

**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 (2.00)

**Project Rating:**

<b>Project</b>	<b>Title</b>	<b>Average Score</b>
1085301	Selective and Therapeutic Elimination of Cells that Produce Hepatitis B Virus	Favorable (2.00)

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**Project Number:** 1085301  
**Project Title:** Selective and Therapeutic Elimination of  
Cells that Produce Hepatitis B Virus  
**Investigator:** Block, Timothy

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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:

Strengths: The researchers demonstrated a proof-of-concept for identification of compounds with 'selective' killing of hepatitis B virus (HBV)-replicating hepatocytes; provided internship opportunities to undergraduate students from universities within Pennsylvania; and, strengthened community outreach programs.

Weaknesses: The proposed objectives described in the original application were completely altered without an explanation; 'selective' killing of the HBV-producing hepatocytes by Oubain and BH3 domain mimetics was very poor.

##### Reviewer 2:

The overall scientific goal of this project was to identify new molecules that kill hepatitis B virus (HBV)-infected, but not uninfected, hepatocytes. This is an interesting and novel approach for anti-HBV therapy, as it has the potential to selectively eliminate virus-producing cells and therefore cure HBV infection.

The proposed research design and methods would have been adequate to address the project objectives. However, the data provided in the final progress report bear little resemblance to what was described in the original proposal. For example, the original plan was to evaluate statins and polyketides as anti-HBV drugs, while the progress report describes experiments with Na-K ATPase ion channel inhibitors and BH3 domain mimetics. No explanation is provided as to why this change was made. Furthermore, the amount of data provided in the progress report (what appear to be the results of two individual experiments) is inadequate in relation to the budget for this project.

##### Reviewer 3:

More than 350 million individuals are currently infected with hepatitis B virus (HBV), and HBV accounts for 1.2 deaths annually. Despite recent advances in treatment of chronic HBV infection, the progress is hindered by the inability to eliminate highly stable HBV covalently close circular DNA (cccDNA). Progress in developing an effective strategy to eliminate cccDNA is hindered by poor understanding of molecular mechanisms controlling HBV replication, including cell-

cycle related transcriptional regulation of HBV and interaction between transcriptional factors and viral enhancer/promoter sequences. This is a well-written and an interesting application, which proposes to develop a new approach to eliminate infected cells. The proposed research hopes to provide effective ways to treat chronic HBV infection and identify new chemical leads for future antiviral development.

***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 aimed to identify effective therapies for treatment of viral hepatitis B, one of the unmet medical needs in global health. Dr. Block successfully recruited three undergraduate students from Pennsylvania state universities to test a highly innovative hypothesis that HBV-infected and replicated hepatocytes can be selectively killed by small molecule drugs. Both Oubain and ABT-737 were found to have two to three times of selectivity in killing HBV-producing hepatoma cells compared to control cells that do not produce HBV. However, the selective killing of HBV-producing cells was marginal. It is very challenging to discover and develop effective drugs to completely eliminate HBV-replicating cells. The studies described in the final report appeared to be completely different from those proposed in the original application. It is not clear why Dr. Block and his team did not follow through with those proposed studies instead of shifting to less selective compounds.

#### Reviewer 2:

In a broad sense, the hypotheses explored in this proposal have the potential to have a wide impact on public health, since the general approach may not only be effective against HBV but may also be applied to other viral pathogens. However, the beneficial scientific and health impact of the specific work described in the progress report is low, since too little information is provided, too few experiments were performed, and future plans are not adequately addressed.

#### Reviewer 3:

**Strengths:** This is a well-written and organized report of accomplished work. The strength of the proposed work is the ability to utilize well-developed tools and environment to explore an innovative approach to treat chronic HBV infection. Overall, clinical significance is reasonably high, since current therapies are failing to eliminate HBV. The report summarizes work completed by the end of the grant award period. The PI reports identification of several potential candidates with selective ability to target infected cells.

**Weaknesses:** The proposal's major weakness is the premise that by selectively killing cells infected with actively replicating HBV, cells harboring HBV cccDNA also will be eliminated. This is highly unlikely, since no cell "modifying" proteins are produced in cells harboring cccDNA. Furthermore, HBV replication is cell cycle dependent, and both laboratory and clinical evidence suggests inverse correlation between cell activation/proliferation and HBV replication. As a result, any event that results in cell division/proliferation may eliminate HBV infection as reflected by near universal recovery from acute/severe hepatitis B in a competent host. It is also

well-known that in immunosuppressed subjects HBV infects almost every single cell (see early studies, prior to introduction of PI, in subjects with HIV). The problem with utilizing these ideas is in developing therapies that will produce “controlled” cell death with induction of cell regeneration/proliferation without killing the host. Hypothetically, hepatectomy may work but it is highly unlikely that this approach will be utilized. In summary, it is highly unlikely that “targeted” cytotoxic regimens will be utilized to treat chronic HBV infection.

From a technical point of view, one can consider that utilizing RNAi or other approaches, including known non-toxic antivirals, to suppress productive HBV in controlled experiments will provide “cleaner” data by eliminating cell divergences.

***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:

This project failed to obtain any additional funding or result in submission of a grant application. It appeared that the approach to identify selective compounds to eliminate HBV-producing hepatocytes may not be feasible.

#### Reviewer 2:

No grant applications were submitted, and only a vague statement about future funding plans and expansion of the research is provided. This is somewhat surprising, since it appears that promising preliminary results with some compounds were obtained.

#### Reviewer 3:

It is not clear from the work accomplished how the PI proposes to address elimination of HBV in extrahepatic sites.

***Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted/filed?***

### ***STRENGTHS AND WEAKNESSES***

#### Reviewer 1:

The project did not result in any peer-reviewed publication, license, patent or commercial development opportunities.

#### Reviewer 2:

No peer-reviewed publications, licenses, patents or commercial development materialized from this work. A general statement regarding expected future publications and presentations is provided, but the specifics are unclear.

Reviewer 3:

None

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

The project provided internship opportunities to three undergraduate students from universities in Pennsylvania, although it did not obtain sufficient funding to improve infrastructure or recruit new researchers to the institution.

Reviewer 2:

A significant strength of this project was that the funding went in part to support the research projects of undergraduate research interns. Training the next generation of scientists is an extremely important goal. Although the outcome of these experiments is modest, the future impact could be quite large if one or more of the supported students choose to pursue a career in science as a result of the internship experience.

Reviewer 3:

Yes.

***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 provided excellent opportunities to faculty members at the PI's institution to interact with various universities in the community. In addition, it attracted talented undergraduate students to participate in biomedical research. The project served as an excellent platform for community outreach.

Reviewer 2:

Bringing undergraduate students to the institute to complete research internships represents a significant and important involvement with the community.

Reviewer 3:

Yes.

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

### **SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

#### Reviewer 1:

1. It is not clear why the PI gave up those specific studies proposed in the original application. It would be much appreciated if the PI could provide a reasonable explanation on the modification and alteration of the original research plans.
2. Oubain and ABT-737 did not result in significant selectivity in killing HBV-replicating cells. Their selective killing activity should be corroborated by additional experimentation.
3. Future studies should follow through with those lead compounds described in the original application using more reliable cell culture systems other than the HepG2.2.15 cell clone.
4. The PI should be more cautious to further pursue the approach proposed in the original application. It may not be feasible to selectively kill HBV-producing cells. The rationale to selectively kill HBV-producing cells was not clearly stated in the original application.
5. Alternative approaches should be considered for searching effective therapies to treat hepatitis B.

#### Reviewer 2:

It is not clear why the research proposed in the original plan was not pursued, but rather, different classes of drugs instead were analyzed. An explanation for this change should have been provided. Furthermore, why does it appear as though so little was accomplished? Was this because the work was primarily carried out by undergraduate research interns? If this is the case, then this weakness is understandable.

#### Reviewer 3:

It is highly unlikely that “targeted” cytotoxic regimens will be developed. Furthermore, it will be nearly impossible to generate drugs with controlled cell killing without risk of killing the host. Therefore, this approach most likely will not result in new therapies for hepatitis B but may provide some interesting information which may be utilized for future drug development.