

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
1087001	Role of RD3 Protein in Leber Congenital Amaurosis LCA12	Outstanding (1.33)

Project Number: 1087001
Project Title: Role of RD3 Protein in Leber Congenital Amaurosis LCA12
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:

The overall progress should be considered outstanding. Three specific aims were proposed, and significant progress or completion of the objectives for each has been met. The proposed goal was to characterize the effects of RD3, a gene recently associated with the childhood blinding disorder Leber congenital amaurosis, on human RetGC activity *in vitro*; evaluate mutations found in human genes upon the RetGC regulation; and, begin the process of developing a mouse model to study the role of mutant RD3 *in vivo*. As hypothesized, the research methods and statistical analyses demonstrated direct interaction between RD3 and RetGC. Noteworthy, these interactions were verified using independent assays and the most appropriate methods. Furthermore, the mutant proteins were found to possess altered activity when compared to the wild type allele. The research led to two publications in highly respected journals, a considerable effort given the time frame. Lastly, as planned, significant progress has also been achieved towards the development of an *in vivo* model of LCA12 in mouse. Continued progress should be anticipated.

Reviewer 2:

The applicant made good progress towards accomplishing the three stated objectives of the research plan. However, I have serious doubts about whether the data generated and approaches/strategies pursued will provide significant insights into the molecular pathogenesis of LCA12 disease. This is particularly true in light of new data from a significant report published by Molday's laboratory (*Proceedings of the National Academy of Sciences*, 107, 21158-63, December 2012) just prior to the initiation of the applicant's project. The report, which the applicant appears to be aware of in his application, implicates RD3 in the intracellular trafficking and targeting of GC1 and GC2 to the outer segments (OS) of photoreceptors, whereas the focus of the applicant's proposal is on the role of RD3 (and mutations therein) in the modulation of GC1 activity in the OS of photoreceptors. However, the biological (and disease) significance of the role of RD3 in the modulation of GC1 activity is questionable. This should have led to a reassessment of the objectives and/or approaches of the application.

Reviewer 3:

The project met all of the stated objectives and resulted in a new and interesting hypothesis. Research design and methods were appropriate and successful. The results were provided in the report and have been published.

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:

Leber congenital amaurosis (LCA) is an inherited retinal degenerative disease characterized by severe loss of vision at birth. The main benefit of the results from this project and any basic science research is the discovery of novel mechanisms or functions of components of the cell that when mutated lead to disease. The discoveries made through the initial proposal have yielded a considerable amount of novel data defining a likely mechanism leading to disease. Clinical trials of gene replacement therapy for one form of LCA are now underway, and dramatic improvements in vision after treatment have been observed. Thus the results from this study have high potential to impact future studies that are specifically aimed at identifying drug targets, prevention or diagnosis.

Reviewer 2:

The beneficial impact of the project in basic science and certainly in human health is unclear. The emerging (and convincing) data by Molday's work support that RD3 mice lack GC1 in the OS of photoreceptors, because the *RD3* mutation prevents GC1 association with RD3, an association which is critical to the trafficking and targeting of GC1 from the ER to the OS. Instead, it is most likely that efforts placed on the understanding of the molecular bases of mistrafficking of GC1 by mutations in RD3 will provide significant insights into the biological and pathological roles of RD3. However, the applicant suggests that RD3 may be required to block cGMP production in the inner segments of photoreceptors. Although attractive, testing this hypothesis requires distinct approaches from those attained and the development of tools to discern between mistrafficking and modulation of GC1 activity by RBD3.

Reviewer 3:

The project is an investigation of known human mutations that result in blinding disorders. It does not have a direct impact on disease outcomes; however, it is an important contribution to understanding the processes that lead to retinal degeneration and does have significance for clinical screening. The results produced an important new hypothesis concerning the function of the RD3 disease gene that the PI intends to follow up in future studies.

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 PI is planning to submit an R01 application to the National Institutes of Health based upon the findings generated in this proposal. The publication of two peer-reviewed papers directly relevant to the aims of this project has put this PI in a very strong position to justify continued investigations, but any undue delay may lessen the value or significance of the application. Additional screening of populations has been of limited value.

Reviewer 2:

The applicant declares that the project has not leveraged additional funds or grant applications. It seems to me that if no changes are made in the research strategy on how to approach the roles of RD3 in the biology and disease of photoreceptors, then it is likely that attempts to leverage additional funding may have a low chance to materialize. Regardless, the work derived from this application appears to have been supported also by an NIH/National Eye Institute grant awarded to the applicant.

Reviewer 3:

The project provided preliminary data for a planned R01 submission to NIH. The published results of this project should greatly strengthen that application.

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:

Progress is deemed excellent. Two peer-reviewed papers in a well-respected journal were published and a third is reportedly in preparation. The journal *Biochemistry* is an appropriate venue to publish the work.

Reviewer 2:

The application led to two publications in *Biochemistry* about the properties of RD3 in the modulation of GC activities.

Reviewer 3:

The project resulted in two peer-reviewed publications in the journal *Biochemistry*, a much respected journal from the American Chemical Society with an impact factor of 3.42. This is a very strong result for a pilot project and should add considerable strength to a future grant application.

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

STRENGTHS AND WEAKNESSES

Reviewer 1:

Unfortunately, no students or trainees were involved in this project. A suitable mouse model was acquired from collaborators. Therefore enhancement of the quality or capacity for research is deemed modest but favorable.

Reviewer 2:

The applicant states that the project had an impact on enhancing the research capacity and quality of research at the institution, because a new mouse genetic model (RD3) was acquired that will enhance new research directions. However, it is not clear how the work derived from the project helped to enhance the infrastructure and attract new investigators. A. Savchenko was supported by the application, but the efforts of A. Savchenko did not lead to primary authorships.

Reviewer 3:

The project did not support improvements to infrastructure or to research staff. However, a new mouse genetic line was acquired that should enhance the future of this research effort.

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:

Collaborations were established with two leaders in the field of retinal biology, Dr. Robert Molday at University of British Columbia and Dr. Krys Palczewski at Case Western Reserve University, which significantly broaden the breadth and scope of the research program in the PI's laboratory. Both collaborators appear as co-authors on the publications resulting from the project.

Reviewer 2:

The application appears to have led to collaborations with three independent investigators, who also co-authored the two publications. It is not clear what the exact roles of the collaborators were in the project.

Reviewer 3:

The project reinforced a collaboration with Drs. Wolfgang Baehr (University of Utah, Salt Lake City) and Kris Palczewski (Case Western Reserve University, Cleveland) and led to a new collaboration with Dr. Robert Molday (University of British Columbia).

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

Only negligible weaknesses were found. The PI and institute are strongly encouraged to go to greater lengths to include undergraduate, graduate or post-doctoral trainees in the research. Though this cannot be remedied for the current project, the depth of the studies conducted in the PI's laboratory and medical relevance make it ideally suited for training and would provide excellent experience for talented young trainees.

Reviewer 2:

1. The applicant is an accomplished biochemist, but he should place greater efforts into stepping out of his comfort zone to address and test molecular events of direct biological and pathological relevance.
2. The applicant should directly test the hypothesis that RD3 mice present increased cGMP levels in the inner segments. This will go a long way in designing (or excluding) rationale approaches to address the function of RD3 in photoreceptor function and disease. For example, what difference does it make how RD3 regulates GC1 and its interaction with GCAP in the OS of photoreceptors, if mutations in RD3 prevent the targeting of GC1 to the OS? Hence, the biological relevance of RD3 function in the OS of photoreceptors is unclear. In fact, some of the applicant's data support such a possibility. The native RD3 mutation (F100ter) has no biochemical impact on GC activity, yet it is known to be pathologically relevant. And why should the biochemical effect of this mutation (truncation) differ from K130M?
3. The third aim is problematic, and it is unclear what will be learned from rescuing mutant RD3 mice by expressing the WT RD3 protein, unless it is done in parallel with mutant RD3 constructs. Also, it would be better to use at least the regulatory sequences of RD3 to mimic its own expression. In addition, it is unclear whether the mutated (truncated) RD3 protein is still expressed in RD3 mice. Much more would be learned from probing the physiological role(s) and mechanism(s) of disease mutations in RD3 and those the applicant has already tested biochemically.

Reviewer 3:

All objectives were met. The results were published in two papers of high quality. Significantly, the PI has been able to identify a new, interesting, and testable hypothesis concerning the function of RD3.