, Kathju S. Reversal of TGF- β 1 stimulation of α -smooth muscle actin and extracellular matrix components by cyclic AMP in Dupuytren's-derived fibroblasts. BMC Musculoskelet Disord. 2011 May 25;12:113.

We anticipate that at least one more manuscript will be forthcoming from our continuations of the studies begun here.

3. We have submitted a grant proposal to the NIH as we promised to do, and this proposal was reviewed and scored, although ultimately not funded. Still, we take this as some degree of validation that these ideas and this work have merit and are worthy of further development and refinement.

We thank the Department of Health for the Formula Grant support.

Project Number: 0862305

Project Title: Flooring Renovation of the ASRI Rodent Animal Facility Research
Infrastructure

Investigator: DeFranc, Leslie P.

B. Briefly describe your plans to address each 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 1:

- 1. This institution should provide a funding mechanism for routine maintenance of its animal resource without dependence on extramural funding. Planning for projects of this magnitude should be supported by qualified engineering or materials expertise.*

Response:

Reviewer 1 suggests an internal mechanism for funding routine maintenance of the animal facilities should be available and planning should include qualified engineers. The investigator agrees with this suggestion and provisions are being developed for this effort during the annual budget planning process in conjunction with institutional facility review committees. As with all infrastructure improvements to aging facilities, repair costs sometimes exceed the budget; no matter how carefully they may be planned -- the result being that funds must be found elsewhere. In this particular circumstance, repeated attempts to repair the animal facility floor exhausted internal funds requiring the organization to find an alternative revenue stream. Regarding qualified support from engineering or material expertise, the internal institutional design and construction engineers participated in the evaluation of the original floor failure and the review of replacement products available. The floor product chosen was determined following consideration of cost, function, and durability.

- 2. The only justification given for this project was that regulatory agencies require a sound floor. While this may be true, the emphasis is misplaced. Unless the projects served by the facility are equal to the investment, the need to satisfy regulatory standards is moot.*

Response:

The institution believes that in addition to the compliance motivation, although not clearly identified, there is further justification for the floor improvement based on ongoing funded research as well as for scientific recruitment purposes.

- 3. It is incumbent on the institution to justify the cost of this project based on the need of investigators and research projects served by the facility. Some reasonable assessment of the finished product should be included in the project planning and followed after completion of the project. It is stated that the new flooring is expected to serve for only 5-10 years. Considering the range of flooring materials available and the high cost of the*

material/application used in this product, a service life of only 5-10 years is a serious flaw in planning and product selection.

Response:

Reviewer 1 suggests that a follow-up of the floor project be included in the planning process. The investigator agrees this is a reasonable recommendation and will include such a process to assess the finished product in any future proposals.

Reviewer 2:

1. No necessary improvements are identified from the progress reports.

Response: None.

Reviewer 3:

None.

Response: None.

ADDITIONAL COMMENTS

Reviewer 1:

Based on the project description provided, the fundamental flaws in this project start with planning and end with assessing the finished project. No information is provided about engineering or materials expert advice in selecting the product used. No information is provided about competing products/vendors considered. No information is provided about cost assessment. No details are provided about the quality of research served by this project. No information is provided about the assessment of the finished floor.

Response:

The investigator believes this is a reasonable assessment of the information submitted for review and will incorporate greater detail in future submission requests for funding support. All feedback is considered constructive and can only help the overall mission of the research effort of the organization.

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: Not applicable.

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

Response: None.