

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
0864301	Development of Prognostic Index for Colon Cancer Patients Using Gene Expression Profiling	Favorable (2.00)

Project Number: 0864301
Project Title: Development of Prognostic Index for
Colon Cancer Patients Using Gene Expression Profiling
Investigator: Paik, Soonmyung

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 investigators' initial goal was to develop a predictive marker for use of oxaliplatin as adjuvant therapy for colon cancer patients. They proposed to use samples from NSABP C-07 where patients were randomized to receive either 5-fluorouracil plus leucovorin (FULV) versus FULV plus oxaliplatin or FLOX or FOLFOX. NSABP C-07 showed that FLOX improved disease-free survival (DFS) compared to FULV but not overall survival (OS). The goal of developing a high-risk signature group would then identify a group that benefits from FLOX and another low-risk group which can be spared the toxicity of oxaliplatin.

Three aims were proposed. In Aim 1, candidate prognostic genes would be identified using whole genome DASL array from Illumina from samples in the C-07 trial. In Aim 2, an nCounter assay would be developed for the key candidate genes and tested again in the C-07 samples to build a prognostic algorithm, since nCounter assay can be commercialized, while in Aim 3, this prognostic signature would be validated prospectively using samples from C-05 and C-06.

Strengths: The investigators were able to automate and perform whole genome DASL on 866 samples. In addition, they had the capacity to develop a prognostic signature using both arms of the C-07 trial into low and high-risk groups, and this signature was able to be validated from samples from the C-08 group. Although the prognostic signature did not improve the model used with clinical covariates only, it suggested that this strategy was feasible. Moreover, the investigators were able to refine the markers from Aim 1 into an nCounter colon code for studies in Aim 2. The nCounter assay has more commercial viability, since it requires small amounts of RNA, is simple to use, is a digital readout, and results are concordant with RT-PCR. The nCounter assay will be verified in the discovery cohort (860 samples) and validation cohort (n=915 samples). The nCounter assay includes 282 candidate prognostic and oxaliplatin predictive genes, and the assay has been performed in these 1775 samples already.

Weaknesses: The C-07 trial gave adjuvant therapy FULV or FLOX to both stages two and three colon cancer patients; FLOX showed decreases in DFS in stage three patients but not in stage two patients. The investigators do not account for this fact in their design at all. Currently the

nCounter assay has been done and currently model building is in progress, but it is unclear what the barriers have been in the analysis or will be in its clinical viability.

Reviewer 2:

The study overall is well-performed and on target to meet the original objectives. The overall objective of this study is to identify biomarkers for colon cancer patients in response to chemotherapy so that one can better stratify patients towards different therapeutics. The researchers carried out the whole-genome expression analysis using DASL arrays from Illumina. The prognostic factors were identified. However, in the validation data set, the gene expression profile did not provide additional prognostic value in addition to the clinical covariate. The researchers' most significant work was to apply the nCounter system to the colon cancer samples. The nCounter system has multiple advantages, and may be easier to be applied in the clinical setting. In this second study, the researchers were able to identify ~300 prognostic and predictive genes for oxaliplatin responsiveness. In the final aim, the researchers are currently validating the ~300 gene list in a large (n=1,700) cohort of colon cancer patients, and build an additional prognostic algorithm.

The major strengths include the large number of patients available for the study and that it is an important research topic in personalized medicine. The results provide initial evidence to support the use of biomarkers for selecting patients who will benefit from chemotherapy.

The major weaknesses include the following: 1) The study only considers survival. As survival is affected by many other factors in addition to drug response, this may not be the best end point. 2) A radiologic based drug responsiveness or other biomarkers, such as CEA levels before and after drug treatment, will significantly improve the study. However, both 1 and 2 points may be intrinsic to the original study design, and it is not clear whether drug responsiveness data are available to the researchers. 3) The researchers do not consider other important genetic information for colon cancers, such as APC, K-Ras, PIK3CA, P53 mutation, etc. Incorporating these important genetic data may be important to better stratify patients. 4) It is not clear whether the whole colon tumor tissues were used or any microdissection was performed. Again, the tumor tissues are mixtures of multiple types of cells. The presence of non-tumor cells can significantly alter the gene expression profile and interfere with the identification of prognostic factors.

Reviewer 3:

This project uses whole genome expression analysis to screen colon cancer specimens for developing prognostic tests, to avoid unnecessary toxic therapy. The study compares two treatments (FULV and FLOX or FOLFOX, containing oxaliplatin). RNA profiles were obtained from tumor biopsy specimens in paraffin blocks and analyzed with genome wide transcriptome methods and targeted methods (NanoString). The investigators have largely succeeded in completing the proposed projects, and they have begun to develop a targeted panel of expressed genes carefully selected by robust statistical method. The methodology of the analysis of paraffin-embedded samples is a nice advance. Early predictive models have been partially successful, but the investigator is now embarking on Specific Aim 3, which was predicted to occur after completion of the current grant phase.

Therefore, it remains to be seen whether the approach will bear fruit, while initial biomarker panels were partially successful in predicting who might not benefit from more aggressive therapy.

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:

At present, the potential impact of this research is unrealized, since it has been a negative study so far. However, it is commendable that the investigators have been able to optimize and automate RNA extraction protocols from formalin fixed paraffin embedded samples.

In addition, the investigators are planning to continue the analysis of the C-07 nCounter data and see if gene expression signature can be derived that shows a benefit from oxaliplatin therapy. If a predictive signature can be determined, this will be helpful in management of colorectal cancer, since it can identify a group that benefits from chemotherapy as well as a group that is spared the toxicity of chemotherapy if shown to be low-risk.

In addition, from a technical standpoint the investigators have also optimized the nCounter assay, which is a simple assay that minimizes pipetting and is inexpensive. If the nCounter assay is predictive, this modality can be used in the clinical arena for other tumors also.

Reviewer 2:

The identification of ~300 prognostic factors is significant, and it may represent the first step toward personalized medicine for identifying patients who may benefit from oxaliplatin-based chemotherapy. However, because of the defects in study design (for example, only survival data are used, but not drug responsiveness), it is not clear whether such prognostic factors can be validated or implemented in the clinical setting. Clearly, the next step is to finish Aim 3 and validate the prognostic value of the ~300 gene signature.

Reviewer 3:

Development of any biomarker assay that predicts response to chemotherapy is an important step in consideration of the dire outcome, whether the treatment prevents recurrence or presents severe toxicity or both. The investigators have driven their project forward to the point where a prognostic test can be developed and tested. However, it remains to be seen whether the biomarker test has validity within the narrow definitions of the two therapies under consideration (each complex in its own right), or whether broader application will become successful. Tumors are often heterogeneous and may therefore be misdiagnosed by such a test; also, diversity of transcripts at each protein coding gene locus may limit utility of the approach, as will the lack of attention to non-coding RNAs. In addition, the advent of next-gen sequencing may change the way expression profiles are viewed. Nevertheless, this is a valiant effort that can yield clinically useful tools.

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 project did not leverage additional funds as a result of this grant funding. The investigators are continuing to work on optimizing the expression profiling results to develop a predictive marker for oxaliplatin sensitivity and are hoping to gain additional funding from American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO) or NIH sources.

Reviewer 2:

No additional funds or grants resulted from this study.

Reviewer 3:

National Cancer Institute funding has supported the tumor bank; no further funds have been sought.

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:

Currently no peer-reviewed publications have been submitted. However, the authors are planning eventually to submit a manuscript based on the expression profiling results of the C-07 trial. Based on their prior record, this will presumably be a high-tier journal such as *Journal of Clinical Oncology*.

Currently, no patents have been filed on a prognostic signature. However, if a model can be developed that can improve prognosis or prediction of benefit from oxaliplatin and can be validated in the validation cohort, then they will file a patent.

Reviewer 2:

No publication resulted from this study.

Reviewer 3:

Patent applications are planned, if the models prove sufficiently robust. Also, the investigator plans to publish papers on the results.

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

STRENGTHS AND WEAKNESSES

Reviewer 1:

The project resulted in no infrastructure improvements.

Several new investigators were brought into the institution as a result of the funding, including pathologist Seon-Rim Kim from Seoul, South Korea; Matthew Remillard, a graduate student from Carnegie Mellon university, who automated the RNA isolation process and is now a graduate student at Princeton; Patrick Gavin from Sequenom, who was brought in to automate the DASL and nCounter gene expression process; and finally, Noriko Yamaguchi recruited from Dana Farber Cancer Institute and Harvard School of Public Health, who was brought in as staff biostatistician to build a model for prognosis and prediction.

One post doctoral student was funded by this grant.

Reviewer 2:

The funding allows the researchers to perform high-quality genomic studies, which is clearly in line with the overall goal of the institute.

Reviewer 3:

Research was enhanced by the addition of new investigators, an improved method of RNA extraction, and expanded RNA analysis capacity with the nCounter system.

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:

The project did not lead to research collaborations with other institutions.

Reviewer 2:

The project involved collaboration with scientists from Korea and Dana Farber Cancer Institute/Harvard Medical School (DFCI/HMS).

Reviewer 3:

No new collaborations resulted specifically from this project.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

The investigators are focused on developing a predictive marker for use of oxaliplatin in colon cancer patients. The investigators have access to samples from NSABP C-07 study which randomized stages two and three colon cancer patients to either 5-FU and leucovorin or 5FU/LV and addition of oxaliplatin. The biggest issue is that C-07 improved DFS and not OS for stage three colon cancer patients but not for stage two patients. The investigators did not take this into account in their sample size and planning of the studies, which should have been done.

Reviewer 2:

1. The researchers should perform mutation analysis for key colon cancer pathway genes, such as APC, K-Ras, PIK3CA, P53 mutation analysis. This mutation analysis should be incorporated into the prognostic analysis.
2. The researchers are encouraged to identify whether responsiveness to the treatment data (for example, imaging studies or serum carcinoembryonic antigen data) are available in addition to the patient survival data.

Reviewer 3:

1. mRNA profiles have been under development for some time, and several panels are now in clinical use. In this case, the investigator addresses a very specific question, comparing two complex treatment schedules, one of which includes the additional highly-toxic oxaliplatin. Early results suggest that small increments in predictability of outcomes may be possible, but the scope of intended application is rather narrow. Whether the results can be transferred to other therapies (even those with similar strategies) is questionable.
2. The investigator needs to address the value of his methodology versus newly emerging techniques, in a field that is very rapidly evolving. Also, therapies against colon cancer are in flux, so that biomarker tests for efficacy of drug combinations may be short-lived.