

Drexel University

Annual Progress Report: 2009 Nonformula Grant

Reporting Period

June 1, 2010 – June 30, 2010

Formula Grant Overview

The Drexel University received \$2,769,497 in nonformula funds for the grant award period June 1, 2010 through May 31, 2014. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Therapeutic DNA vaccine for the Prevention of Hepatitis C Virus-associated Cancer - The main object of this project is to test a next generation DNA vaccine strategy for the prevention of hepatitis C virus-associated cancer using preclinical testing to demonstrate immunogenicity and toxicology/safety studies leading to development of a strong platform for clinical testing. In addition, this research consortium will provide a structured mentoring program with students from a collaborating minority institution for the development of future research scientists in highly translational bench research.

Anticipated Duration of Project

6/1/2010 - 5/31/2014

Project Overview

Specific Aim #1 will test the hypothesis that *consensus* antigenic plasmids NS3/4A, NS4B, NS5A, and NS5B from diverse genotype 1a and 1b sequences will exhibit immunogenicity *in vivo* using small animal models (C57Bl6 and HLA transgenic mice). In addition, experiments will be carried out to optimize immunological assay conditions for HCV responses, including ELISpot, polyfunctional flow and CFSE T cell proliferation. Secondly, we will utilize a NHP model to test immunogenicity of the constructs in a larger animal model. The cross-reactivity of this approach will be explored. Finally, our collaborative group will work to determine toxicity, biodistribution and integration studies for HCV antigens using rabbits.

Specific Aim #2 consists of the *Education and Training Component* that will serve as a mechanism for providing education and training through hands-on research experiences and lecture workshops for faculty, undergraduate and graduate students at Cheyney and Drexel Universities. Throughout the course of the work and critical to the research will be the development and application of data generated throughout the project. There are two primary goals of the application with regard to education and training: (1) to encourage undergraduate and graduate students to pursue careers in biomedical research and (2) to provide a framework

for faculty and students to collaborate on research related to the development, engineering, immunogenicity, and protective effects of the DNA vaccine platform.

To achieve this goal, the *Education and Training Component* will offer a 10-week summer internship program at Drexel University for Cheyney University students. By working closely with the faculty in the different components of the project, the students will be provided with valuable research experiences. Students will gain knowledge and skills on how to formulate research questions, develop a scientific methodology, analyze data and present research findings at a conference or through publications. As part of the summer internship program, students will conduct research projects under the supervision and mentorship of program faculty.

Principal Investigator

Jeffrey M. Jacobson, MD
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Other Participating Researchers

Michele A. Kutzler, PhD, Seth L. Welles, PhD, Scott Baliban, John Miamidian – employed by Drexel University
David B. Weiner, PhD, Bernadette Ferraro, PhD, Michael J. Merva – employed by University of Pennsylvania
Sakkar A. Eva, PhD, Abdel A. Bior, PhD – employed by Cheyney University
Niranjan Y. Sardesai, PhD, Amir S. Khan, PhD – employed by Inovio Biomedical Corporation

Expected Research Outcomes and Benefits

With more than 170 million individuals currently infected, hepatitis C virus (HCV) infection is a global pandemic, effecting approximately 3% of the entire world's population. In the United States chronic hepatitis C infection accounts for approximately one-third of all cases of hepatocellular carcinoma. While many important advances have been made in regard to immunotherapies for HCV, the field continues to be hindered by a general paucity of knowledge concerning how the virus not only interacts with the host immune system but more specifically what type of immune responses are critical for control and clearance of the virus. Understanding the immune correlates of protection against the virus is critical for designing vaccine strategies to combat infection. The role of antibodies in HCV infection is still not completely understood, with research being further compromised due to a lack of a widely accessible method of culturing HCV *in vitro*. Additionally, without a small animal model of HCV infection, elucidation of the specific cellular immune responses responsible for control of the virus has been slow, with the majority of what is known about the immune correlates of protection being gathered from chronically infected individuals. While chimpanzee models of infection have been instrumental in understanding the immune responses early in infection, unlike humans, these

animals develop only mild clinical sequelae. Further complicating the situation is the mounting evidence supporting the idea that HCV viral proteins are able to modulate immune responses, which may in part explain the propensity of the virus to persist. Therefore, success in the development of novel immunotherapies to combat HCV is of the utmost importance. Ultimately, by improving the treatment of HCV infection, we would also have an impact on reducing the incidence of HCV-related hepatocellular carcinoma, a difficult-to-treat cancer with a poor prognosis.

Summary of Research Completed

In the first 30 days of the grant period the collaborative research group working on the project has begun the process of putting the necessary administrative paperwork to put funding in place at Drexel as well as at subcontract sites (University of Pennsylvania, Inovio, and Cheyney) so that research outlined in the funded grant can move forward. In addition, the research group has begun to write and submit IACUC animal protocols, establish a working study group monthly meeting schedule, and identify potential undergraduate students at Cheyney that fit within the goals of the mentoring program funded by this grant award. This collaborative research project involves a number of leading scientists in the field of hepatitis research and vaccine development and includes a number of collaborating organizations from academia and industry. The team involved in this study will share infrastructure, resources and expertise with the common goal of developing a DNA based vaccine for the prevention of HCV-associated cancer, as well as mentoring future research scientists in highly translational bench research. The aims of this grant are to carryout preclinical animal studies that will address immunogenicity and safety of a DNA vaccine that encodes the HCV antigens (1) pNS3A/4A/4B and (2) pNS5A).

Project Summary, Collaboration, Management and Staffing Plan

Oversight of the research consortium will be directed by Dr. Jeffrey M. Jacobson, the Chief of the Division of Infectious Diseases and HIV Medicine at the Drexel University College of Medicine (DUCOM) in Philadelphia. The other participating institutions will be the University of Pennsylvania and Cheyney University. Drs. Michele A. Kutzler (Project 1) of DUCOM and David Weiner (Project 2) of the University of Pennsylvania will provide the immunology laboratory expertise and perform the immunologic assays for the *preclinical studies outlined in aim 1*. Dr. Weiner's laboratory developed the HCV DNA-based vaccine. Inovio is the manufacturer of the vaccine and provider of the electroporation equipment. Dr. Niranjan Desai will lead the Inovio team on the program (Project 3). Dr. Seth Welles of the Drexel University School of Public Health will provide the statistical input to the design of the study, and will oversee further statistical design refinements, data collection, safety data oversight, and final data analysis. The educational core will entail a collaboration between DUCOM and Cheyney University (PI: Sakkar Eva, Ph.D.) and includes training and collaborative research related to the development and testing of DNA vaccines. Dr. Jacobson has worked with Drs. Weiner, Kutzler, and Welles on several other research studies.

We have also put together a Scientific Advisory Board that includes Timothy Block, Ph.D., Brian Wigdahl, Ph.D., Stephen Cox, B.S. M.S., and Jeffrey Ulmer Ph.D., all of whom will provide scientific and *pre-clinical* guidance, as well as expertise in the field of HCV

immunotherapy. An overview of the Key Personnel and Scientific Advisory Board is shown in Figure 1.

Figure 1. Overview of Key Personnel and Scientific Advisory Board

