

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
0865001	Molecular Mechanisms of Leber's Congenital Amaurosis	Favorable (2.33)

Project Number: 0865001
Project Title: Molecular Mechanisms of Leber's Congenital Amaurosis
Investigator: Dizhoor, Alexander M.

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:

Leber Congenital Amaurosis (LCA) is a group of hereditary disorders of the retinal function that profoundly affect photoreceptor and retinal pigment epithelium function from early life. At least 15 causal genes have been identified, some of which code for intracellular enzymes, others of which encode structural components of cilia and thus fit into the classes of ciliopathies, often with substantial constitutional influences. 5-prime-cyclic guanosine monophosphate (cGMP) is the intracellular second messenger regulating phototransduction in mammals. The concentration of cGMP in photoreceptors is controlled in part by a family of cGMP-producing enzymes called guanylate cyclases, thus retinal guanylyl cyclases. The predicted protein sequences of this family show that the structural domains are well conserved and human GUCY2D retains about 80% identity to its twin mouse account. The gene has been mapped to chromosome 17p13.1 and contains 16 Kb and about 20 exons. Because the enzyme functions as a retinal guanylate cyclase, the condition requires two defective copies of the gene to cause disease, the defect usually transmits as an autosomal recessive, manifesting 87% identity to the mouse counterpart. However, some mutations behave as a dominant form of a combined cone and rod dystrophy (called CORD6).

About 25% of guanylate cyclases behave as autosomal dominant traits. Various phenotypes have been associated with each pattern of genotype, although most guanylate clashes manifest with poor vision even in bright light; some even maintain usable vision until late teens. Again, a variety of retinal pathologies have manifested in these adult, human events, which are non-localizing and non-specific.

The specific objective of this project was a pilot study of the physiologic implications of two recently identified mutations, called D639Y and R768W, of LCA in transgenic mice to define their relevance of LCA, both the physiologic function, viability of photoreceptors, morphological organization of the retina, and the possible link between the mutations and photoreceptor cell death and/or signal transduction abnormalities in vivo.

Specific Aims:

1. Develop transgenic mice expressing each of the two RETGC mutants.
2. Characterize the morphological, electrophysiological, and biochemical properties of the retinas in the transgenic animals.

Background and Significance:

The two mutations were identified in two unrelated families with “very limited pedigree data available;...in each case both a parent and a child had the same mutation in heterozygous state, yet in contrast to the parent, the child developed LCA symptoms. One simple possibility was that it could merely be some additional gene that was causing (or contributing to) the disease, but functional analysis of the recombinant RETGC itself also revealed strikingly abnormal properties of the cyclase...”

While an intriguing observation, this has no relevance in explaining why the parent (presumably a carrier) has no disease and the child with the same single copy mutation has some (not defined or characterized) disease. Alternative, untested, and unexplained solutions include: failure to do complete exon and intron sequencing for the second (point-) mutation; failure to declare the DNA analysis of the other parent; a null or deleted allele in the other parent that thus escaped detection by PCR technologies; failure to confirm parentage of the child and thus, a missing parental allele; the possibility of a second single gene mutation (among the known 15 LCA genes) other than RETGC but in the same physiological pathway and thus, in the simplistic approach, missing biallelic, digenic inheritance. The unpublished but currently in-review possibility for LCA, as shown previously for Bardet-Biedl Syndrome, inter alia, of digenic, triallelic inheritance in which the collaborator found merely the single isolated allele but never completed the screening of the other known LCA genotypes; and the possibility that there is an as yet, undiscovered LCA gene with one or more mutant alleles at play here. The authors have thus put a good deal of faith in this duo of single mutations is the only possible explanation for the disease in the affected child; ignoring the unexplained lack of disease in the reportedly unaffected, and unspecified parent.

Conceptually, this is a major flaw in the logic of the entire program: failure of due diligence in the absence of confirmable information in these two isolated families rather than working with other fully analyzed families where the parentage can be assured, segregation has been tested and confirmed, and all alternative models and genotypes have either been tested or excluded.

Thus since Aim#1 was ill-deployed and Aim#2 was not completed within the frame of which the PI proposed in the initial application, the objectives were not completed as designed. Despite these limitations, the design and the methods were indeed adequate, but the timeline was not met. The principal investigator (PI) does acknowledge this flaw and substantive progress has been made, but one wonders if the Final Progress Report carries enough weight to permit the PI to apply for alternative funding.

Reviewer 2:

Strengths: The research design and methods were appropriate and adequate. Data were developed in line with the original research protocol. Sufficient data and information were provided to support the fact that the project made acceptable progress. The data and information

provided were applicable to the project objectives listed in the strategic research plan.

Weakness: The primary weakness, as acknowledged by the PI, was the stated goals were overly ambitious. The project did not meet its stated objectives, but did make progress appropriate to the timeframe.

Reviewer 3:

Two specific aims were proposed in the original proposal. First, is to generate the transgenic mice expressing two naturally-occurring RetGC mutants. These mice will then be bred on the RetGC-null background. Second, morphological and electrophysiological characterization will be carried out in the mice generated in Aim. 1. According to the report, these investigators have not yet generated any transgenic mice even though the proposed egg injection date was mentioned. As a result, they are not able to conduct any proposed experiments.

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:

Conceptually, this program was too limited to tell its overall probability for improving the health of persons with LCA, let alone other genetically determined visual impairments. First, neither of the selected mutations have been published elsewhere, and the second or modifying allele, depending on monogenic or digenic inheritance, was not identified in either family. Second, while the research techniques for showing pathogenicity were standard and were appropriate, every experiment would have to be tailor designed for every new mutation, in a situation where RETGC represents only about 6 to 12% of all LCA, depending on the geographic and ethnic selection of the population.

The future plans for this program are not specified since Aim#2 was not completed.

Reviewer 2:

Strengths: This is a pilot project to produce an animal model that will lead to better understanding of Leber's congenital amaurosis, a congenital blinding disorder. These studies could lead to investigations to find approaches to treating inherited blinding diseases by means of genetic therapy. The investigators plan to continue the studies as proposed and have applied for external funding.

Reviewer 3:

The overall goal of this application is to examine the casual relationship of two novel mutations in the gene encoding retinal guanylyl cyclase 1 and the pathogenesis of Leber's congenital amaurosis (LCA). LCA is a severe form of retinal degeneration. The proposed studies may shed light into the underlying mechanism responsible for some type of LCA. These investigators suggested that they will continue their investigations based on the support of National Institutes of Health funding for a related/overlapped project.

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 budget and its consumption were not provided

The investigators stated that they would seek additional funding, but no resource(s) are provided, nor is a proposed budget request or disbursement.

Reviewer 2:

Strengths: The investigators have applied for \$431,465 in external funding from the National Institutes of Health, with the proposal currently under review. Additionally, they plan to apply for additional funds in the future.

Reviewer 3:

The investigators successfully secured NIH funding to continue and/or expand their research.

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:

One peer-reviewed publication is listed by the principal investigator. No additional manuscripts are listed as being “in preparation” or “in press.” The sole publication is technical and descriptive in nature.

No licenses or patents seem to have arisen from these experiments, nor are any filings reported.

Reviewer 2:

Strengths: An article was published in a highly ranked, peer-reviewed journal. Less than one publication would have been acceptable for this short-term project. A future publication is anticipated when additional data has been obtained.

Reviewer 3:

During this grant period, there was one paper published in Biochemistry based on the prior in vitro studies.

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

STRENGTHS AND WEAKNESSES

Reviewer 1:

This project does not enhance the primary institution. A broader approach, a more judicious selection of either genes or mutations, a thoughtful search for the second mutation in each of the two families, confirmation by segregation analysis, and choice of more common mutant alleles, might have made the program more appealing and coruscating.

No new investigators or researchers were added to the institution for this program.

The funds were used for research performed by one research associate.

Reviewer 2:

Strength: New genetic models of human disease were created. This will strengthen the position of the institution as a recognized center for investigations of retinal blinding disorders.

Reviewer 3:

There were no improvements to infrastructure, and no investigators, researchers, or pre-/post-doctoral students were added to the research.

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:

Extramural research collaborations are not a component of the work completed here, except in the donation and acquisition of various components and reagents used.

Clinical research was not part of this program.

Reviewer 2:

Collaborations were established with University of Alabama at Birmingham, and at Harvard Medical School. These collaborations strengthen the position of the institution as a recognized center for investigations of retinal blinding disorders.

Reviewer 3:

No new collaborations were generated as a result of the research.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

1. Failure to identify all possible mutations in the two families and thus assess the real mechanism of disease damaged the concept of the entire experiment. The specific mutations in parents and affecteds (and excluded in non-affecteds) would have truly justified the selection of the two isolated mutations in this program
2. While the development or acquisition of RETGC-mutant or -deficient (knockout) mice was Aim 1, it is unclear how much other work could have been done to select other mutant pairs, whose individual expression may have influenced the development of the project and permitted the completion of Aim #2.
3. Although the authors devote lip service to “the role of newly found mutation as potentially causing blindness and thus...design future strategies of gene therapy,” nothing in these listed experiments as constructed, is targeting gene therapy for ocular diseases. Paradoxically, the stated objective is the “study of the physiologic implications of two recently identified mutation.”

Reviewer 2:

1. The PI may try a more realistic appraisal of the time line when writing the proposal and be prepared to move forward rapidly as soon as a funding decision is announced, but there is a strong tendency to be optimistic, so this is a minor weakness.

Reviewer 3:

1. The rationale of generating transgenic mice carrying variable copy numbers of RetGC mutant in the RetGC-null background mice is not well justified. The better way to study the proposed goal is to produce knock-in mice instead.

Generic Recommendations for Salus University

Reviewer 2:

This is good work that warrants further support.

ADDITIONAL COMMENTS

Reviewer 1:

The investigator states that this “ information is expected to benefit future studies....to treat(ing) the inherited blinding diseases.” However, no substantive explanation is offered of how these experiments did or will achieve that goal.

Another goal is to “evaluate the role of newly found mutations as potentially causing blindness and thus ...design future strategies of gene therapy.” However, nothing in the experiments, as constructed, is targeting gene therapy. The stated objective is the “study of the physiologic implications of two recently identified mutations.”

Reviewer 3:

The information provided support the fact that the project did not met any of its objectives or made reasonably acceptable progress.