

## Response Form for the Final Performance Review Report\*

1. Name of Grantee: Duquesne University

2. Year of Grant: 2008 Formula Grant

***A. For the overall grant, briefly describe your grant oversight process. How will you ensure that future health research grants and projects are completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) are submitted to the Department in accordance with Grant Agreements? If any of the research projects contained in the grant received an “unfavorable” rating, please describe how you will ensure the Principal Investigator is more closely monitored (or not funded) when conducting future formula funded health research.***

All grants received by Duquesne University are administered by the Office of Research. In the case of the CURE grants, once the amount of funding that the University will receive is established by the State and is transmitted to the Office of Research, a call for proposals to faculty is issued from said office. An internal University review committee is formed to evaluate and determine which proposals will be forwarded to the State. The pre-award grants coordinator and budget officer meet with the Principal Investigators (PIs) to help them develop budgets for the projects and assemble the electronic proposal package to be sent to the State.

Upon notification of funding of the proposal, the budget administrator notifies the Manager of General Accounting to establish a new General Ledger (G/L) account number within the financial accounting G/L system. When a G/L account is established, the budget administrator prepares a grant award notice, which is distributed to several directors and offices, including General Accounting, the Planning and Budget Office, and the Controller's Office. The grant award notice establishes the account codes for the grant and includes the line-item budget established by the budget administrator and the PIs during the proposal process, in accordance with funding agency guidelines, as well as the total grant award received for the year. Objective codes include items such as faculty and other salaries, travel, and supplies, etc. When interest-bearing accounts are required, the University Controller's Office allocates interest on a monthly basis. The Research Accounting department of the Controller's office inputs the budgeted amounts into the appropriate G/L account.

Once the G/L account has been established, all activity related to the award is maintained within the G/L system and monitored by the Research Accounting Department. Further, the University has implemented additional procedures whereby PIs certify, on an annual basis, that the salary distributions to their respective grants are reasonable based on the level of effort performed. These certifications are also reviewed and signed by an appropriate level of University management. The University also obtains conflict of interest statements annually

\* Please note that for grants ending on or after July 1, 2007, grantees' Final Performance Review Reports, Response Forms, and Final Progress Reports ***will be made publicly available on the CURE Program's Web site.***

from the PIs. Such statements are reviewed and signed by an appropriate level of University management.

The Office of Research maintains a database of grant report due dates. For all CURE reporting deadlines, the PIs are repeatedly notified via e-mail concerning the due dates and, beginning two months prior to the reporting deadline, the Office of Research intensifies their efforts reminding the PIs of the due dates of the reports. The research accountant contacts and works with the PIs to complete the financial status reports for the grants. All financial and non-financial reports are compiled by the grant coordinator, who then electronically uploads the reports to the States web portal. The Office of Research plays an integral part in all facets of the grant oversight and reporting processes for the CURE grants.

**Project Number:** 0863301

**Project Title:** Investigation of the Hepatitis C Virus 3'-Untranslated Region,  
as a Potential Target for new Antiviral Nucleic-acid-based Strategies

**Investigator:** Mihailescu, Mihaela

***B. Briefly describe your plans to address each specific weakness and recommendation in Section B of the Final Performance Summary Report using the following format.*** As you prepare your response please be aware that the Final Performance Review Summary Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

Reviewer Comment on Specific Weakness and Recommendation (*Copy and paste from the report the reviewers' comments listed under Section B - Specific Weaknesses and Recommendations*):

Response (*Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts*):

Reviewer 1:

1. Development of a PNA based antiviral approach based on RNA base pairing or kissing interaction between two RNA domains is not a very attractive antiviral strategy. The project is at a very early stage of development. The overall enthusiasm for this project is low because there is no cell culture data available to evaluate how effectively this antiviral strategy will block HCV replication.

Response:

- The PI disagrees with this general statement; if the kissing interaction formed between two RNA domains is essential for the viral life cycle and, moreover, it involves sequences of 100% conservancy among all HCV strains, it follows that its disruption is a feasible antiviral target. Cell culture experiments evaluating the PNA antiviral activity against HCV have been performed in the Lemon lab at UNC; however, these were not included in the final report of the CURE grant, as this was beyond the scope of the funded Specific Aims 1 and 2 of the project.
2. The prospects of treating HCV infection with small molecule drugs targeting the viral polymerase, protease and NS5A are good. The cure rate of chronic HCV infection using triple combination therapy has been improved significantly. It is also expected that the response rate will be higher with newer antivirals targeting the NS5B and NS4A. It is not clear how effective this PNA based antiviral strategy will be. There will be an issue of inhibiting HCV RNA by PNA by avoiding cellular cytotoxicity. There are a number of issues that need to be addressed in case this PNA based antiviral approach is developed against HCV.

Response:

This is true; however, at the time the project was initiated this was not the case. The point about the PNA cellular cytotoxicity is valid; preliminary results (not included in the final report) from the Lemon lab at UNC indicate that there is no cellular cytotoxicity associated with the PNAs tested.

3. Another challenge will be how to deliver this PNA to the infected cells in the liver.

Response:

Again, this is a valid point; preliminary results from the LY lab at CMU (not included in the final report) indicate that the PNAs administered i.v. in mice are found in the liver.

4. The PI has not developed this project rigorously to make a strong case that this antiviral approach inhibits HCV replication. Most of the work during the last three years has been focusing on determining the RNA-RNA interaction and designing PNA. The PI has selected only one target. What will they do if this approach or target is not effective or in case HCV develops resistance to this target?

Response:

There were several additional targets selected, and one of the possible options is to use PNAs against multiple HCV targets simultaneously. If HCV develops resistance to the target, new PNAs could be synthesized to target the new sequences.

5. The PI did not provide a realistic plan for how she will succeed in developing an antiviral strategy against HCV using the novel peptide nucleic acid drugs. At present there is less enthusiasm about the overall success of this project.

Response:

Again, the CURE-funded project did not plan to develop a drug; it is impossible to do this within the two years of the grant and with the limited funding provided. This study was intended to analyze the potential HCV targets and design and analyze the interactions of PNAs with these targets by biophysical methods, and these goals have been accomplished.

Reviewer 2:

1. The long-range RNA-RNA interactions between the 3'UTR kissing-loop and the NS5B-coding region need to be confirmed structurally by enzyme digestion and/or NMR studies. NMR studies proposed in Aim 1 should be pursued in future studies in order to validate the RNA structures.

Response:

The 3'-UTR region adopts two different conformations, co-existing in equilibrium (Shetty, S., Stefanovic, S., & Mihailescu MR, [Nucleic Acids Res.](#) 2013 Feb 1;41(4):2526-40), making structural studies difficult. We have proved by using other biophysical methods that indeed these interactions exist in vitro, and there is genetic data in the literature, confirming their existence in vivo as well.

2. The inhibitory activity of the PNA tested in vitro appeared to be weak. The PI should continue the screening for additional PNA aptamers as proposed in the original application.

Response:

We have selected other targets, which show stronger in vitro activity.

3. The PNA antiviral activity needs to be examined at least in cell culture.

Response:

Cell culture experiments evaluating the PNA antiviral activity against HCV have been performed in the Lemon lab at UNC, however, these were not included in the final report of the CURE grant, as this was beyond the scope of the funded Specific Aims 1 and 2 of the project.

Reviewer 3:

It was a well-executed study that performed pretty much the intended tasks and led to high-quality publications, collaborations and preliminary data for funding. It was a good project with good significance.

Response:

The PI thanks the reviewer.

***C. If the research project received an “unfavorable” rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive “unfavorable” ratings.***

Response:

***D. Additional comments in response to the Final Performance Review Report (OPTIONAL):***

Response:

**Project Number:** 0863302

**Project Title:** Impact of Parental Smoking Cessation and Residential Hazard Reduction on Pediatric Respiratory Health: A Pilot Investigation

**Investigator:** Kabala, Stanley

***B. Briefly describe your plans to address each specific weakness and recommendation in Section B of the Final Performance Summary Report using the following format.*** As you prepare your response please be aware that the Final Performance Review Summary Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

Reviewer Comment on Specific Weakness and Recommendation (*Copy and paste from the report the reviewers' comments listed under Section B - Specific Weaknesses and Recommendations*):

Response (*Describe your plan to address each specific weakness and recommendation to ensure the feedback provided is utilized to improve ongoing or future research efforts*):

Reviewer 1:

1. With baseline data for the n=30 families that participated, these data need to be analyzed more rigorously with respect to parental smoking. The biomarker data are helpful but are limited by the short half-life of expired CO. Cross-tabulating the self-reported smoking data by the biomarker, cross-tabulating the parent-child expired CO by ordered categories that also included rules about smoking in the home and car would be helpful. If possible, integrating the secondhand smoke exposure data with exposure to other allergens in relation to the health outcomes would be a very good idea. There may be limitations in the technical expertise to carry out sophisticated analyses, but hopefully at least the cross-tabulations and thinking through the data in a more thorough fashion would be very helpful and not unreasonable to ask for, given the investment of resources to generate these data.
2. This write-up needs to be edited to clarify more precisely exactly what data were collected and when. The reviewer appreciates that the Healthy Home Resources shutdown had a major adverse impact on the project as planned, but the details with respect to what actually was accomplished and what the revised plan called for were not delineated in a clear and precise fashion. For the actual data related to the originally planned project, explain whether or not any longitudinal follow-up was collected for these n=30 families. If it was, it should be incorporated into the analyses described above even if the numbers are small.

Response:

The investigators agree that the suggested statistical analysis could be quite informative. Regrettably, additional analysis was not possible due to the dissolution timeline of Healthy Home Resources (HHR): First, after the organization ceased operation, the investigators sought to contract with former staff to complete the proposed follow-up home visit CO measurements and surveys. The staff qualified to perform the work found other employment

and declined the contract. Second, the physical and electronic participant records collected and maintained by HHR were destroyed in compliance with HIPAA regulations. Without the knowledge or approval of the investigators, this inadvertently included the destruction of the anonymous (PIN code) protected files to be used for further statistical analysis for the final report.

Reviewer 2:

1. The literature review regarding in-home service delivery models for childhood asthma was sparse and could be more comprehensive and detailed.

Response:

The review by Clark, et al (2009), suggests that the AT HOME residential assessment and intervention methodology used in the pilot investigation had the essential characteristics of successful programs: (1) addresses the multiple factors affecting pediatric asthma; (2) assesses participant risk factors; (3) tailors the intervention to address relevant risk factors; (4) addresses both physical and social environments; (5) offers effective individual and community-level education and outreach.

Clark, Noreen M., Mitchell, Herman E., Rand, Cynthia S., “Effectiveness of Educational and Behavioral Asthma Interventions” Pediatrics, 2009

2. The evaluation of the CBO's activities lacked detail and specificity and should include more quantitative data.

Response:

All physical and electronic participant records collected and maintained by HHR were destroyed in compliance with HIPAA regulations. Without the knowledge or approval of the investigators, this inadvertently included the destruction of the anonymous (PIN code) protected data files. This precluded a more specific and quantitative narrative for the final report.

3. The conclusions drawn from the small pilot study are not substantiated.

Response:

The investigators agree that the broad conclusions made in the final report would not be quantitatively substantiated by the incomplete results of the pilot study alone. This study did give anecdotal information on the longer-term adherence to the overall intervention. As noted in the final report, participant families continued to employ the equipment, supplies, and housekeeping principles from their initial AT HOME intervention. While the initial intervention did not lead to smoking cessation, there was clear evidence that parent/caregivers had taken steps to reduce child exposure to tobacco smoke, such as smoking less and smoking outdoors.

Also, half of the parent/caregivers expressed considerable concern over their own elevated CO breath levels, suggesting its utility as a motivational tool in spite of its inherent limitations as a biomarker.

Reviewer 3:

The project failed to meet the objectives. The project was unable to recover from the loss of the opportunity to complete the initial set of objectives. Some of the initial objectives were not well thought out and vetted (e.g., use of CO as a metric for tobacco smoke exposure, statistical power). New revised specific aims were not well developed and failed from methodological flaws that could have been recognized before committing to aims that were not feasible.

1. In future projects, the investigators should be sure to fully develop methodological and analytical plans that can support the aims and are clear to reviewers and others interested in their work. Vetting them with researchers or colleagues who have more experience with the methods and content would be helpful for setting the stage for success.
2. In future related work, the investigators should become familiar with the rich literature on the use of cotinine measures in biological samples (hair, urine, saliva) for such purpose.
3. Connecting with the multitude of national organizations, state level activities, or investigators doing similar healthy homes work might have provided some helpful suggestions on formulating successful alternative aims when faced with challenges.
4. Recognize the fragility of community organizations and develop a strategy that will enhance successful sustainability, perhaps by linking to more than a single organization and organizations that are not reliant on single, soft money funding sources.
5. Be clear about your statistical power or sample size needed if doing quantitative analyses.

Response:

The investigators appreciate the useful comments and suggestions provided by Reviewer 3. The points regarding the potential drawbacks and research limitations involved in partnering with a community organization are well-taken. In addition to the fiscal fragility of soft-funded support organizations, the investigators acknowledge that the overall project design was constrained by the resources and expertise of the organization. For example, the use of CO breath levels in lieu of cotinine measures was a clear compromise, as biological sample collection, preservation, and chain of custody were far beyond the capacity of the support organization to manage.

***C. If the research project received an “unfavorable” rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive “unfavorable” ratings.***

Response:

***D. Additional comments in response to the Final Performance Review Report (OPTIONAL):***

Response: