

# **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 (1.84)

**Project Rating:**

| <b>Project</b> | <b>Title</b>   | <b>Average Score</b> |
|----------------|--|----------------------|
| 0989801        | Tirapazamine and a Novel Drug in the Control of Hypoxic Human Colon Cancer Cells | Favorable (1.67)     |
| 0989802        | The Role of IDO in B Cell Activation and Memory                                  | Favorable (2.00)     |

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**Project Number:** 0989801  
**Project Title:** Tirapazamine and a Novel Drug in the Control of Hypoxic  
Human Colon Cancer Cells  
**Investigator:** Ayene, Iramoudi

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*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:

There were three specific aims proposed to assess the combination of hydroxyethyl disulfide (HEDS) with tirapazamine as a rational combination for the treatment of cancer. In the first specific aim, the combination was tested across a broad range of doses and with modulation of oxygen and glucose levels as originally proposed. A range of treatment durations was proposed, but no data were presented indicating this was done. In the second specific aim, the effects of tirapazamine on HEDS metabolism were determined as proposed, as well as the effects of glucose and hypoxia. Finally, in the third specific aim, the effects of HEDS, tirapazamine and hypoxia on glutathione (GSH) oxidation were examined. In these studies, the investigators were faced with some unexpected results, and the studies were altered accordingly (e.g., higher concentrations of tirapazamine). The data are generally sound, although some graphs are presented without error bars, making interpretation of significance difficult. Unfortunately, the results of the studies did not support the original concept that HEDS would specifically synergize with tirapazamine in hypoxic tumor cells thus widening the therapeutic window.

**Strengths:** The hypothesis is well-conceived. Most of the proposed studies were done. Data are generally robust.

**Weaknesses:** Time-course studies were not done. There was a lack of effect at low doses of tirapazamine. It is not clear if *in vitro* systems recapitulate the complexity of the tumor microenvironment.

Reviewer 2:

On the whole, the project met the stated objectives. The methods and analysis were appropriate. There was sufficient data and information provided to indicate that the project met its objectives or made acceptable progress.

Reviewer 3:

**Strengths:** This project made reasonable progress addressing some of the key points raised in three specific aims, although the proposed experiments were partially accomplished. The results, by and large, confirmed, previously published observations that HEDS detoxification was strongly blocked in a glucose-free condition and Tirapazamine (TPZ) had pronounced toxicity at

higher doses ( $\geq 10 \mu\text{M}$ ). However, this study's data suggest that there is no synergistic effect between TPZ and HEDS under hypoxic or normoxic conditions.

Weaknesses: The project lacks a strong rationale or a mechanistic model. The choice of 1% O<sub>2</sub> as the hypoxia condition is not clearly justified. There is a lack of details (statistical analysis of data in graphs and experimental details in figure legends) for proper appreciation of the results. Some of the proposed experiments, such as different cell numbers and treatment times, were not performed.

***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:

The hope was that HEDS would synergize with tirapazamine in hypoxic tumor cells, thus enabling tirapazamine to be used at lower doses ameliorating some of the side effects seen in the clinic. The current studies required high dose tirapazamine, and there was no difference between normoxic and hypoxic cells. The current results, therefore, do not support the original concept. Furthermore, these concepts were only tested in cell culture systems, and no *in vivo* animal studies were done. Therefore, any potential translation to clinical application would be many years away.

Strengths: The hypothesis is directed at improving the use of tirapazamine for patients.

Weaknesses: The original concept is not supported by the data. There is a lack of *in vivo* data to support the concept.

#### Reviewer 2:

The impact of this project lies in understanding the interaction of tirapazamine in hypoxic cancer cells. Although not particularly novel or innovative, the work funded was sound and the group undertook the study exactly as funded. Future plans include translating the findings to other tumor types.

#### Reviewer 3:

The impact of this project appears to be limited, largely because the results showed no significant synergy between HEDS and TPZ, as shown by a flat HEDS dose curve at a given dose of TPZ. Perhaps combining HEDS+TPZ with interventional radiology (IR) or chemotherapy may be worth considering 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:

It is not clear that other funds were leveraged to perform this study. The principal investigator (PI) listed a \$100K grant from NIH that is pending and is based on the study results.

Strengths: External funding is being sought.

Weaknesses: The level of funding being sought is modest.

Reviewer 2:

There is a pending application to NIH for \$100K using the preliminary data from this grant.

Reviewer 3:

One NIH application was submitted in June 2010, but it is not yet funded. Two other projects/applications are intended.

***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:

A single manuscript has been submitted, and others are planned. However, the subject of the manuscript (a radiation combination with HEDS) is not the work funded by the current grant (tirapazamine and HEDS).

Weaknesses: The submitted manuscript does not contain data resulting from the funded work. Productivity was marginal.

Reviewer 2:

There was one paper submitted. This is a weakness; it would have been nice to have seen more papers, etc.

Reviewer 3:

One manuscript was submitted to *Radiation Research* in September 2010.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

No clear improvements to infrastructure were made as a result of this grant. The funding did help support an undergraduate student.

Strengths: Support for training of an undergraduate is a strength. The project helped the PI continue his laboratory.

Reviewer 2:

Enhancement was modest. It was a small grant and did help a new PI in training and development.

Reviewer 3:

One undergraduate student was involved in this project.

***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:

The PI established a new collaboration with Dr. DeNittis.

Strength: One new collaboration was fostered by the grant.

Weakness: The collaborator is internal to the Lankenau Institute for Medical Research.

Reviewer 2:

The PI established a new collaboration with Dr. Albert DeNittis.

Reviewer 3:

The PI has established a collaboration with Dr. Albert DeNittis, Chief of Radiation Oncology, Lankenau Hospital. However, Dr. DeNittis's contribution or involvement was not clearly stated.

## ***Section B. Recommendations***

### **SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

#### Reviewer 1:

1. Productivity from the funding was marginal, with a single manuscript and a single small-scale grant submitted. Moreover, the subject of the submitted manuscript (radiation + HEDS) does not seem to match with the funded project (tirapazamine + HEDS), and it is not clear from the title whether the submitted grant truly resulted from the funded project. This discrepancy should be clarified.
2. The data do not support the original concept that tirapazamine and HEDS would synergize in hypoxic tumor cells. The PI should clarify whether the data disprove the concept, or whether the experimental systems are limited in their ability to model a hypoxic tumor. How will these results be followed up? The PI indicates that tirapazamine will be tested at higher doses; however this will engender concerns about toxicity.
3. The work does not appear to have enhanced external collaboration, since the only listed new collaborator is internal to the Lankenau Institute for Medical Research. The PI should expand collaboration beyond the local institution.

#### Reviewer 2:

None.

#### Reviewer 3:

1. This project would benefit from a more mechanism-oriented hypothesis or model for designing appropriate experiments to determine the interactions between the HEDS- and TPZ-regulated pathways that affect cell survival or response to therapy.
2. The design of hypoxia experiments should take into consideration that half maximum OER occurs at approximately 3 mmHg or 0.5% O<sub>2</sub>. Other controls should be included to confirm hypoxia responses in treated cells.
3. Since HEDS does not appear to synergize with TPZ for cell killing, it may be worth considering using HEDS and TPZ together with IR or chemotherapy under normoxia or hypoxia.

### ***Generic Recommendations for Lankenau Institute for Medical Research***

#### Reviewer 1:

Overall, the PI performed most of the studies as originally proposed. The productivity was marginal although perhaps not out of line with what is to be expected from a pilot funding mechanism. The results are not sufficiently promising to warrant further funding.

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**Project Number:** 0989802  
**Project Title:** The Role of IDO in B Cell Activation and Memory  
**Investigator:** Mandik-Nayak, Laura

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*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:

Results: The data presented indicate that in the IDO knockout mice, the serum IgG1 titers did not increase during the early phase of the secondary response but did so in the late phase. This delayed response was not observed when CFA was used instead of alum as adjuvant. In addition, loss of IDO activity does not inhibit B cell responses to NP-CGG in alum. Figure 2 is not interpretable as presented.

Comments: The application was generated from the principal investigator's observation that IDO paradoxically drives B cell-mediated autoimmunity (*Journal of Immunology*, 2009, 182: 7509-7517). The hypothesis was that IDO has a direct effect on B cell response in adaptive immune response. The major difficulty in the postulation of the hypothesis is that the data in the *Journal of Immunology* paper could have easily been explained by the effect of IDO on T cells, dendritic cells, and inflammation in general. Thus the stated hypothesis was not well-supported by the data. The results presented for this review support the above assertion in that the data do not support the stated hypothesis.

The use of serum titer as a biomarker for B cell memory pool is not appropriate. The use of PFC assay is recommended.

Strengths: The principal investigator (PI) is well-trained and has been moderately productive.

Weaknesses: The stated hypothesis is not well-formulated in that it is difficult to demonstrate specific effects on the B cells in view of the broad metabolic effect of IDO on a variety of cells and the inter-connectedness of various cell types in the adaptive immune response.

The data have been over-interpreted. The measurement of secondary response by serum titers may not reflect the memory pool. The observed effect is antigen- and adjuvant-dependent and may not have general applicability.

Reviewer 2:

The stated objectives of this project were: 1) to determine the role of IDO in the development of B cell memory; and 2) to define the mechanism by which IDO drives B cell activation in

response to foreign antigens. Some progress was made toward each of these objectives. Blockade of IDO by genetic mutation or pharmacological treatment was demonstrated to cause significant reductions in antibody production following secondary immunization, a marker of B cell memory responses. Affinity maturation, lymphoid follicle formation, and isotype switching were also affected by the absence of IDO. Thus progress was made in Aim 1 to demonstrate that IDO plays a role in B cell memory development.

In Aim 2, a comparison was made between different immunization regimes and the production of antibodies. Some progress was made in defining different levels of control mediated by IDO depending on the antigens and adjuvants used.

The main weaknesses of this project center on inadequate investigation of the mechanisms by which IDO mediates its effects. This may be in part due to the experimental design and methods being more focused on descriptive aspects of the B cell response rather than mechanistic aspects. The researchers followed the strategic plan faithfully and presented sufficient data to demonstrate progress toward the stated goals. However, many questions remain in the research design and interpretation of the results that are insufficiently addressed. Secondary antibody responses, isotype switching and affinity maturation toward the antigen used in Aim 1 are not solely dependent on activation of B cells, but are also highly dependent on T cell activation. The researchers did not analyze any aspect of T cell responsiveness in this system, which does not seem justified in light of the well-characterized role of IDO in skewing T cell responses. Of particular interest in consideration of the information presented would be the impact of IDO blockade on the presence and activation of T follicular helper cells and other populations involved in B cell maturation. The concept of how varying the antigen and adjuvant regimes in Aim 2 would have resulted in information about the mechanism of action of IDO is insufficiently developed in the research plan and not addressed in the progress report. Also not discussed are the major differences between the antibody responses elicited by alum (preliminary data) and Titermax (Figure 4), which the researchers describe as being nearly equivalent in their mechanism of action. It would seem plausible that the relative lack of effect of IDO blockade in systems using different adjuvants (Titermax, CFA) or a different antigen (CGG) with alum has to do with the activation threshold. The efficacy of IDO in the NP-KLH alum model as well as in the spontaneous arthritis model that does not involve adjuvant could be due to low-level B cell activation that could be more dependent on help from T cells or other non-B cell intrinsic effects. Thus the project yielded useful preliminary data suggesting that IDO is involved in B cell activation and maturation but fell short of providing a direct mechanism of action.

### Reviewer 3:

The stated project aims were to determine the role of indoleamine 2,3-dioxygenase (IDO) in B cell memory *in vivo*, using the K/BxN murine model of rheumatoid arthritis (RA) as well as adjuvant injections into control and IDO knockout (KO) mice to look at antibody titers and isotype class switching. One other model that was utilized inhibited IDO using a specific inhibitor 1-methyl-tryptophan (1MT). The investigators successfully showed that IDO has a critical role in B cell activation and memory.

The research design and methods were appropriate for the study proposed. The data obtained in the final report were sufficiently developed and fully answered the original questions proposed.

No changes in the project were noted.

***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:

The project adds support to the thesis that IDO has an immunomodulatory effect in immune responses. The contribution is minor. It is not expected that a beneficial impact will be significant irrespective of the budget.

#### Reviewer 2:

The project provided new insight into the complicated roles of IDO in immune regulation, as well as justification for further study. The potential impact of this project will depend in large part on whether or not IDO blockade becomes a clinical goal. Given the well-established role of IDO in diminishing the immune response to tumors, it is rather likely that clinical trials will be performed involving blockade of IDO and that these will show some efficacy. The current project would suggest that IDO blockade will affect antibody responses toward protein antigens encountered during or after treatment. This may result in decreased clearance of infectious microorganisms and significant negative side effects. The benefit of this project toward treatment of autoimmunity is less clear, since patients who present with clinical symptoms most often already have significant levels of memory B cells producing highly evolved antibodies. The data would suggest that the point of action of IDO blockade would have already passed in these patients. Thus, the project provided useful insights into the potential outcome of clinically relevant treatments mostly outside the realm for which it was originally intended.

#### Reviewer 3:

These findings are important and could be used to develop promising therapeutics for diseases such as RA and lupus and rheumatologic inflammatory diseases that have altered B cell responses and antibody expression. Interestingly, IDO inhibition did not seem to alter T cell activity in the investigators' model (although this was not specifically examined). However, the investigators examined the effects of inhibiting B cell memory with a pharmacologic in a relevant animal model of RA. If similar results could be obtained in an RA patient population, IDO inhibition could be a novel therapeutic approach for treating diseases with altered B cell activity.

The project objectives were met, and the investigators used this data to compete successfully for an NIH R01 grant.

***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:

Two applications were stated. One application was submitted to the Alliance for Lupus Research (ALR), and the other was to NIH. The application to ALR was not successful; the application to NIH was awarded on May 11, 2010. It is doubtful that the NIH grant was awarded on the basis of the data funded by this grant.

Reviewer 2:

The researchers have been granted an NIH R01 to study the role of IDO in mitral valve complications related to rheumatoid arthritis.

Reviewer 3:

As stated above, the researchers competed successfully for NIH funding at the R01 level. They also applied for an NIH R21 examining IDO inhibition in mitral valve disease (a comorbidity in RA); however, this application did not appear to receive 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 peer-reviewed publications, licenses, or commercial development opportunities have been submitted or filed. The publications listed are not related to this grant.

Reviewer 2:

The researchers state that they are planning to submit the results of this project as part of a future article.

Reviewer 3:

There are sufficient data/findings for a solid peer-reviewed manuscript, but none were noted. Also, no commercial development, licenses, or patents were listed.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

One pre-doctoral student was supported by this grant.

Reviewer 2:

The project involved the work of one undergraduate student. No new researchers were recruited to the institution to perform this work. No capital improvements were made. The researchers state that new collaborations were formed within the institution, but details are not provided. The NIH R01 funding that was leveraged as a result of these studies could be expected to provide funds for recruitment of research personnel and capital improvements.

Reviewer 3:

There were no improvements to infrastructure listed. The PI listed herself, a research assistant, and a student intern as the only investigators on the project. Funds were used to support only those listed above (no master's, pre-doctoral or post-doctoral students were listed). No out-of-state researchers were listed.

***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:

The project did not lead to collaboration with research partners outside the institution or new involvement with the community.

Reviewer 2:

This was not a stated goal of the initial research project and therefore was not expected.

Reviewer 3:

No out-of-state researchers were listed and no additional collaborators were mentioned in the current proposal.

***Section B. Recommendations***

**SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

Reviewer 1:

The PI should re-think the hypothesis. It may be difficult to seek evidence to support the hypothesis. The experimental design may not be appropriate, and she should guard against over-interpretation. Although the NIH application was successful, she should think carefully about the direction of the research so that she may be able to renew her R01 competitively.

Reviewer 2:

1. The project lacked mechanistic data regarding the role of IDO in B cell memory formation. A likely mechanism affecting B cell memory could have to do with activation of T follicular helper cells. Analyze parameters related to T<sub>FH</sub> cells (histological staining, flow cytometry for CXCR5+ T cells, IL-21 production, etc.). Additionally, consider setting up culture systems of purified B cells from primary immunized mice with anti-CD40 antibodies and/or

cytokines in the presence or absence of IDO to show direct effects on B cell activation, antibody production and maturation.

2. The differences between alum and Titermax are not addressed. It seems likely that NP-KLH Titermax overcame the effect of IDO that was seen with NP-KLH alum treatment by being a stronger adjuvant. This could be investigated in side-by-side comparisons, with an analysis not only of B cell activation but also of T cell and cytokine involvement. This could have important implications for patients being treated with IDO blockers who are in need of immunizations against pathogenic microorganisms.
3. The project demonstrates the effects of IDO blockade on establishing a memory B cell response but does not address maintenance of the memory response. This would be important for determining whether IDO blockade could be useful in patients with established auto-antibody-mediated diseases. Modify the treatment regimen to begin instillation of IDO blocker after memory B cell formation, and follow maintenance of antibody titers.
4. The project does not address B cell responses to naturally occurring antigens. A potentially important contribution of this work could be an understanding of the side effects of anti-IDO treatment on community acquired infections. To address this, experiments could be done using viral, bacterial, and/or fungal infections of mice treated or untreated with IDO blockers.
5. The research project does not appear to emphasize collaboration. Many of the recommendations made above could be aided by establishing collaborations within and outside of the institution. It is expected that these would broaden the scope of the research and give new perspectives on the planning and interpretation of results.

Reviewer 3:

1. The weakness of this study is primarily in the characterization of the K/BxN arthritis model. Since the KRN gene is expressed on only one allele (homozygotes cannot survive), gene typing of the mice should be confirmed to eliminate the possibility of homozygous negative mice being included in the study (this could severely skew the results and was not discussed). In addition, use of only three-week-old mice that were just off weaning was shown. Do older mice (i.e., six to eight weeks) show reduced arthritis development to 1MT treatment? If so, reversal of the arthritic phenotype may be a powerful finding and of significant interest, since most, if not all, RA patients initially present at the later stages of RA development. Also, measuring mouse joint homogenates for pro-inflammatory cytokine expression would strengthen the findings. Finally, having the K/BxN tissues scored by histology for leukocyte infiltration, as well as vascularity and/or bone destruction, would be helpful and would validate the model and the effects observed by inhibiting IDO both pharmacologically and by gene deletion.
2. The PI may be aided by additional collaborators; none are listed either internally or externally.

## ***Generic Recommendations for Lankenau Institute for Medical Research***

### Reviewer 3:

All in all, this was a very interesting study using sophisticated animal models to study B cell activity and IDO inhibition in RA models. Only minor weaknesses were noted. Lastly, it is highly recommended that the PI publish the results, since none were listed pertaining to this application.

## ***ADDITIONAL COMMENTS***

### Reviewer 1:

The PI is well-trained and has been moderately productive. The project adds support to the thesis that IDO has an immunomodulatory effect in immune responses. The contribution is minor. One pre-doctoral student was supported by this grant.

The stated hypothesis is not well-formulated in that it is difficult to demonstrate a specific effect on B cells in view of the broad metabolic effect of IDO on a variety of cells and the inter-connectedness of various cell types in the adaptive immune response.

The data have been over-interpreted. The measurement of secondary response by serum titers may not reflect the memory pool. The observed effect is antigen- and adjuvant-dependent and may not have general applicability.

It was stated that two applications were submitted as a result of this grant. One application was submitted to the Alliance for Lupus Research (ALR), and the other was submitted to NIH. The application to ALR was not successful. The application to NIH was awarded with a start date of July 1, 2010. It is doubtful that the NIH grant was awarded on the basis of the data generated by this grant.

No peer-reviewed publications, licenses, or commercial development opportunities have been submitted or filed. The publications listed are not related to this grant.

The project did not lead to collaboration with research partners outside the institution or new involvement with the community.

### Reviewer 3:

This was a strong project that used state-of-the-art *in vivo* models, such as K/BxN murine arthritis, to show that IDO inhibition can reduce arthritis development. The strengths include the well-published PI, the use of murine gene KO mice, and the *in vivo* adjuvant studies. The researchers showed the involvement of B cells in these models, determined how IDO inhibits B cell memory and antibody production, and related this to disease attenuation in an acute model of RA. These findings could reach far beyond RA, since diseases such as lupus and cancer may respond similarly to IDO inhibition. This was a conceptually interesting study with many strengths, and only minor weaknesses.