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DOE Award Number: DE-FG02-08ER64670 New York University School of Medicine

Project Title: Development of Biomarkers for Chronic Beryllium Disease in Mice

Principal Investigator: Terry Gordon, PhD

Team Members: Andrew Fontenot

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Background

Animal models provide powerful tools for dissecting dose-response relationships and pathogenic mechanisms and for testing new treatment paradigms. Mechanistic research on beryllium exposure-disease relationships is severely limited by a general inability to develop a sufficient chronic beryllium disease animal model. Discovery of the Human Leukocyte Antigen (HLA) - DPB1Glu69 genetic susceptibility component of chronic beryllium disease permitted the addition of this human beryllium antigen presentation molecule to an animal genome and development of a better animal model for chronic beryllium disease. In this project, we proposed to use the transgenic and 'normal' inbred strains of mice to identify biomarkers for the progression of beryllium sensitization and CBD. To achieve this goal, we compared the sensitivity and accuracy of the lymphocyte proliferation test (blood and lymph nodes) with: 1) the ELISPOT test in the three HLA-DP transgenic mice strains throughout a 6 month treatment with beryllium particles; and 2) changes in potential protein biomarkers in beryllium-treated mice.

Aim

The purpose of this project was to provide the scientific community with biomarkers of sensitization and disease progression for CBD. These biomarkers may then serve as critical tools for development of improved industrial hygiene and therapeutic interventions.

Outcomes

- 1. The transgenic mice, originally developed with DOE funding, are available at NYU for research collaborations. In addition, 2 of the transgenic strains (the most sensitive and the most resistant) have been cryopreserved at The Jackson Laboratory in Bar Harbor, ME.
- 2. To compare the functional expression of biomarkers with beryllium-induced granulomas, immune tissues and serum were isolated from mice treated with beryllium particles for 5 months. The immune tissues were processed to isolate lymphocytes and the lymphocytes shipped to Dr. Fontenot's lab in Denver for comparison of the lymphocyte proliferation test and the Elispot. Despite repeated attempts, the viability of the lymphocyte preparations were low and unsuitable for the proliferation test.

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The serum samples were processed for high throughput proteomics in Dr. Newman's lab in Denver. Using the Ciphergen proteomics system, protein biomarkers in serum were successfully identified. Classification and regression tree (CART) analysis determined that the use of 2 or more pathway linked proteins provided greater predictability than a single protein in linking the protein biomarker(s) to beryllium-induced granulomas. These pilot data have not been published but were a part of Dr. LM Tarantino's PhD thesis completed at NYU in 2009.

3. We successfully transferred one of the transgenic strains to Dr. Fontenot's lab and a publication has recently been submitted:

Douglas G. Mack, Amy S. McKee, Michael T. Falta, Allison K. Martin, Philip L. Simonian, Terry Gordon, Robert R. Mercer, Mark D. Hoover, and Andrew P. Fontenot. Generation of a Beryllium-Specific Adaptive Immune Response in HLA-DP2 Transgenic Mice. (submitted).