Response Form for the Final Performance Review Report*

1. Name of Grantee: Wistar Institute

2. Year of Grant: 2010 Formula Grant

A. For the <u>overall grant</u>, 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.

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. Joyce Macauley, to serve as the sole liaison with the Department. Ms. Macauley gathers all documents, communicates with all researchers, assures appropriate certifications and assembles all grants, progress and final reports. She has had this responsibility since the inception of the Tobacco Formula Funding program. Her experience and familiarity with personnel in the Department of Health assures the Institute's immediate response to all requests.

* 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: 1087901
Project Title: Isoform Specific p73 Regulatory Networks in Neurogenesis
Investigator: Davuluri, Ramana

B. Briefly describe your plans to address <u>each</u> specific weakness and recommendation in <u>Section B</u> 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*):

<u>Reviewer 1:</u>

1. The bioinformatics analysis has been very limited to date. Additional analysis of the target genes for the different p73 isoforms could improve the understanding of the roles of these proteins. The current status report lists summary statistics for differential binding events but does not substantially delve into the differential function. Some gene functions are listed, but the methods and significance of these findings are not discussed in any detail. A fuller analysis and specific hypotheses that arise therefrom would greatly improve the significance of the work.

   <u>Response:</u>
   We thank the reviewer for this excellent suggestion. We recently developed a Tree-based Position Weight Matrix (PWM) – (TPWM) approach to accurately model the interaction between TF and its binding site. The whole tree-structured PWM could be considered as a mixture of different conditional-PWMs. We propose a discriminative approach, called TPD (TPWM based Discriminative Approach), to construct the TPWM from the ChIP-Seq data. To achieve the maximum discriminative power between the positive and negative datasets, the cutoff value is determined based on the Matthew Correlation Coefficient (MCC). The resulting TPWMs are evaluated with respect to accuracy on extensive synthetic datasets. We then apply our TPWM discriminative approach on several real ChIP-Seq datasets to refine the current TFBS models stored in the TRANSFAC database. Experiments on both the simulated and real ChIP-Seq data show that the proposed method has consistently better performance than existing tools in detecting the TFBSs. The improved accuracy is the result of modeling the complete dependent structure of the motifs and better prediction of true positive rate. The findings could lead to better understanding of the mechanisms of TF-DNA interactions. This methods paper is now published in PLOS One (Bi, Y., Kim, H., Gupta, R. and **<u>Davuluri, R.V.</u>** (2011) Tree-based Position Weight Matrix Approach to Model Transcription Factor Binding Site Profiles, ***PLOS One 6****(9):* e24210).

We will continue to focus our research efforts in better characterizing tp73 binding sites and target genes.

2. There is no discussion of the development of computational models that might explain the cis-regulatory modules and target promoters. This is an interesting problem, and the grantee has designed a study that makes such modeling tractable. The current work is more descriptive than predictive, but developing models would greatly improve potential impact.

   Response:
   One of the main bottlenecks in developing computational models for predicting cis-regulatory modules and target promoters is lack of experimental data. For example, we developed such models for ERalpha and SMAD, which we published earlier – Qin et al. 2009, ***BMC Syst Biol***, **3**, 73; Jin et al. 2004, ***Nucleic Acids Res.*** **32**: 6627-6635; Cheng et al. 2006, ***Molecular Cell*** **23**:393-404. We have encountered problems with ChIP grade antibodies for Tap73 and DeltaNP73 (isoform-specific antibodies). We are modifying our experimental strategies to generate high-quality experimental data in order to prepare the training and test-data for model building.

3. Although a substantial amount of data has been collected and analyzed, the missing data substantially limits the interpretability of the study. Global data for isoform knockdowns and differentiated cells, as originally proposed, would be helpful.

   Response:
   Thank you very much for this excellent suggestion. We are going to proceed with generation of global data for isoform knockdowns and differentiated cells.

Reviewer 2:

1. The significant concern is that the PI did not provide detailed information about the computational methods for Specific Aim 2. Develop the computational models specified in Specific Aim 2 to better understand the combinatorial regulation for the different P73 isoforms.

   Response:
   Some of the computational models are published in our previous studies listed above. We will continue to develop novel methods depending on the experimental data that will be generated in the future.

2. Expand the integrative analysis to prioritize candidates for subsequent validation, since it is unclear how candidates are currently chosen.

   Response:
   The computational analysis will involve integration of RNA-seq and ChIP-seq datasets. We are currently optimizing our methods to generate ChIP-seq datasets for different time points. The informatics analysis will follow the guidelines outlined in our previous publications (Qin

et al. 2009, ***BMC Syst Biol***, **3**, 73; Jin et al. 2004, ***Nucleic Acids Res.*** **32**: 6627-6635; Cheng et al. 2006, ***Molecular Cell*** **23**:393-404).

3. Increase the translational impact by identifying potentially actionable interactions in human disease.

   Response:
   Thank you for the excellent suggestion; we are performing integrative analysis of our data and The Cancer Genome Atlas data to identify potentially actionable interactions.

Reviewer 3:
This is a strong researcher with an excellent track record.

1. I recommend that a publication be prepared with specific results on isoforms of p73 using P19 cells with replication, as well as with other cell lines or experimental platforms, to support the assertions of the differential roles of TAp73 and DNp73.

   Response:
   We thank the reviewer for this suggestion. We are preparing a publication based on the data generated so far.

2. I recommend that computational methods developed under this proposal be described in a peer-reviewed publication.

   Response: We thank the reviewer for this suggestion. We are preparing a publication based on the data generated so far. One publication is already published (Bi, Y., Kim, H., Gupta, R. and **Davuluri, R.V.** (2011) Tree-based Position Weight Matrix Approach to Model Transcription Factor Binding Site Profiles, ***PLOS One 6****(9):* e24210).

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: Using the results obtained through this research, we have successfully competed for the following NIH R01.

1R01 LM011297 (PI: DAVULURI) 5/2/13–4/30/16
NLM/NIH Grant amount: $378,000 per year
Title: Informatics platform for mammalian gene regulation at isoform-level

The major goal of the proposed research is to develop novel algorithms and an integrated database for understanding and modeling gene regulation at isoform-level between normal and disease conditions by integrating heterogeneous datasets from high throughput and next generation sequencing experiments including ChIP-seq and RNA-seq.

Project Number: 1087902
Project Title: SECTM1 is a Novel Mediator of Melanoma Tumorigenesis and Progression
Investigator: Kaufman, Russel

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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*):

<u>Reviewer 1:</u>

1. Systematic analysis of SECTM1 production (expression in cytoplasm, cell surface, and secreted form) in the panel of up to ten melanoma cell lines is highly recommended in order to establish the general phenomenology of SECTM1 expression in melanoma and establish the localization and secretion pattern. The expression and functionality of CD7 receptor on the surface of melanoma cells need to be shown. It is clear that some melanoma cell lines such as B16 cannot tolerate overexpression of SECTM1, and the potential biology behind this needs to be defined.

   <u>Response:</u>

   A) Systematic characterization of the expression pattern of SECTM1 is problematic because the pattern and level of expression is affected by cytokines and interferons, and this is a dynamic state. We have no evidence that overexpression occurs due to specific genetic mutations in SECTM1 and more likely is due to either the influence of the microenvironment or epigenetic factors. We also know that it is difficult to identify SECTM1 on the surface of cells that express the full-length molecule by western blotting. However, forced expression of SECTM1 in certain cell lines permits us to detect SECTM1 on the surface.

   B) We cannot show the functionality of CD7 on the surface of melanoma cells.

   C) We have explored the forced expression of SECTM1 on a variety of cell types, and some cells undergo apoptosis. In an earlier report, we introduced genes encoding either the soluble or full length forms of K12/SECTM1 into HEK 293 cells along with a luciferase reporter gene driven by the NFκB promoter. The full-length gene produces a 5X increase in luciferase activity compared to the most potent activator of NFκB, IKKβ, which produces an approximately 20X increase in activity. Since NFκB has many effects on cells, its overexpression in different cells could affect cell viability or tendency toward apoptosis in those cells.

2. The project lacks the direct evidence that SECTM1 is able to induce differentiation of monocytes to macrophages. The factors from melanoma-conditioned media (MCM), some of which express SECTM1, were capable of this; but the results regarding SECTM1 alone are missing. Thus, it is not completely clear if SECTM1 by itself could induce differentiation and what additional factors are required.

   Response:
   We agree that the report does not conclusively prove that SECTM1 can induce differentiation. We are currently using recombinant SECTM1 to answer this question.

3. It was shown that factors from MCM-induced macrophages (MCMI-M) express both M1 and M2 macrophage markers, but microarray analysis revealed that the majority of genes expressed by this mixed population were associated with tumor invasion. Since M1 and M2 have opposing influences on tumor progression this conflict of microarray data and macrophage marker expression needs to be discussed. Additionally, the macrophages produce factors which inhibit melanoma-specific T-cell proliferation, while SECTM1 induces robust proliferation of T cells and IFN-gamma production. These two opposing effects in the melanoma microenvironment also need to be discussed, especially in the prospective attempts to inhibit SECTM1 production during tumor progression.

   Response:
   We are confident in the accuracy of the data that were produced and cannot easily explain why the MCM-induced macrophages express both M1 and M2 markers. We have tried to explain this in our publication in Pigmented Cell Research and have compared our induced cells with tumor associated macrophages (TAMs). Most TAMs characterized to date demonstrate an M2-Mϕ phenotype. However, some current evidence suggests that TAMs are a mixed population bearing both M1 and M2 phenotypes (Umemura et al., 2008). It has also been proposed that M-CSF and GM-CSF induce macrophages as both M2 and M1 macrophages, respectively (Sierra-Filardi et al., 2011; Svensson et al., 2011). These results may simply reflect the complexity of biological systems.

4. The further development of *in vivo* models is strongly encouraged in order to test applicability of obtained knowledge in clinical practice. This reviewer suggests using NSG immune compromised mice, since they lack functional T, B and NK immune cells and defective macrophages, but have monocytes to test the hypothesis of differentiation of monocytes into functional macrophages through expression of SECTM1 by melanoma. This model could be humanized and populated with selected classes of human immune cells, including macrophages which could be labeled with GFP marker or produced from GFP mice to test and visualize the infiltration of implanted 3D skin reconstruction model of melanoma by injected GFP-macrophages or monocytes. The production of SECTM1 in melanoma cells could be silenced by anti-SECTM1 targeting shRNAs (constitutive or doxycycline inducible) thus allowing researches to gauge the requirement for SECTM1 production in order to get macrophages and monocytes into primary site.

Response:
We are now having some success with *in vivo* model systems and are conducting some of the studies proposed earlier.

5. Introduce SECTM1 in B16 cells under inducible promoter to allow for fine manipulation in expression levels and opportunity to induce expression after the tumor cells were injected into animals.

   Response:
   We are considering this approach and will do this if funds become available.

Reviewer 2:

1. The overall rationale for the project is weak. If SECTM1 activates T cells and induces macrophage differentiation, it is not clear how it promotes tumor progression. The researchers need to provide a better mechanistic explanation for the observed effects of SECTM1.

   Response:
   We believe the effects of macrophages are well described in the literature, and that the recruitment of monocytes/macrophage to tumors can have an important role in tumor progression.

2. If SECTM1 is highly expressed in melanoma cell lines and tissue lesions (as shown in Figure 1), the rationale for overexpression of SECTM1 is not clear. The researchers should consider genetic knockdown strategy to investigate the role of SECTM1 on biology of melanoma cells per se.

   Response:
   These studies are in progress.

3. The overall writing and presentation of the project is weak. For example, the experimental design and methods section of the strategic research plan is poorly written with many typographical errors, such as "mass spectrum analysis." The PI's biosketch appears to be incomplete with no list of publications and ongoing grant support, etc. A better proofreading of the writing will help the reviewer to better understand the researcher's intent and research plans.

   Response:
   We apologize for this area of weakness.

Reviewer 3:
The most evident weakness is the failure to date to establish a working 3D organotypic model involving SECTM1 overexpression that is associated with survival of the macrophages. Secondarily, a B16 mouse melanoma model also failed due to lack of macrophage survival. At least one and ideally both of these models must be developed into a successful model system for the current research to have a high likelihood of obtaining R01 or equivalent funding. However, nothing is seen that indicates the problems encountered to date are insoluble.

Response:
We agree that these problems are not insolvable and are working to develop these model systems.

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: The funding to support this work has been essential to help us understand the functions of SECTM1, a molecule that is expressed in many tumors and normal cells, but has not had a well- defined function. This molecule sits at the intersection of the immune system and tumor cells and may have a very important role in modulating the immune system by tumors.

Project Number: 1087903
Project Title: Regulation of EBV Infection and Latency by Editing of Viral MicroRNAs
Investigator: Nishikura, Kazuko

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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*):

<u>Reviewer 1:</u>
While the applicant made some progress on Specific Aim 2, no work on Specific Aim 1 was reported; and there were not any significant publications based on this work. The applicant needs to design experiments that look at <u>endogenous</u> miR-BART6 function using miR-BART6-specific antagomirs and/or EBV viruses lacking miR-BART6. Indeed, the widely used laboratory EBV variant B95-8 lacks miR-BART6. Experiments looking at ADAR function, and more precisely demonstrating whether miR-BART6 editing is significant, are also needed.

1. The applicant needs to address the function of endogenous, virally encoded miR-BART6 in BLs, NPCs and LCLs using antagomirs and in EBV strain B95-8 derived LCLs by rescue using physiologically relevant levels of miR-BART6, e.g., expressed from a lentivector.

   <u>Response:</u>
   Perhaps we did not make clear that relevant experiments pointed out by the reviewer were in fact carried out. We investigated the function of miR-BART6 in EBV-positive GM607 lymphoblastoid, Daudi and Mutu I and III BLs, and C666-1 NPC cells by using the miR-BART6-5p antagomir. We revealed the Dicer targeting function of miR-BART6-5p. The cell lines investigated here express a wide range of miR-BART6-5p levels (physiologically relevant levels), and we demonstrated that the Dicer expression is inversely regulated by the miR-BART6-5p levels.

2. Experiments using RNAi to examine the role of ADAR1 in miR-BART6 function need to be performed, as originally proposed in Aim 1.

   Response:
   Although we have not conducted the ADAR1 knockdown experiment suggested by the reviewer, we recently obtained interesting data on the relationship between miR-BART6-5p, Dicer, and ADAR1 expression levels (**Fig. 1**). We conducted qRT-PCR screening for EBV infection (detection of EBER1 non-coding RNA) using commercially available human breast tumor RNA samples (OriGENE, 20 samples: 10 each of samples derived from Stage I metastasis-negative and Stage III metastasis-positive breast tumors). First, we found approximately 85% EBV infection rate, which is consistent with previous reports. Second, there is a trend of higher levels of miR-BART6-5p in Stage III specimens as compared to Stage I specimens (**Fig. 1A**). Finally, we noted also that there is a trend of lower expression levels of Dicer and ADAR1 in Stage III specimens as compared to Stage I specimens (**Fig. 1B, 1C**). These new results provide strong support for our hypothesis that ADAR1 antagonizes the miR-BART6-5p function and consequently upregulates Dicer expression.

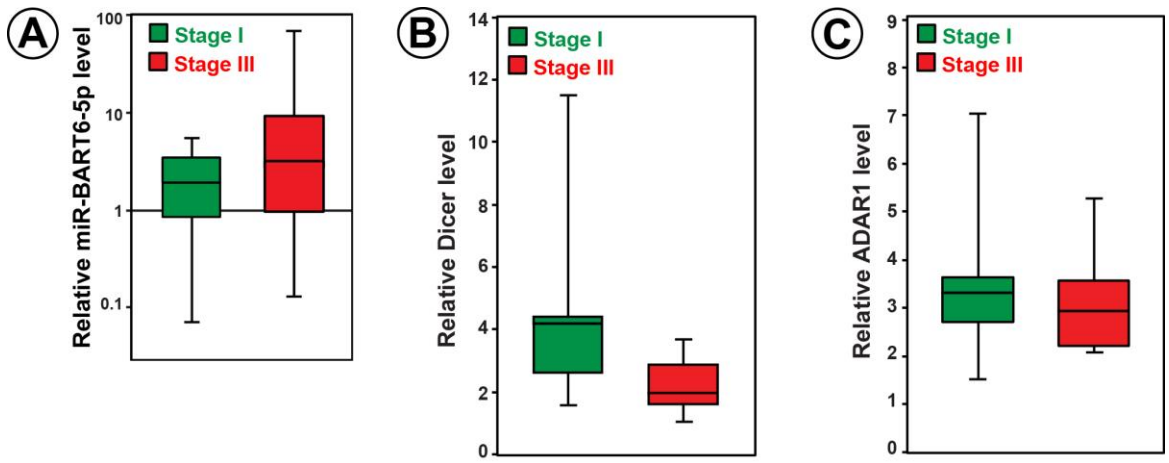

Fig. 1. Altered expression levels of miR-BART6-5p, Dicer, and ADAR1 in Stage I and Stage III breast cancer specimens. miR-BART6-5p (**A**), Dicer (**B**) and ADAR1 (**C**) expression levels determined by qRT-PCR are compared between Stage I and Stage III breast cancer specimens by box-and-whisker plot analysis. The median performance measure divides the box; while the upper boundary of the box corresponds to the 3rd quartile and the lower boundary corresponds to the 1st quartile. The minimum and maximum values extend as bars from the bottom and top of the box.

3. Experiments using physiological levels of miR-BART6 expression need to be performed to examine how miR-BART6 affects Dicer expression.

   Response:
   See our responses in the previous sections (**Fig. 1**).

Reviewer 2:
None

Reviewer 3:
There is a discrepancy between the stated aims and the actual specifics of what the investigator proposed to do, which were somewhat narrower than stated in the aims. In the aims, the investigator stated that she will determine the significance of pre-MiR-BART6 editing and miR-BART6 on latency and lytic replication, but she stopped short of fully realizing these outcomes by only looking at changes in latent or lytic viral gene RNA expression. So while the details of what she proposed to do were achieved, the significance of the findings remains unclear. For example, the data indicate that miR-BART6 may play an important role in suppressing the expression of some latency genes, such as EBNA2. However, this was only measured at the level of RNA, and there is no indication that this had any effect on expression of the EBNA2 protein. Moreover, it remains unknown whether any of the changes in gene expression as a result of miR-BART6 expression (or editing) affect the actual growth or viability of EBV-associated tumor cells. The significance and importance of these studies could be enhanced if the investigators can develop functional assays to address this last issue. The investigators need to publish the results generated from this grant proposal.

Response:
I admit that we did not conduct more in-depth investigation on miR-BART6-5p functions in control of EBV replication and latency as planned originally. This is due to our exciting and unexpected findings on direct ADAR1-Dicer interactions revealed during the tenure of this grant support (Ota et al. 2013 *Cell* 153: 575-589). We found that ADAR1 forms a complex with Dicer to promote miRNA processing, RISC loading, and RNA silencing. Our results indicate that ADAR1 not only edits pre-miR-BART6 and antagonizes miR-BART6-5p function (suppression of Dicer) but also directly promotes Dicer functions, which in turn affect EBV replication and latency.

All publications, original research papers and reviews related to the mission of the Cure grant support, are listed below.

Original Papers:
Tsuruoka, N., Arima, M., Yoshida, N., Okada, S., Sakamoto, A., Hatano, M., Satake, H., Arguni, E., Wang, J., Yang, J., **Nishikura, K.**, Sekiya, S., Shozu, M., and Tokuhisa, T. 2013. ADAR1 protein induces adenosine-targeted DNA mutations in senescent Bcl6-deficient cells. *J. Biol. Chem.* 288: 826-836.
Ota, H., Sakurai, M., Gupta, R., Valente, L., Wulff, B-E, Ariyoshi, K., Iizasa, H., Davuluri, R.V., and **Nishikura, K.** 2013. ADAR1 forms a complex with Dicer to promote microRNA processing and RNA-induced gene silencing. *Cell* 153: 575-589.
Morita, Y., Shibutani, T., Nakanishi, N., **Nishikura, K.**, Iwai, S., and Kuraoka, I. 2013. hEndV is a ribonuclease specific for inosine-containing dsRNA. *Nat. Commun.* 4: 1-10.

Reviews:
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.

Valente, L., Kawahara, Y., Zinshteyn, B., Iizasa, H., and **Nishikura, K.** 2012. Post-transcriptional gene regulation by an Editor: ADAR and its role in RNA Editing. Post-transcriptional gene regulation: RNA processing in eukaryotes. (Ed. Jane Wu) Wiley-VCH book, pp41-81.

Mallela, A. and **Nishikura, K.** 2012. A-to-I editing of protein coding and noncoding RNAs. *Crit. Rev. Biochem. Mol. Biol.* 47: 493-501.

Nishikura, K. 2013. A-to-I RNA editing in human disease: Topical Talks: Talks of interest in the biomedical and life sciences, The Biomedical & Life Sciences Collection, Henry Stewart Talks Ltd, London (online at http://hstalks.com/?t=BL1003208-Nishikura).

Slotkin, W. and **Nishikura, K.** 2013. RNA editing in disease and potential for therapy. *Genome Med.*, in press.

Nishikura, K., Sakurai, M., Ariyoshi, K., and Ota, H. 2013. Antagonistic and stimulative roles of ADAR1 in RNA silencing: an editor's point-of-view. *RNA Biol.*, in press.

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: We plan to continue our research efforts, aiming for an outstanding outcome and impact on public health. I am very grateful for the Cure Grant support, which allowed us to secure a new NIH R01 grant (1 R01 CA175058: Control of Breast Cancer Metastasis by Epstein-Barr virus microRNA).

Project Number: 1087904
Project Title: Laboratory Renovation Research Infrastructure
Investigator: Altieri, Dario

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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*):

<u>Reviewer 1:</u>
None

<u>Response:</u>
We appreciate the time and effort of the reviewer in evaluating our proposal. We are delighted that no concerns were raised as part of the review process.

<u>Reviewer 2:</u>
It would have been useful to know in evaluating this proposal whether their recruitment was successful.

Apparently their lead candidate had visited four times and was pleased with progress. They anticipated finalizing recruitment by early 2013. Did a new investigator arrive in early 2013?

<u>Response:</u>
We appreciate the comments of the reviewer. Indeed, we were successful in the recruitment of Dr. Dmitry Gabrilovich, M.D., Ph.D., to the Wistar faculty, effective April 15, 2013. Dr. Gabrilovich joins The Wistar Institute from the Moffitt Cancer Center in Tampa, Florida, and brings to our institution an internationally-recognized program in translational tumor immunology. This is especially focused on the immunosuppressive role of Myeloid-Derived Suppressor Cells (MDSC), a discrete cellular subset of demonstrated importance in reducing the efficacy of the immunologic response to tumors in patients. The renovation of the first floor of the Wistar 1894 building, as supported by the present application, proved instrumental to successfully complete the recruitment of Dr. Gabrilovich and bring to Wistar his innovative research program. As a Wistar faculty member, Dr. Gabrilovich has been appointed to the rank of Professor and is the recipient of the Davis Chair in Cancer Research.

Supported by the new experimental setup, we anticipate that Dr. Gabrilovich will lead a successful research program in mechanisms of tumor-associated immunity.

Reviewer 3:
This renovation project was well planned and executed. This new space helped to recruit a senior researcher in cancer research. The Wistar Institute match helped to move the project forward.

Response: We appreciate the time and effort of the reviewer in evaluating our proposal. We are delighted that no concerns were raised as part of the review process

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:

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Response: