

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 (2.33)

Project Rating:

Project	Title	Average Score
0863801	Targeted Killing of Cancer Cells	Favorable (2.33)

Project Number: 0863801
Project Title: Targeted Killing of Cancer Cells
Investigator: Cassimeris, Lynne

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:

Weaknesses: The goal of the grant was to evaluate the role of stathmin in the regulation of apoptosis in the context of loss of p53. Early results must have shown that depletion of stathmin resulted in cell cycle arrest rather than apoptosis. This result would make Aim 1 (the creation of a GFP-cytochrome C expressing line) unnecessary and also recast the goals of the remaining aims. In this light the project did not meet its stated aims.

Strengths: However, the PI continued on a logical research path following on from the finding that stathmin depletion resulted in cell cycle arrest, and determined that the N-terminal portion of the protein may be sufficient (although the data in Figure 2 are quite preliminary and not yet convincing).

Reviewer 2:

Strength: The goal of this proposal is to study efficient induction of apoptosis of human cancer carrying mutant p53. In particular, the PI is interested in the roles of stathmin, a microtubule regulatory protein, in this process. Overexpression of stathmin is observed in many cancer cells, and reduction of the protein can cause apoptosis of those cells. Importantly, stathmin knockout mice do not show pathological phenotypes, suggesting that targeted reduction of stathmin could be effective only in cancer cells. These are summarized in Finding 1.

Weakness: Synergy between stathmin and ABT-737 (Bcl2 blocker) was not observed. Depletion of stathmin causes mitotic delay of p53 mutant cells. Immunocytochemistry of TPX2 and CDK1 is shown in a graph, but there are just observations, and the mechanistic analyses are missing. Localization of GFP-stathmin is interesting but not informative to explain the phenotypes.

Reviewer 3:

This was a relatively small grant that mainly supported the partial salaries of five pre-doctoral students. The science theme was to discover why a protein (stathmin) is required in cancer cells and not normal cells. By understanding the mechanism involved, this could potentially lead to new therapeutic opportunities for treating cancer.

The investigators found that stathmin depletion is synthetically lethal with loss of p53, since when both p53 and stathmin are depleted cells undergo a delay in cell cycle progression and an increase in apoptotic cell death. The investigators also found that stathmin depletion relays a signal via increased microtubule (a cytoskeleton protein) stability.

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:

Weaknesses: The project as it stands today has no clear significance for improving health.

Strengths: The PI appears to have formulated new goals and is pursuing experiments, suggesting that future plans are in hand. They are not clearly articulated.

Reviewer 2:

This is basic research, and the immediate clinical impact is unclear. In other words, the potential application for cancer treatment is not discussed.

Reviewer 3:

When cells are depleted of a microtubule regulatory protein, stathmin, and when p53 is depleted, cells have a cell cycle delay and an increase in apoptotic cell death. The mechanisms causing this are still under investigation, but they offer the possibility of targeting stathmin in p53-deficient cancer cells. This has the potential to lead to novel therapeutic opportunities, and if progress is made in the future on this project it could significantly improve cancer outcomes and health in general.

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:

Weaknesses: No leveraging is indicated.

Reviewer 2:

One R01 was submitted to NIH in 2010, but it was not funded. Another NIH grant and an Army grant are now in pending status.

Reviewer 3:

The investigator applied for three additional sources of funding but none have been awarded at the time of the final report. The investigator is planning to apply for additional funding.

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:

Two primary research papers were published (below). They are in journals of moderate impact but summarize well the research performed.

Stathmin/oncoprotein 18, a microtubule regulatory protein, is required for survival of both normal and cancer cell lines lacking the tumor suppressor, p53.

Carney BK, Cassimeris L.

Cancer Biol Ther. 2010 May;9(9):699-709. Epub 2010 May 8.

PMID: 20200495

The microtubule cytoskeleton is required for a G2 cell cycle delay in cancer cells lacking stathmin and p53.

Carney BK, Caruso Silva V, Cassimeris L.

Cytoskeleton (Hoboken). 2012 Mar 7. doi: 10.1002/cm.21024. [Epub ahead of print]

PMID: 22407961

Reviewer 2:

Functional collaboration between stathmin and p53 in apoptosis has been well illustrated in a publication from the PI's group in *Cancer Biology and Therapy*.

Reviewer 3:

One solid publication on Stathmin was published. A second manuscript was in preparation at the time of the final report.

There were no major discoveries, licenses or patents according to the report, but the findings as reported appear to be quite important and could have been described as a major discovery.

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

STRENGTHS AND WEAKNESSES

Reviewer 1:

The project is very likely to have had a moderate positive impact on the research infrastructure of the institution, but this is not detailed in the progress report.

Reviewer 2:

A total of five pre-doctoral students have been involved in the project. Research collaboration within the Department of Biological Sciences has been well established.

Reviewer 3:

There were no out-of-state researchers recruited. Funds were used to pay for pre-doctoral student stipends.

Infrastructure of the lab was enhanced by having a critical mass of students. This permits more interactions in the Department of Biological Sciences.

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 collaborations are mentioned in the progress report.

Reviewer 2:

Outside collaboration has not been established. It is desired that additional scientists would join this project to investigate deeply whether stathmin could be a clinical target of cancer therapy.

Reviewer 3:

There were no new collaborations outside the university established. There were no commercial developments and no community involvement.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

1. If the proposal had been based on some preliminary data directly relevant to the central mechanism (apoptosis), this may have avoided the situation where the majority of the initial aims could not be completed, since they quickly became irrelevant. The recommendation is that in the future some key experiments be performed that can be used as the basis of a proposal.
2. Collaborations are central to successful research programs. It is recommended that some funds be set aside for travel to conferences with the goal of making connections with researchers in the field. This may lead to the formation of collaborations.
3. The final report could have made mention of the impact of the grant on the research infrastructure, training opportunities for students and the activities in the investigator's program.

Reviewer 2:

1. The mechanistic analysis is weak. The PI should focus on how depletion of stathmin could cause apoptosis only in p53 mutant cells. Protein synthesis/degradation, gene transcription, translation, etc. are not well pursued.

2. The clinical implication is unclear from this research. Preliminary data indicate that depletion of stathmin can cause apoptosis/cell cycle delay only in p53 mutant cells. These are very interesting observations, but the following analyses are not deep. Perhaps, different cancer cell lines could be tested for phenotypes caused by stathmin depletion.

Reviewer 3:

1. Publish more papers.
2. Obtain additional funding to move the project forward.

Generic Recommendations for Lehigh University

Reviewer 1:

To help support the endeavors of the faculty, it is recommended that there be support for investigators to connect with the research community at large to help build collaborations.