Response Form for the Final Performance Review Report*

1. Name of Grantee: Allegheny-Singer Research Institute

2. Year of Grant: 2010 Formula Grant

A. For the <u>overall grant</u>, 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.

* 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: 1084001
Project Title: Complement Activation Product C4d Binding to Platelets in Systemic Lupus Erythematosus
Investigator: Passineau, Michael

B. Briefly describe your plans to address <u>each</u> specific weakness and recommendation in <u>Section B</u> of the Final Performance Summary Report using the following format. As you prepare your response please be aware that the Final Performance Review Summary 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)*:

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*):

<u>Reviewer 1:</u>
This is a very important study which when completed could potentially identify markers for the disease and therapeutic targets for intervention. However, there are important concerns and weaknesses. Although the studies are straightforward and timely, the lack of detail and the experimental design dampen the enthusiasm.

1. A major weakness lies in the lack of detail. Lupus is a very complex disease with periods of flares and quiescence. When were the samples collected? Was every sample collected during the same phase of the disease?

<u>Response:</u>
Complement C4 deposition on platelets is a phenomenon that once established, remains roughly constant throughout the courses of a patient's disease, regardless of flare status. Given the difficulty inherent to sample collection in a relatively rare disease such as SLE, and the added complexity of powering our study with sufficient numbers of C4d positive and negative SLE patients, we collected samples during clinic visits regardless of flare status.

2. The samples being pooled raise the concern that one outlier could skew the study. The gels are run only once and any skewing of the data will not be realized. The samples should be run individually and the significant changes studied.

<u>Response:</u>
The sample cohorts were never pooled. We agree with the reviewer that individual gels are preferable and this is how the study was performed.

3. Each table and figure should be stand-alone. Figure 4 is very unclear.

Response:
Figure 4 lacks a caption explaining its content. This omission was an error.

4. An important piece missing is a secondary method for substantiating the results obtained. Once the proteins are identified, if they are known proteins with available antibodies then each individual sample can be stained for the protein of interest. Can these changes be emulated by platelets *in vitro*?

Response:
We have undertaken Western blotting of platelets samples to confirm proteomic findings.

5. No manuscripts have been published and no patents filed. This is a lacuna that needs to be rectified.

Response:
Our institutional legal department is pursuing an appropriate patent strategy.

Reviewer 2:
1. Analysis of the clinical data (Table 4) lacks sophistication. I recommend obtaining a clinical statistician collaborator with experience in biomarkers.

Response:
The reviewer's critique is justified, based upon the lack of a caption describing the contents of Figure 4. However, Figure 4 is the final output of a robust statistical analysis module of the DeCyder software suite.

2. There is very limited collaboration despite the requirement for a substantial amount of resources needed to move forward. I suggest seeking collaborators with larger cohorts of patients and controls, and possibly partners in industry.

Response:
The SLE Center of Excellence of the Allegheny Health Network has a very large and diverse SLE patient base sufficient to achieve the aims of this project. As this technology moves forward, additional centers could be recruited. Notably, Drs. Manzi and Ahearn have successfully partnered with industry in the past, resulting in a licensed diagnostic biomarker panel for SLE. Such an approach will be considered moving forward.

At present, there are 5 independent labs within the Allegheny Health Network using the proteomics equipment purchased with grant funds.

Reviewer 3:

1. The goals and aims of this project were accomplished and exceeded. This is impressive because substantial technical development had to go into the study. To protect the intellectual property derived from these studies, the applicant has chosen to redact his data analysis. This is understandable, but it does make it difficult to evaluate the significance and quality of the results.

Response:
We appreciate the reviewer's praise for the results of the study. Interpreting the identities of the protein biomarkers identified is an ongoing process.

2. It would have been helpful if the applicant had addressed the future plans for developing this project. There is uncertainty about how the data accumulated thus far will be used and what the next steps in assay development are. A more concrete future plan would have helped to establish that the project would move forward.

Response:
We appreciate the reviewer's perspective on future plans. At present, we are working toward understanding the significance of our biomarker findings upon platelet biology. We are also evaluating the usefulness of this methodology for other blood borne cells (e.g. leukocytes) in SLE.

3. As of yet, there remains no tangible evidence of productivity other than the progress report. Once a patent application has been filed, publication needs to become the priority.

Response:
We agree.

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:

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

Response: