

Hepatitis B Foundation

Annual Progress Report: 2009 Formula Grant

Reporting Period

July 1, 2010 – December 31, 2010

Formula Grant Overview

The Hepatitis B Foundation received \$1,073 in formula funds for the grant award period January 1, 2010 through December 31, 2010. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Identifying Novel Antiviral Agents against Hepatitis B Virus - The purpose of this project is to identify new viral targets for development of antiviral agents against hepatitis B virus. Identified targets will be tested for antiviral activity. This will lead to potential future antiviral development, necessary to augment the short-comings of existing antiviral therapies, including the development of resistance.

Duration of Project

1/1/2010 – 12/31/2010

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: To screen compounds regulating HBV replication from the Library of Pharmacologically Active Compounds-1280.

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 15-40% 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. The Library of Pharmacologically Active Compounds-1280 (LOPAC) includes 1280 drug-like compounds that have been developed against all major

target classes. This library will be screened for anti-HBV activities via a series of assays, with the goal of identifying novel virus targets for antiviral agents. 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

Chari A. Cohen, MPH
Associate Director of Public Health
Hepatitis B Foundation
3805 Old Easton Road
Doylestown, PA 18902

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 15-40% of them will develop cirrhosis or liver cancer, which are both associated with high rates of mortality. It is expected that the results of this research project will result in the identification of new viral targets for development of antiviral agents, and may reveal new chemical leads for future antiviral development. Augmenting existing antivirals, which suffer from the frequent emergence of resistant viruses, 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: To screen compounds regulating HBV replication from the Library of Pharmacologically Active Compounds-1280.

The summer project goal was to screen compounds from the Library of Pharmacologically Active Compounds-1280 (LOPAC) for potential in regulating HBV replication. A total of 29 compounds were successfully screened by a designated summer undergraduate intern, under the

tutelage of an experienced principal investigator, and a PhD student in the PI's lab. All 29 compounds screened showed promise in preliminary studies via simple dot blot measurement of total HBV DNA present in infected cells that had been treated with the LOPAC compounds, followed by Southern blot analysis measuring HBV DNA that had been packaged into the viral capsid (representing true replication intermediates).

In the secondary assay, compounds were purchased from the commercial vendors, and dose-response analysis of the 29 compounds was completed, across the range 0.3-30 μM . The toxicity profile of those compounds has been determined, and their antiviral activity against viral RNA transcription and DNA replication has been analyzed by Northern and Southern blot assay, respectively. The ultimate goal of the study was to determine which of the 29 compounds would result in a 50% reduction (IC_{50}) in viral replication, and to determine if at least one of the compounds would result in a 90% reduction (IC_{90}) in HBV DNA. After withdrawal of compounds with CC_{50} less than 10 μM , 4 compounds were identified as secondary hits with IC_{50} less than 10 μM . The most potent compound among those hits, namely Ancitabine hydrochloride, displayed an IC_{90} about 1 μM , and IC_{50} less than 0.3 μM . Chemically, Ancitabine belongs to a category of cyclocytidine nucleoside analogues, it inhibits HBV reverse transcription and DNA replication by blocking the viral polymerase activity, which is the same antiviral mechanism of FDA approved nucleoside analogues for treatment of chronic hepatitis B, such as Lamivudine and Entecavir. Interestingly, the current clinical application of Ancitabine is anti-cancer chemotherapy, considering HBV reactivation is not uncommon during chemotherapy of cancer patients who have inactive or even resolved HBV infection (presumably due to suppression of the host immune system and/or alteration of the intracellular restriction environment limiting HBV replication), Ancitabine may be recommended to treat those patients under this concern. The above study thus encourages us to further extend our effort to screen a large list of antineoplastic drugs for their antiviral activity against HBV, which may ultimately provide information to guide the prescription of chemotherapy for the group of cancer patients carrying HBV.

Ms. Hess presented her findings to over 100 scientists and entrepreneurs at a special seminar, held at the Pennsylvania Biotechnology Center of Bucks County (PABIO).

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 2010 Hepatitis B Foundation (HBF) summer research internship was successfully completed. A total of 13 undergraduate students completed 100% of their summer 2010 internship. This was the largest summer intern group that the HBF has ever hosted. The student representation was 54% female (7/13); 77% Pennsylvanian residents (10/13) and 77% attend Pennsylvania colleges or universities (10/13).

All thirteen summer interns spent 70% of their time conducting laboratory research with their appointed laboratory mentors. Each student also attended and presented at 10 weekly journal

clubs, 10 laboratory “lunch and learn” seminars, and 7 weekly seminars by visiting scientists and biotechnology experts. Special Seminar topics included “Choosing Biotechnology as a Career Path,” “Introduction to Public Health and Health Disparities,” “Patenting Biotechnology Inventions,” and “Building for a Cure.” The students 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, and an emphasis has been on informing the students about the many biotechnology opportunities there are in Pennsylvania.

Upon completion of their summer research projects, all students presented their findings to over 100 scientists and entrepreneurs at a special seminar, held at the Pennsylvania Biotechnology Center of Bucks County (PABIO).

Faculty members and mentors evaluated each intern, and all 13 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. While students expressed an interest in spending more time in the lab, the lectures, science lunches, seminars and journal clubs were well received, as well. The fact that students were able to concretely see their data at the end of the summer was very appreciated by all students. Many of the 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.

