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: Outstanding (1.33)

Project Rating:

Project	Title	Average Score
0990801	Mechanisms of Signal Transduction and Degenerative Diseases in the Retina	Outstanding (1.33)

Project Number: 0990801
Project Title: Mechanisms of Signal Transduction and Degenerative Diseases in the Retina
Investigator: Dizhoor, Alexander

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:
Strengths: Most of the objectives of this well-designed pilot project were achieved. Aim 1, which was to develop a genetic construct consisting of the RetGC1AC mutant driven by the rhodopsin promoter, was successfully completed. Extensive biochemical tests, performed using additional mutant constructs that the grantee developed, confirmed that RetGC1AC catalyzes the production of cAMP and interacts with GCAP1 in a fashion identical to that by RetGC1. Aim 2 was to generate transgenic RetGC1AC mice and then transfer the transgene to a mouse lacking endogenous RetGC1. Eleven mice expressing the transgene were produced, and a breeding program is underway to transfer the transgene to RetGC1 null mice. Thus, the project made excellent progress considering the short period in which it was conducted, and it met most of its goals.

Weaknesses: The strategic plan indicated that the sensitivity of retGC1AC to Ca^{2+} regulation would be tested, but it is not clear from the final progress report if this experiment was done. Also, it is unknown at this time whether the transgene is expressed at an optimal level in any of the lines. However, given that the grantee is starting with eleven founders, it seems likely that a useful transgenic mouse line will be established.

Reviewer 2:
This research project was a high-risk pilot study to produce a new genetic mouse model suitable for in-depth study of the role of cyclic nucleotides in retinal degeneration. The research project was well designed and methods were appropriate, enabling the project to successfully achieve the two stated objectives. Specifically, data obtained within the scope of the project demonstrate that the investigators 1) successfully made the desired genetic construct, and 2) were successful in producing transgenic mice incorporating the construct. Further characterization of the model is continuing beyond the scope of the project.

Reviewer 3:
The strategic plan described two specific aims. Aim 1 involved the mutagenesis of guanylyl cyclase (retGC1) to generate an enzyme that would synthesize cAMP instead of cGMP (retGC1AC) and determine its selectivity for generating the proper cyclic nucleotide by expression in HEK-293 cells. This construct had been shown previously to respond to calcium

and GCAPS, so there is every expectation that similar regulation should occur when expressed in mouse photoreceptors. Aim 2 would place the retGC1AC construct in transgenic mice under the control of the rhodopsin promoter. These mice will be crossed with retGC knockout mice to produce mice that could generate cAMP in response to GCAPS in rod photoreceptors.

The research design and methods were adequate for the proposed research and accomplished the stated goals. During the first part of the project, the investigator demonstrated the appropriate targeting of retGC1AC to the membrane in HEK-293 cells using the binding of GCAP-GFP to the mutant enzyme (and localization by immunofluorescence microscopy) as an assay. They also demonstrated that this construct stimulated the synthesis of cAMP from ATP in membranes from transfected cells only in response to the addition of GCAP1, indicating that the native regulation of retGC1 is preserved in the mutant.

During the second part of the project, the investigator generated transgenic mice expressing retGC1AC under the control of the rhodopsin promoter for rod cell-specific expression. Positive F0 founders have been identified, and these mice are being crossed into the RetGC1 knockout background so that the level of expression by western blot can be evaluated and the biological consequences of its expression can be studied.

Although the fact that the investigators did not complete the generation of the proposed mouse might be considered a weakness, they have made acceptable progress, considering the difficulty of completing this goal in such a short period of time. Their preliminary studies indicate that they will ultimately achieve their goal of generating a mouse in which light, Ca^{2+} and GCAPs can regulate the synthesis of cAMP in photoreceptors. After completing the cross with the retGC1 KO, the resulting mouse will be used for investigating the role of cAMP in photoreceptor health and the progression of disease processes in the retina. The investigators plan to apply for long-term funding for the functional studies.

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

<u>Reviewer 1:</u>
Strengths: The RetGC1AC mouse model promises to provide a novel tool for manipulating cAMP levels in rod photoreceptors, which may provide insight into the role of this cyclic nucleotide in retinal physiology. Additionally, the mouse model may help answer questions about the role of cAMP in photoreceptor signaling and death in the context of mutations that produce disease in human patients. The grantee has plans to cross the RetGC1AC mouse with a variety of mouse models with mutations related to congenital human retinal disease to determine if increased production of cAMP slows the rate of photoreceptor degeneration.

Weaknesses: None

Reviewer 2:
The investigators have developed a unique genetic model that will serve as a tool to increase our understanding of the role of cyclic nucleotide metabolism in inherited retinal blinding disorders. Our best hope for successful treatment of these diseases is to increase our understanding of the basic biological mechanisms that cause them. This animal model can be used for a new line of studies that otherwise would be impossible to conduct. In keeping with the nature of a high-risk pilot project, the short-term impact on health outcomes is low. However, the successful development of the animal model provides a strong basis for federal funding to continue the research. The beneficial impact is very reasonable in light of the project budget.

Reviewer 3:
This project is designed to evaluate the role of cAMP in photoreceptor health and define potential roles in photoreceptor degeneration. The prevalence of various types of blindness with few therapeutic strategies for intervention or reversal means that these studies address an important aspect of human health that affects productivity as well as quality of life. Understanding cAMP signaling in the retina could lead to improved strategies for delaying or reducing the severity of retinal dystrophies.

The future plans of the investigators are to use this mouse to evaluate the role of cAMP in photoreceptor signaling and cell death and to have a method for direct manipulation of cAMP levels (by exposure to light) in order to test its effect on critical cellular pathways.

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:
Strengths: The grantee states that federal funding will be sought after preliminary data using the RetGC1AC mouse is obtained. This seems like a reasonable expectation given the potential usefulness of this mouse model to answer questions of high significance.

Weaknesses: None.

Reviewer 2:
This work was not expected to and did not enable the investigators to leverage additional funds within the time frame of the grant. However, it can be anticipated that the results of this grant will bring in additional NIH funds in the future.

Reviewer 3:
No funds were leveraged during this grant period. The investigators plan to apply for additional funding once the transgenic mouse is established and basic physiological assays have been performed.

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:
Strengths: No publications resulted from this short-term project, which is understandable given its time frame. The grantee states that the RetGC1AC mouse will be used to investigate the impact of light- and Ca^{2+}-controlled cAMP synthesis in photoreceptors on retinal physiology, biochemistry, and morphology and that the results will be published in peer-reviewed journals. This is a reasonable expectation.

Weaknesses: None.

Reviewer 2:
This work was not expected to and did not enable the investigators to produce peer-reviewed publications, licenses or patents within the time frame of the grant. However, the investigator's past track record provides a strong expectation that the results of this grant will be published in a high-impact peer-reviewed journal in the future.

Reviewer 3:
No peer-reviewed publications were expected during this grant period. Articles will be submitted in the future once the mouse is established and experiments can be performed.

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

STRENGTHS AND WEAKNESSES

Reviewer 1:
Strengths: The project has not yet enhanced the quality or capacity of research at the grantee's institution; but assuming that a RetGC1AC expressing mouse line is established, the availability of this novel mouse model will allow the grantee to conduct a new line of research that otherwise could not be performed.

Weaknesses: None.

Reviewer 2:
The research enhanced the quality and capacity for research at the grantee's institution by producing a unique genetic model for studying the role of cyclic nucleotide metabolism in retinal function and disease.

Reviewer 3:
None mentioned.

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

STRENTHS AND WEAKNESSES

Reviewer 1:
Strengths: The genetic model created in this project will result in a collaborative study with an investigator at Harvard Medical School.

Weakness: None.

Reviewer 2:
The project will lead to a collaborative study using single-cell physiology conducted at Harvard Medical School.

Reviewer 3:
It is anticipated that this mouse model will be shared on a collaborative basis with investigators at Harvard University who have expertise in single cell recording. These studies should maximize the potential of this mouse to provide information on the affected signaling pathways in photoreceptors.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:
None.

Reviewer 2:
None.

Reviewer 3:
No data have come from this project during the period of funding, which might be considered a weakness. On the other hand, the progress was very good considering how long it takes to make a mouse of this sophistication. Also, the potential for useful information from this mouse is very high. Therefore, it is difficult to truly find a weakness, since the grant was funded specifically for the purpose of making this mouse and not for generating data.