

# Hepatitis B Foundation

## Annual Progress Report: 2008 Formula Grant

### Reporting Period

July 1, 2009 – December 31, 2009

### Formula Grant Overview

The Hepatitis B Foundation received \$2,537 in formula funds for the grant award period January 1, 2009 through December 31, 2009. Accomplishments for the reporting period are described below.

### Research Project 1: Project Title and Purpose

*Characterizing the Antiviral Activities of Small Interferon-Stimulated Genes against Hepatitis B Virus* - Interferon-alpha is currently used to treat people with chronic hepatitis B (HBV), to reduce viral activity and prevent liver damage and liver cancer. However, response rates are moderate, and there are many side effects. It is anticipated that this research will ultimately lead to development of more finely targeted Interferon therapy with improved long-term response rates and reduced side effects. The research will be conducted at the Hepatitis B Foundation and its research affiliates at the Pennsylvania Biotechnology Center of Bucks County, by select undergraduate students during a summer internship. In addition to studying promising new methods for treatment of chronic HBV, this project encourages Pennsylvania students to seek careers in biomedical research, increasing the future pool of biomedical researchers in the state.

### Duration of Project

1/1/2009 - 12/31/2009

### Project Overview

Objective 1: To reduce the burden of chronic hepatitis B and its associated liver disease, including liver cancer, through the identification and development of successful treatment methods.

Specific Aim 1A: Characterizing the antiviral activities of small Interferon-Stimulated Genes against hepatitis B virus (HBV).

Objective 2: To expand and diversify the future pool of biomedical researchers in Pennsylvania.

Specific Aim 2A: To train and encourage young investigators, with an intensive 10-week summer internship, to pursue careers in biomedical research focusing on the prevention and treatment of viral hepatitis and liver cancer.

There is currently no cure for chronic hepatitis B, and up to 25% of the 2 million Americans infected with chronic hepatitis B will develop cirrhosis or liver cancer. The currently available therapies have varying levels of long-term response and multiple side-effects, which can affect a favorable outcome for the patient. Thus, it is necessary to find new and improved therapeutic methods for treatment of chronic HBV. Interferon (IFN) alpha is currently an FDA-approved treatment for chronic HBV, used as an immune modulator. However, the molecular basis for the antiviral effects observed is incompletely understood. Understanding the relevant antiviral mechanisms of Interferon is desirable, as the pleiotropic effects of the drug are associated with considerable morbidity in many patients. It is known that Interferons turn on a group of Interferon-Stimulated Genes (ISGs), the products of which have a variety of activities that can be considered antiviral in nature.

Through this research project, student summer interns who are recruited from Pennsylvania colleges and universities will work to characterize the antiviral activities of small Interferon-Stimulated Genes against hepatitis B virus. Student recruitment will focus on minority students of Asian and Pacific Islander or African American descent, the two ethnicities in Pennsylvania that are disproportionately affected by both chronic hepatitis B and liver cancer. The results of this project will give new insight into the mechanisms by which Interferon alpha modulates an immune response against HBV, and can offer a new direction for future hepatitis B therapy. It will also expand and diversify the future pool of biomedical researchers in Pennsylvania.

### **Principal Investigator**

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### **Other Participating Researchers**

Pamela Norton, PhD - employed by Hepatitis B Foundation

### **Expected Research Outcomes and Benefits**

There are approximately 2 million Americans living with chronic HBV, and research indicates that up to 25% of them will develop cirrhosis or liver cancer, which are associated with high rates of mortality. It is expected that the results of this project will offer important insight into the antiviral mechanisms of Interferon alpha. This can lead to the development of more targeted methods for the treatment of chronic HBV that will have enhanced long-term response rates and reduced side effects. The current low to moderate long-term response rates of Interferon, coupled with the moderate to severe side effects are barriers for patients to initiating and remaining on Interferon therapy. Increasing antiviral activity and reducing side effects will help to overcome these barriers, and can ultimately translate to reduced rates of cirrhosis, liver failure and liver cancer for the 2 million Americans living with chronic hepatitis B.

## Summary of Research Completed

Objective 1: To reduce the burden of chronic hepatitis B and its associated liver disease, including liver cancer, through the identification and development of successful treatment methods.

Specific Aim 1A: Characterizing the antiviral activities of small Interferon-Stimulated Genes against hepatitis B virus (HBV).

The summer project goal was to investigate the antiviral profile of the ISG IFITM3, taking advantage of a human cell line that expresses IFITM3 in a tetracycline-inducible manner. After confirmation of inducible protein expression by immunoblot assay, the ability of IFITM3 to interfere with virus replication was tested by using a modified version of vesicular stomatitis virus (VSV), a well-characterized RNA virus. Plaque assays and flow cytometry revealed that IFITM3 over-expression did reduce viral replication and decreased the number of virus infected cells. Studies to dissect the vulnerable step in the virus life cycle demonstrated that the antiviral protein inhibited VSV envelope glycoprotein pseudotyped lentivirus entry into cells by disruption a post endocytosis step. Further studies were performed with a number of other viruses of interest.

IFITM3 did not inhibit the entry of HCV into cells. Because IFITM3 acts at an early stage of the virus life cycle, and there are no good cell-based infectivity assays for HBV, we were unable to test whether HBV entry is affected by IFITM3. However, it was found that IFITM3 inhibited the entry into cells of the flaviviruses West Nile virus and dengue virus, both important human pathogens of bioterror concern for which no treatment is currently available.

Objective 2: To expand and diversify the future pool of biomedical researchers in Pennsylvania.

Specific Aim 2A: To train and encourage young investigators, with an intensive 10-week summer internship, to pursue careers in biomedical research focusing on the prevention and treatment of viral hepatitis and liver cancer.

The 2009 Hepatitis B Foundation (HBF) summer research internship program was successfully completed. Eight undergraduate students (doubling last year's internship program) completed 100% of their summer 2009 internship (10 out of 10 weeks), and met all research requirements. The student representation was 50% female; 75% were Pennsylvania residents and 63% currently attending Pennsylvania colleges or universities.

Students spent the final 6 weeks completing the research described above, with their appointed laboratory mentors. Each student attended and presented at weekly journal clubs, laboratory "lunch and learn" seminars, and weekly seminars by visiting scientists and biotechnology experts. Special Seminar topics included "choosing biotechnology as a career path," "patenting biotechnology inventions," and "building for a cure." The students also attended weekly educational seminars given by Hepatitis B Foundation public health and outreach staff, to enhance their understanding of the public health impact of hepatitis B on a local, national, and global level. The students also learned about the Pennsylvania Keystone Innovation Zone program, with an emphasis on informing the students about the many biotechnology opportunities there are in Pennsylvania.

Faculty members and mentors evaluated each intern, and all 8 interns achieved high scores for their research skills, as well as for their presentations and journal club sessions. Each intern successfully met the goals and objectives of their summer research plan.

Student feedback was collected at the end of the internship, focusing on their experience at HBF and ideas for future internship programs. All students felt that the summer internship program was a valuable experience, and they all responded that they would highly recommend this program to other students. The structure of the internship program was particularly appreciated, as each undergraduate student was mentored by a senior scientist and also had the opportunity to interact with graduate students at different levels of study. The lectures, science lunches, seminars and journal clubs were well received. The fact that students were able to concretely see their data at the end of the summer was very appreciated by all students. A majority of students plan to continue exploring the possibility of choosing biomedical/biotechnology research as a career. Follow up will continue with the student interns through college graduation and future plans to enter a career in biomedical research.