

Pennsylvania Department of Health Final Performance Summary Report Formula Grants

Overview of the Health Research Project Performance Review Process and Criteria

An applicant that receives a health research grant under Tobacco Settlement Act / Act 77 of 2001, Chapter 9, is subject to a performance review by the Department of Health upon completion of the research project. The performance review is based on requirements specified by Act 77 and criteria developed by the Department in consultation with the Health Research Advisory Committee.

As part of the performance review process, each research project contained in a grant is reviewed by at least three experts who are physicians, scientists or researchers. Reviewers are from the same or similar discipline as the research grant/project under review and are not from Pennsylvania. Reviewers use the applicant's proposed research plan (strategic plan), the annual progress report and final progress reports to conduct the review. A grant that receives an unfavorable performance review by the Department may be subject to a reduction in funding or become ineligible for health research funding in the future. The overall grant evaluation rating is based on the ratings for the individual research projects contained in the grant.

This performance review report contains the outcome of the review for the grant as a whole (outstanding, favorable, or unfavorable), strengths and weaknesses of each research project, as well as recommendations for future improvement.

The following criteria were applied to information submitted by research grant recipients:

- **Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?**
 - Did the project meet the stated objectives?
 - Were the research design and methods adequate in light of the project objectives?
 - Consider these questions about data and empirical results: Were the data developed sufficiently to answer the research questions posed? Were the data developed in line with the original research protocol?
 - If changes were made to the research protocol, was an explanation given, and, if so, is it reasonable?
 - Consider (only for clinical research projects) the extent of laboratory and clinical activities initiated and completed and the number of subjects relative to the target goal.
 - Were sufficient data and information provided to indicate or support the fact that the project met its objectives or made acceptable progress?
 - Were the data and information provided applicable to the project objectives listed in the strategic research plan?

- **Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?**
 - What is the significance of this project for improving health?
 - Consider the value of the research completed towards eventual improvement in health outcomes.
 - Consider any changes in risk factors, services provided, incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of impact and effectiveness of the research being conducted.
 - Consider any major discoveries, new drugs and new approaches for prevention, diagnosis and treatment, which are attributable to the completed research project.
 - What are the future plans for this research project?

- **Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?**
 - If leveraging of funds were expected, did these materialize?
 - Are the researchers planning to apply for additional funding in the future to continue or expand the research?

- **Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted/filed?**
 - If any of the above listed were expected, did these materialize?
 - Are the researchers planning to submit articles to peer-reviewed publications, file for any licenses, or patents or begin any commercial development opportunities in the future?
 - Consider the number/quality of each.

- **Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?**
 - Were there improvements made to infrastructure?
 - Were any new investigators added or were any researchers brought into the institution to help carry out this research?
 - Were funds used to pay for research performed by pre- or post-doctoral students?

- **Criterion 6 - Did the project lead to collaboration with research partners outside the institution, or new involvement with the community?**
 - Are the researchers planning to begin any collaborations as a result of the research?
 - For clinical research only: consider the number of hospitals and health care professionals involved and the extent of penetration of the studies throughout the region or the Commonwealth.

Overall Evaluation Rating

An overall evaluation rating is assigned to each research project. The rating reflects the overall progress the project attained in meeting the stated goals and objectives. The rating is based on a scale of 1–3, with 1 being the highest. An average rating is obtained from all the reviews (minimum of 3) of each project and is the basis for the determination of the final overall rating for each project as follows:

1.00 – 1.33 = *Outstanding*

1.34 – 2.66 = *Favorable*

2.67 – 3.00 = *Unfavorable*

The grant level rating is an average rating from all projects as above. The numerical rating appears in parentheses for the grant and each project in the ***Overall Grant Performance Review Rating*** section of the report.

Overall Grant Performance Review Rating

Grant Rating: Favorable (2.00)

Project Rating:

Project	Title	Average Score
1084001	Complement Activation Product C4d Binding to Platelets in Systemic Lupus Erythematosus	Favorable (2.00)

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

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The strengths of this proposal are:

1. The concepts to be examined are novel, important and timely.
2. Reasonable progress has been made.

The weaknesses of this proposal include that the experimental methodology lacks detail and consistency:

1. The time of blood draw is not mentioned. Was it during a flare, etc.?
2. An important concern is the practice of pooling samples to run them on a single gel. Tables 2 and 3 show differences in the patient disease manifestations and medications. Are there any outliers that could have skewed these results? The most effective method still remains to run each sample individually, identify proteins that have altered significantly in each sample compared to controls, and then proceed to prioritize and validate them.
3. The extended data analysis module is a very important feature of the project. Therefore this has to be described in detail so that Table 4 will become more meaningful.

Reviewer 2:

This project has several strengths. First, it was able to meet most of its stated objectives, including standardizing platelet isolation and sample preparation, performing and analyzing 2D-DIGE from ten sample cohorts, and identifying several relevant spots. Second, the research design was altered to include: a) a third cohort of healthy volunteers, which added another important dimension to the analysis and enhanced translational utility; and, b) a more complex analysis to prioritize 2D gel spot identification, both of which greatly improved overall study design. Third, the results suggest outstanding application of the various proposed approaches, including the use of the Ettan Spot Picker robot that was purchased by this award. Fourth, the study identified a group of differentially expressed protein spots that reportedly had excellent positive and negative predictive values for systemic lupus erythematosus (SLE) and C4d-positive platelets. Fifth, five spots with potential biomarker relevance were identified, but their names were not revealed because of intellectual property concerns.

In terms of weaknesses, the original purpose of this project was based on the hypothesis that platelet C4d+ patients are a distinct subset of SLE patients; however, there is minimal difference

in disease manifestations between the C4d+ and C4d- groups (Table 2), making it unlikely that the results will address this issue. The purpose of the project seems to have shifted toward biomarkers for identifying SLE patients. To address this would require cohorts with other related diseases. Another weakness is the sometimes superficial presentation of results, particularly the data in Table 4, which is missing the legend. Also, one of the C4d-negative SLE patients appeared to be classified based on spots as a healthy volunteer, which is not consistent with the 100% positive predictive value stated in the text. The analysis of the data could be more sophisticated. The lack of information about the identity of the spots makes it difficult to assess significance and relevance.

Reviewer 3:

The stated objective of this project was to compare the proteome of platelets which were either positive for C4d or negative for C4d from patients with systemic lupus erythrohematosis (SLE) and also to compare the patterns to that of platelets from healthy adults. This information was then to be interrogated to identify the most significant differences (ten proteins) in the proteomes of the three categories of platelets. This objective was fully met and high-quality data were obtained.

To achieve this objective, the applicant had to develop techniques to obtain highly purified platelets; to develop conditions for a two-dimensional electrophoresis system to optimally separate the platelet proteins; provide the instrumentation to identify and quantify the “spots” that were significantly different in the three target cohorts; and, to statistically analyze that data to choose those proteins with maximal changes in levels. The research design required meticulous attention to detail and careful execution. Through the methods implemented the PI did achieve his objectives.

The research design was executed successfully, and the data developed were in line with the originally proposed hypothesis.

There were two minor refinements of the studies. First, the cohorts were expanded to include a third arm, healthy subjects. This change was in response to prior comments and was appropriate. The second change was that the number of “hits” was increased slightly based on the difference in profiles. This change was also well-justified.

This was a clinical study in the sense that it involved analysis of blood samples from three categories of patients. The number of subjects within each of the three cohorts was recruited as specified in the original design of the project.

Sufficient information was collected and analyzed to conclude that the project did meet its original objective. Progress was very acceptable and objectives were met.

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The strengths of this proposal are:

1. The work is highly relevant to increasing our understanding of SLE.
2. It will increase our understanding of the role of platelets in the disease process that might help direct future human therapy for this devastating and complex complication of lupus.

The weaknesses of this proposal include that the experimental methodology lacks detail and consistency. They say they have identified a limited number of proteins that may be a unique SLE signature and could potentially act as biomarkers. However, an important lacuna is the absence of publications and/or patents.

Reviewer 2:

This is an excellent small preliminary study that has presumably identified potential biomarkers relevant to SLE. The data, although not completely revealed, nevertheless suggests the possibility of a set of biomarkers on platelets that could be used to diagnose SLE. The identification of spots may yield new mechanistic insights. There is thus the possibility of substantial benefit to patients. The findings may also have commercial value. Much more work, however, will be needed to validate this in terms of larger sets of patients, subset analysis, and additional control groups of patients with related diseases. A weakness is that the data fails to support the original hypothesis that the presence of C4d on platelets is associated with a clinically relevant subset of SLE patients. Future plans are reasonable; the plans include publishing the identities of the biomarkers and diagnostic algorithm after patent filing, performing a blinded validation study, and transitioning the biomarker identification to a clinical diagnostic.

Reviewer 3:

There is extensive evidence to indicate that vascular disease, including predisposition to thrombosis, is a major risk in patients with SLE. There is also ample evidence in the literature that the C4d that is generated can deposit on platelets in SLE patients. This project seeks to extend these observations to a mechanism by which C4d deposition on platelets can lead to prothrombotic and other pathogenic tendencies in SLE patients. As such, the studies executed in this project may provide a mechanistic foundation for the pathogenic sequelae of SLE and establish new diagnostic tools to predict such tendencies. Therefore, the studies in this project have the potential to provide new diagnostic and prognostic tools to evaluate SLE patients.

The applicant indicates that he intends to patent his results as a panel of diagnostic markers for SLE. With further evaluation (extensive) this goal could be realized and could lead to new diagnostic approaches and the ability to follow the responses of SLE patients to therapy.

Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The researchers did have internal funding and applied to NIH but were not given the grant.

Reviewer 2:

The cost of the Ettan spot picker and protective hood was shared evenly with an “internal cost center” at the institute. An NIH grant application entitled, “Proteomic profiling to enable cellomic fractionation of Sjogren’s salivary glands,” was submitted but not funded. An NIH R01 grant submission is planned.

Reviewer 3:

The applicant intends to submit manuscripts based on the results. Dr. Passineau has applied for an NIH grant using the approaches developed in this project, but the application was not funded. He intends to apply for a patent based on his results; and once the intellectual property has been protected, he will be in a position to publish and apply for additional funds.

Most of the funds from this grant were used to purchase equipment which can be used to support further studies. The data obtained can also be analyzed in many different ways as well. In a sense, these possibilities do constitute leveraging.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Weaknesses include that there were no patents filed and no publications.

Reviewer 2:

The applicant intends to submit an article for peer review and file a patent based on the results generated by this project.

Reviewer 3:

As noted above, the project has yet to yield a publication. There is an intention to file a patent application, and this impedes publication of results at the current time. It would have been reassuring to know that a patent disclosure had been filed with Allegheny-Singer Research Institute, but this is not clear from the progress report.

Since the primary data has been “redacted” from the application, it is difficult to judge the quality of the data.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:

During this project a spot-picker robot was purchased for the section, and a number of researchers use it currently.

Reviewer 2:

The Ettan spot picker provides support for multiple projects at the institute. The research project directly supported part of the salary for a senior research associate. Another senior research associate and two pre-doctoral students also participated in this project.

Reviewer 3:

As noted above, a substantial portion of the funding was used to purchase equipment, an Ettan spot picker and protective hood. Such equipment will be valuable to the PI and to his institution for a long time.

Other portions of the funds were used to support the modest commitments of senior research associates on the grant.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution or new involvement with the community?

STRENGTHS AND WEAKNESSES

Reviewer 1:

No new collaborations resulted.

Reviewer 2:

No collaboration outside this institute or community involvement was developed.

Reviewer 3:

There is no evidence that the project led to new collaborations. Presumably, the accrual of patient samples involved collaboration with clinicians, although this is not clearly specified.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

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?
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.
3. Each table and figure should be stand-alone. Figure 4 is very unclear.
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*?
5. No manuscripts have been published and no patents filed. This is a lacuna that needs to be rectified.

Reviewer 2:

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

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.
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.
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.