

**Response Form for the Final Performance Review Report—
Wistar Institute 2008F***

1. Name of Grantee: Wistar Institute
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.

RESPONSE: In order to ensure an appropriate and timely response to all requests for reports from the Department of Health, The Wistar Institute has designated a single person, Ms. Maureen Leidy, to serve as the sole liaison with the Department. Ms. Leidy gathers all documents, communicates with all researchers, assures appropriate certifications, and assembles all grants, progress and final reports. While new to the Institute, she has many years experience in nonprofit grants and works closely with Legal Affairs and Finance in ensuring accuracy and compliance in the Institute’s grant process.

For each research project contained in the grant, please provide a response to items B-D as listed on the following page(s). When submitting your response please include the responses for all projects in one document. The report cannot be submitted as a ZIP file, because the Department’s exchange server will remove it from the email. If the report exceeds 2MB, please contact the Health Research Program for transmittal procedures: 717-783-2548.

* 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.***

Project Number: 0865701

Project Title: Critical Roles of Transcription Factor Foxp1 in Thymocyte Development and Peripheral T Cell Function

Investigator: Hu, Hui

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

Reviewer 1:

None.

Reviewer 2:

1. More sophisticated analysis of the microarray data is recommended, perhaps obtaining a collaborator with bioinformatics expertise, if there is not already one on board.

RESPONSE:

We agree with Reviewer 2 that a collaborator with bioinformatics expertise and more sophisticated analysis of our microarray data are needed. Currently we are collaborating with Dr. Ramana V. Davuluri, Director of Computational Biology at the Wistar Institute, a bioinformatics investigator, who has extensive experience in analyzing genome-wide ChIP-sequencing and microarray data.

Our research supported by this grant has led to two publications:

1. Feng, X., Ippolito, G. C., Tian, L., Karla, W., Oh, S., Sambandam, A., Willen, J., Bunte, R. M., Maika, S. D., Harriss, J.V., Caton, A. J., Bhandoola, A., Tucker, P. W., and Hu, H. (2010) Foxp1 is an essential transcriptional regulator for the generation of quiescent naïve T cells during thymocyte development. *Blood*. 115, 510-518
2. Feng, X., Wang, H., Takada, H., Day, T., Willen, J. and Hu, H. (2011) Transcription factor Foxp1 exerts essential cell-intrinsic regulation of the quiescence of naive T cells. *Nature Immunology*. 12, 544-550 (see News and Views in Nat. Immunol. 12, 522-524; also featured as Article of the month)

Reviewer 3:

None.

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: N/A.

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

Response: None.

Project Number: 0865702

Project Title: Impact of Latent Cytomegalovirus Immediate Early Protein Expression on Embryonic Development

Investigator: Maul, Gerd G.

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

Reviewer 1:

1. The impact of cytomegalovirus on brain development is being actively investigated by multiple labs around the world. Published work, "Murine Cytomegalovirus Infection of Neural Stem Cells Alters Neurogenesis in the Developing Brain," Manohar B. Mutnal, Maxim C.J. Cheeran, Shuxian Hu, and James R. Lokensgard, demonstrates that the murine model system can be used to investigate the effects of the virus on the brain. The effects of targeted mutant viruses are likely to be more informative than the overexpression of a few viral genes.

Reviewer 2:

1. Unfortunately, the MIEP was used in these transgenics to drive the expression of IE1 and IE3. It appears that Dr. Maul was correct in his assumption that he should use an inducible construct to control the timing of expression; however, a construct under the control of a constitutive promoter that he knew would be expressed once recombination occurred, should also have been constructed. At this point, once the negative situation was encountered, these animals could have been brought into play.

Reviewer 3:

1. This was an ambitious and well-reasoned proposal; however, progress was very limited, and detailed data confirming any of the results reported relating to the studies with cell lines, or the investigation of transgenic mouse embryonic brain development described in the Progress and Final Reports, has not been provided. The inclusion of additional data to clarify and confirm results presented in the reports would have been appropriate.
2. Data relating to various organs in the adult transgenic mouse lines lacked appropriate detail and resolution to allow for an objective evaluation of the stated results. Additional figures, identification of labeled cells using immunophenotyping, and other relevant supporting data as proposed originally in the Strategic Plan should have been included.
3. The proposed immunohistochemical, Western blot, in situ hybridization, and morphological analyses proposed for studies of the developing embryos from the various transgenic mouse lines generated have not been conducted. Notably, no attempts to clarify the identity of GFP expressing cells by immunophenotyping was conducted as planned. Given limited expression of GFP in cells, immunostaining with anti-GFP antibodies would have been a useful approach to boost cellular signals.

4. Due to overall negative results, and the absence of any significant findings, the principal investigator has appropriately elected not to pursue further funding for this line of research.

RESPONSE: Dr. Maul has unfortunately passed away prior to receipt of the Final Performance Review Report; therefore, we are unable to provide a response regarding weaknesses and recommendations of this specific research project.

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: N/A

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

Response: None.

Project Number: 0865703

Project Title: Frequency, Fate and Significance of MicroRNA Editing

Investigator: Nishikura, Kazuko

Project Number: 0865703

Project Title: Frequency, Fate and Significance of MicroRNA Editing

Investigator: Nishikura, Kazuko

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

Reviewer 1:

1. Although the results of the project are described in considerable detail, more discussion regarding the translational impact of the study findings would have been helpful. The PI did not comment on the value of the research towards eventual improvement in health outcomes.

RESPONSE: Thank you for pointing out the translational value of our research. Of course, I am aware of the potential impact of our findings on future development of nucleic acids based therapeutics. There are many companies trying to develop microRNA-based therapeutics against viral infections (HIV and HCV) and cancer. The strategy and design of such therapeutics need to reflect our findings: many microRNAs are subject to A-to-I RNA editing, and editing affects their expression and function. Furthermore, certain edited microRNAs change their target genes because of a single A-to-I sequence change in the seed sequence. One may utilize or develop an edited microRNA as a therapeutic that specifically targets viral or oncogenic genes without targeting host or normal genes.

2. The only publication listed by the PI was a review paper. The PI indicated plans to submit a manuscript to *Nucleic Acids Research*. An update regarding plans to publish the results of this project as an original research paper, would be helpful.

RESPONSE: All publications, original research papers, and reviews related to the mission of the CURE grant support, are listed below;

Original Papers:

Kawahara, Y., Grimberg, A., Teegarden, S., Mombereau, C., Sui, L., Bale, B.L., Blendy, J.A., Nishikura, K. 2008. Dysregulated editing of serotonin 2C receptor mRNAs results in energy dissipation and loss of fat mass. *J. Neurosci.* 28: 12834-12844.

Iizasa, H. Wulff, B-E, Alla, N.R., Maragkakis, M., Megraw, M. Hatzigeorgiou, A., Iwakiri, D. Takada, K., Wiedmer, A., Showe, L., Lieberman, P., and Nishikura, K. 2010. Editing of Epstein-Barr virus-encoded BART6 microRNAs controls their Dicer targeting and consequently affects viral latency. *J. Biol. Chem.*, 285: 33358-33370.

Mombereau, C., Kawahara, Y., Gundersen, B.B., Nishikura, K. and Blendy, J.A. 2010. Functional relevance of serotonin 2C receptor mRNA editing in antidepressant- and anxiety-like behaviors. *Neuropharmacol.* 59: 468-473.

Reviews;

Iizasa, H. and Nishikura, K. 2009. A new function for the RNA-editing enzyme ADAR1. *Nat. Immunol.* 10: 16-18.

Zinshteyn, B. and Nishikura, K. 2009. Adenosine-to-inosine RNA editing. *WIREs System. Biol. Med.* 1: 202-209.

Wulff, B-E and Nishikura, K. 2010. Substitutional A-to-I RNA editing. *WIREs RNA* 1: 90-101.

Nishikura, K. 2010. Functions and regulation of RNA editing by ADAR deaminases. *Annu. Rev. Biochem.* 79: 321-349.

Wulff, B-E, Sakurai, M., and Nishikura, K. 2011. Elucidating the inosinome: global approaches to adenosine-to-inosine RNA editing. *Nat. Rev. Genetic.* 12: 81-85.

Wulff, B-E and Nishikura, K. 2012. Modulation of microRNA expression and function by ADARs. *Curr. Top. Microbiol. Immunol.* 353: 91-109.

Reviewer 2:

None.

Reviewer 3:

None.

Generic Recommendations for the Wistar Institute

Reviewer 3:

This is a fine project in a very significant area of research. What I found most impressive is that the PI was able to find a new angle and unique insight in what is a very important but also very crowded area. I would recommend continued support, if at all possible.

RESPONSE: I appreciate very much your enthusiasm and recommendation for continued support of our research.

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:

Thank you for “Outstanding” score (1.33). We plan to continue our research efforts aiming outstanding outcome and impact on public health.

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

Response:

I am very grateful for the CURE Grant Support we received, which allowed us to secure an NIH R01 grant and to prepare an additional R01 grant application aiming for submission in this summer.

Project Number: 0865704

Project Title: Diagnosis of Lung Cancer from Peripheral Blood Using Genomics

Investigator: Showe, Louise C.

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

Reviewer 1:

None.

Reviewer 2:

None.

Reviewer 3:

None.

Response: None.

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: N/A

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

Response: None.