

**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 (1.67)

Project Rating:

Project	Title	Average Score
1086001	Effects of Environmental Tobacco Smoke Exposure on Cough in Adolescents and Adults	Favorable (1.67)
1086002	Effects of Chemotherapeutic Agents on the Peripheral Taste Structure and Function	Favorable (1.67)

Project Number: 1086001
Project Title: Effects of Environmental Tobacco Smoke Exposure on
Cough in Adolescents and Adults
Investigator: Wise, Paul

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 project endeavored to enroll and test 40 mother-child pairs to determine the impact of cigarette smoke exposure on children's cough sensitivity, while examining influential covariates including potential genetic determinants. Only 34 parents were recruited, but 46 children were recruited, since some mothers had more than one child. This was not anticipated in the study plan or in the analysis approach, however. The correlation between children leads to a decrease in power and an increase in variance of the estimates. The worst case is if there is perfect correlation between siblings, the sample size is reduced to 34 parent-child pairs. The actual sample size was even lower (38 children and 27 mothers) due to non-compliance and other drop-out. Considerable heterogeneity in mothers was observed (schooling, income) and in children (grade level, race, basal metabolic rate). The reduction in sample size leaves open questions regarding other significant effects (e.g., interaction effects) for which insufficient power was available. Exploratory analysis of genetic factors turned up some mildly significant genotypes (SNPs) associated with taste.

Reviewer 2:

The goal of this project was to determine whether adolescents who are exposed to environmental tobacco smoke have impaired cough sensitivity compared with adolescents of non-smokers. The investigators successfully recruited 46 children and 34 mothers who provided cough challenge tests on two days, anthropometry, questionnaires (to assess respiratory and otitis media health history, nicotine dependence in the adults, and the National Youth Tobacco Survey for the adolescents), weight and body composition measurements, and saliva for genetic analysis. The resulting data has been analyzed and demonstrated that smoking impairs the cough reflex in mothers who smoke and also impairs cough sensitivity in their children who are exposed to environmental tobacco smoke in the home. Preliminary analyses suggested the possibility of an association between genes that encode a particular taste receptor and cough threshold. This result should be interpreted very cautiously due to low power and also the possibility of an elevated alpha level due to multiple comparisons.

That the project met its accrual and analysis goals is commendable given the one-year funding period.

Reviewer 3:

This is a small grant for a pilot investigation regarding the relationship between environmental tobacco smoke and cough sensitivity. Although the results are still preliminary, the stated objectives have been met, and these results might be used to support future larger-scale studies if additional funding can be obtained.

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:

Statistical analysis found significant effects of environmental tobacco smoke for both airway sensation and cough threshold, but there seem to be some inconsistencies in the quoted standard errors compared to the standard deviations. Assuming this issue does not affect the validity, these findings are important to understanding the impact of parental smoking on adolescent lung health. Cough insensitivity can lead to more frequent lung infections, in turn leading to poorer adult lung health and lower academic achievement due to missed school days. Further, the genetic polymorphisms that the results indicated were potentially associated with cough sensitivity may be important. However, some skepticism must be raised due to the heterogeneity of the racial mix between exposure groups and the inability to control the genetic analysis for underlying differences in mutation frequencies.

Reviewer 2:

The project demonstrated that exposure to environmental tobacco smoke impairs cough reflex sensitivity in adolescent children. The investigators acknowledge that this information may not in itself be sufficient to motivate parents to stop smoking. However, it can be helpful in combination with other information to promote smoking cessation within the community.

Reviewer 3:

The major finding is that cough reflex sensitivity is impaired in environmental tobacco smoke exposed children. This information should be helpful for educating the public regarding the danger of exposing children to smoking. The study of genotyping is interesting as well, and it may provide further information regarding those who are particularly sensitive to environmental tobacco smoke. The investigators correctly pointed out that this study will need a much bigger cohort size, and they do plan to study this in the future.

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:

No co-funding or additional funding was obtained during the project, but a large (\$1.3M) NIH proposal was submitted and is under review. The investigators have no concrete plans other than an intention to submit further proposals as the ideas develop.

Reviewer 2:

The investigators successfully used this funding to develop a project as part of a P50 clinical center grant involving researchers at the Monell Chemical Senses Center and the University of Pennsylvania. They also plan to apply for additional funding.

Reviewer 3:

The investigators plan 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:

No publications were submitted. Two abstracts were submitted and accepted for presentation at a scientific conference.

Reviewer 2:

The investigators are writing a manuscript for a peer-reviewed journal. This is appropriate given the one-year funding period. Two abstracts have been accepted for the 2012 Annual Meeting for the Association of Chemoreception Sciences.

Reviewer 3:

There have been no publications so far, but the investigators plan to submit papers on this study in the future.

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

STRENGTHS AND WEAKNESSES

Reviewer 1:

Equipment to facilitate the research was obtained and implemented and is available for future research. No new investigators were added nor were students involved in the work.

Reviewer 2:

The CURE funding allowed the investigators to purchase two research nebulizer systems which allow for precise control of inhaled aerosols. They therefore now have a functional cough reflex laboratory that can be used for future projects. Funds also provided computers to support personnel.

Reviewer 3:

The funding allowed purchase of two nebulizers that enhanced their capacity to perform cough reflex 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:

No collaborations with external partners emerged during the research. However, outreach to the community occurred, and some education regarding smoking awareness resulted.

Reviewer 2:

The research project provided an opportunity for parents to participate regardless of race or income. Some participants were recruited through the WIC (Women, Infants, and Children) programs, which helped to raise awareness about the effects of smoking and second-hand smoke exposure in lower income individuals.

Reviewer 3:

The project did allow the investigators to perform epidemiological studies that by definition involve the community.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

1. The accrual of subjects is key to the success of any research. The grantee should consider additional accrual to meet the sample size as originally proposed.
2. The analysis of genotype data in the context of mixed race must take into account racial background and the potential for variability by race, especially if the two exposure groups diverge in this characteristic. Further, it may be better to focus on interactions here, as the plausible causal mechanisms would change the slopes of the response curves much more than the raw intercept. In this instance, depending upon the frequency of the mutations in the population, the interaction effects may be more easily detected than the main effects.

Reviewer 2:

None

Reviewer 3:

As the investigators already pointed out, a larger cohort will be needed to reach a solid conclusion. But given the amount of funding, the preliminary studies are excellent.

Project Number: 1086002
Project Title: Effects of Chemotherapeutic Agents on the
Peripheral Taste Structure and Function
Investigator: Wang, Hong

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 project met the stated objectives to determine the separate effects of three chemotherapy medications (5-FY, cisplatin, and PTX) on taste bud structure and taste function at defined time points through an experimental approach with male C57BL/6 mice. The research design addressed the specific aims, and the methods were designed to examine these objectives. The research team used their expertise in peripheral taste system defects within the inflammatory process to study how these chemotherapeutic agents disrupt the structural integrity of taste buds (gross structure, taste bud size and cell number) by inhibiting the formation of new taste buds (taste progenitor cells) or by inducing taste bud cell death with immunostaining. The team assessed taste functioning through lickometer tests or brief-access tests. These tests record preference or avoidance behavior as a proxy for taste functioning used by standardized procedures published by other taste research laboratories. The final program report showed sufficient and applicable data for both specific aims, demonstrating success in meeting the objectives.

Reviewer 2:

This project had two specific aims, and each aim involved two experiments. Specific Aim 1 examined the effect of three chemotherapy drugs (5-FU, cisplatin, and PTX) on taste bud structure. Specific Aim 2 was intended to examine the effect of the same three drugs on taste function. However, due to an insufficient number of behavioral testing apparatuses (i.e., Davis rigs), the effect of cisplatin on taste function was not investigated.

Strengths: The histological and immunohistochemical experiments of Specific Aim 1 seem well-conducted and appear to reveal that all three drugs decreased the number of progenitor cells while increasing the number of apoptotic cells in the taste epithelium. These three drugs also decreased the number of taste receptor cells in the taste buds.

Weaknesses: These anatomical deficits might be expected to lead to changes in taste function, and this is exactly what is claimed to have occurred in the research conducted under the auspices of Specific Aim 2. Unfortunately, this is a misguided impression, and the data of Specific Aim 2 are uninterpretable due to the poor design of the behavioral experiments. Moreover, data from

the second behavioral experiment were not reported because “in Experiment 1, 5-FU- and PTX-treated mice showed stronger effects on taste responses.” It is noted that Experiment 1 involved two injections of each drug whereas Experiment 2 involved only one injection of each of the two chemotherapy drugs. Furthermore, the statistical analyses (t-tests) were inappropriate for present purposes, because the high number of such tests that were conducted on the data favor the incursion of Type 1 errors (false positives). Overall, the design, conduct, and analysis of the two experiments in Specific Aim 2 are major weaknesses.

Reviewer 3:

The project made solid progress in generating what should be described as strong preliminary data in support of their overall hypothesis that chemotherapeutic agents such as 5-FU, PTX and cisplatin yield untoward effects on the structural integrity of the peripheral taste system.

The psychophysical data obtained, while showing some evidence of a behavioral effect, was less strong compared to the anatomical data.

With regard to the behavioral data, there is concern about the potential effect of multiple testing after treatment. This reviewer would suggest testing animals only once after they complete treatment. Further, there was no way to judge the extent to which motivation effects due to treatment-induced illness are contributing to the data presented. Do the animals complete the same number of trials in the pre- vs. post-testing sessions? Does this vary with treatment (i.e., PBS vs. agent)?

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:

Cancer therapies are worse than the disease itself on an individual’s health and well-being. Altered oral sensations and decreased appetite or anorexia is a significant problem, since it challenges a cancer patient’s ability to maintain normal nutrition and withstand the noxious effects of the chemotherapy. Well-controlled studies are needed that provide information on how chemotherapies alter oral sensations to contribute to anorexia and decreased enjoyment from eating. The present project addresses this significant health problem, using a well-controlled study with straightforward aims to provide preliminary data toward understanding the mechanism of altered taste, which can influence overall sensation. The impact is completely reasonable given the size of the grant award. Less certain are the future plans for this research toward translating this information from an animal model to a human health application.

Reviewer 2:

The basic idea for this research, that disruptions of taste bud structure by chemotherapy drugs should cause taste function deficits, has high face validity. Indeed, it was surprising to read that this issue had not previously been investigated.

The failure of the research in Specific Aim 2 to produce interpretable results substantially decreases the value of the present project. Although deficits were reported for Specific Aim 1 research, it is not known whether those deficits have any functional influence on taste-guided behaviors.

Reviewer 3:

From a health perspective this project has high clinical relevance. Understanding the factors contributing to cancer treatment-induced reductions in food intake, etc. is highly significant.

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 research team was able to utilize the research findings and methods to apply for NIH funding (application was pending) to study taste functioning in aging. They plan also to apply for NIH funding to investigate the combined effects of cancer and multiple cancer therapies on taste.

Reviewer 2:

A grant proposal entitled, "Cellular and molecular bases of age-associated taste disorders," with a budget of \$1,712,281.00 was submitted to NIH in February 2012. The PI awaits the decision on this submission.

Reviewer 3:

There was no leveraging of additional funds. However, the data obtained was used to submit a proposal to NIH that is awaiting review.

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:

The research team presented preliminary findings from this research at the Association for Chemoreception Sciences in April 2012 and plans to prepare and submit a full paper to a peer-reviewed journal sometime this year.

Reviewer 2:

No publications, licenses, patents or commercial developments have occurred to date. However, the PI states that a manuscript will be submitted to a "peer-reviewed journal sometime this year."

Reviewer 3:

To date there have been no abstracts or publications prepared or submitted. The investigators indicate the intent to do so. It is not clear to this reviewer from the presentation provided whether the existing data, especially the behavioral work, is ready for publication beyond the abstract phase at this time.

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

STRENGTHS AND WEAKNESSES

Reviewer 1:

The funding enhanced the principal investigator's ability to secure additional extramural funding and provide training opportunities for junior scientists and student interns. This research also provided basic research experience to professionals trained as MD-clinicians.

Reviewer 2:

There were no clear improvements made to infrastructure. However, it was noted that the project partially supported a research associate and a research specialist, who were trained as MDs, and that their expertise will benefit future research.

Reviewer 3:

In this reviewer's opinion the project did not enhance the quality and capacity for research. Rather, it supported individuals engaged in studying an important research topic.

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:

Although this research did not appear to address this criterion, the research facility, The Monell Center, is an inter-disciplinary research center that provides the environment to expand these research findings into a broader research investigation.

Reviewer 2:

This project did not result in any new collaborations.

Reviewer 3:

No.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

My only recommendation is to seek a broader, interdisciplinary approach to increase the understanding of chemotherapy-related changes in oral sensation from peripheral to central mechanisms. This broader approach would require significantly more funding, definitely beyond the parameters of the present project and funding.

Reviewer 2:

1. The PI needs to develop skills in the analysis of behavioral data. In Specific Aim 2, it appears that t-tests were used to analyze differences between Control (PBS) versus 5-FU treatment and Control (PBS) versus PTX treatment for each concentration of each tastant on each of the three test days (1 pre- and 2 post-drug injection days). If my count ($2 \times 3 \times 6 \times 3$) is correct, that's a total of over 100 t-tests. Such an extremely high number of tests will lead to a high incidence of false positives (i.e., Type 1 statistical errors). These data should have been analyzed with repeated measure analysis of variance for each tastant.
2. However, the major weakness here involves the design of the behavioral experiments of Specific Aim 2. The performance of the control (PBS) group was particularly problematic. In many instances, the control group performance was changing substantially across test days, suggesting that performance levels were not allowed to stabilize before the drug treatments were initiated. Here are some examples of control group performance:
 - a. Day 6 lick ratio for 0.1 M sucrose was ~2.5 but was ~4.5 on Day 8.
 - b. Day 6 lick ratio for 0.6 M sucrose was ~4.0 but was ~8.0 on Day 8.
 - c. Day 6 lick ratio for 16 mM saccharin was ~3.5 but was ~7.0 on Day 8.
 - d. Day 6 lick ratio for 64 mM saccharin was ~3.5 but was ~7.0 on Day 8.
 - e. Day 6 lick ratio for 10 mM IMP was ~2.3 but was ~0.9 on Day 8.

If the baseline performance of the control group is not stable across days it is impossible to evaluate the effect of a treatment (in this case, chemotherapy drugs) on that behavior. One might reasonably expect that a drug treatment would consistently either increase or decrease the lick ratio for, at least, the same concentration of a given tastant. This is not the case in the present results. For example, 5-FU is reported to significantly increase the lick ratio for each of the three concentrations of sucrose of Day 6. Yet, on Day 8, 5-FU is reported to significantly decrease the lick ratio for each of the three concentrations of sucrose. Furthermore, by looking more closely at these particular results we see that if the performance of the control group had remained stable between Days 6 and 8 then there likely would have been no influence of 5-FU on Day 8.

These concerns all add together to indicate that the design of the behavioral experiment was inadequate. It is suggested that the researchers need to conduct more preliminary studies with normal mice to obtain parameters that afford stable performance across days. This will include, but will not be limited to, separating taste test days with water only days, perhaps

testing only one tastant each day, increasing the number of water trials on taste test days, and increasing the number of mice per group.

3. The work of Specific Aim 1 appears sound. However, the mice in Specific Aim 1 were non-deprived whereas the mice in Specific Aim 2 were water deprived (and hence also food deprived). Why are the mice in each specific aim on different deprivation schedules? This issue has relevance, since Experiment 1 of Specific Aim 2 was terminated early because “several 5-FU and PTX treated mice became ill and some of them died on days 11 and 12...” This raises at least two issues. First, were results from the mice that died excluded from all data analyses? One assumes they would be because their taste performance might have been disrupted for reasons unrelated to the intended effect of the drug treatment. Second, is there an interaction between deprivation (or possibly the stress induced by deprivation) and drug treatment that increases morbidity? If this is the case, then the results of Specific Aim 1 cannot readily be compared to the results of Specific Aim 2.
4. Following on from the previous point, one wonders why the two specific aims were not combined. Why not examine taste function in the same mice that will subsequently be examined for taste bud structure and integrity? With this approach, it would be much easier to relate disrupted functions to deficient structure.

Reviewer 3:

Strong preliminary data support the hypothesis that chemotherapeutic agents such as 5-FU, PTX and cisplatin yield untoward effects on the structural integrity of the peripheral taste system. The preliminary behavioral data is not as strong as the anatomical studies. More studies of more animals need to be done in all regards.

With regard to the behavioral testing, this reviewer would suggest evaluating animals only once per tastant after they complete treatment and extending the concentration range. This will likely require a reevaluation of the testing design to avoid confounds of tastant testing order. The data on treatment-induced illness, i.e., number of trials completed, and number of licks to water need to be provided.

With regard to the behavioral data, there is concern about the potential effect of multiple testing after treatment. This reviewer would suggest testing animals only once after they complete treatment. Further, there was no way to judge the extent to which motivation effects due to treatment-induced illness are contributing to the data presented. Do the animals complete the same number of trials in the pre- vs. post-testing sessions? Does this vary with treatment (i.e., PBS vs. agent)?